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Australasian Anaesthesia 2019

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Australasian Anaesthesia 2019

Invited papers and selected continuing education lectures

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Contents

Preface

Welcome to the 2019 edition of *Australasian Anaesthesia*.

This edition has a variety of "hot" topics that I hope you find interesting and relevant to your practice. This is despite several colleagues suggesting to me that the golden age of anaesthesia is over. They argue that the drugs are so good now, the technology is superb and the techniques so well developed that research funding has largely moved away from anaesthesia to other specialties, such as oncology and immunology. The implication is that return on investment in anaesthesia-related pharmaceuticals or equipment is possibly lower than other fields and that we should not expect to witness monumental discoveries in anaesthesia as all the innovation has been largely achieved. Certainly, I feel privileged to have seen the introduction of remifentanil, isoflurane, then followed by sevoflurane and desflurane; the adoption of capnography, oximetry and processed EEG; and the transition from simple mechanical anaesthesia machines to complex, computerised anaesthesia delivery units with integrated monitoring that rival ICU systems. Further, airway management has broadened its armamentarium with the advent of the laryngeal mask airway, videolaryngoscopy and fibreoptic bronchoscopy. Similarly, ultrasound has been adopted by anaesthetists to enhance the practice of regional anaesthesia, vascular access and even airway management and to aid perioperative diagnosis of various crises. And we should not forget the pioneering work of anaesthetists in the hybrid field of simulation in healthcare. Simulation-based learning has contributed to the education of anaesthetists, and all their colleagues in acute-care medicine, and to assist in understanding how we work and, finally, to enhance patient safety.

So if I have learned one thing about those who practice anaesthesia it is that they are innovative. Although one age is over, there will be another. There will be better and safer drugs, newer technologies to remove some of the guesswork and enhance decision-making in our practice, and additional strategies to make the perioperative process lower risk. And this will be taking place while facing demands of patients with greater age, body mass index and number of comorbidities; and hospital managers who strive to contain hospital budgets.

This is my last edition as editor and I wish to thank the authors, the faculty and regional editors and ANZCA's Liane Reynolds, Frankie Rowsell and Vanessa Hille for their work and support in producing this edition. Please take the opportunity to thank our authors personally when you can and also consider writing yourself for the next edition. Finally, please continue to give us feedback. This is your publication and we would like to make it better.

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Airway

The Vortex Approach to airway management

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INTRODUCTION

While technical competence and adequate planning are crucial to effective airway management, it is well recognised that even well-prepared airway clinicians can sometimes fail to perform basic interventions under stress[1].

The major airway guidelines are valuable resources that can be referred to *prior* to the occurrence of an airway crisis, to lay a foundation of knowledge on which subsequent airway management decisions can be based ("foundation tools"). They are not, however, usually presented in a format that makes their content readily accessible in real-time to teams of potentially highly stressed clinicians nor are they intended to be referred to *during* the process of managing a challenging airway[2]. In addition, difficult airway guidelines typically provide guidance predominantly directed at anaesthetists and largely restricted to the circumstance where the primary plan for airway management is endotracheal intubation[2-4].

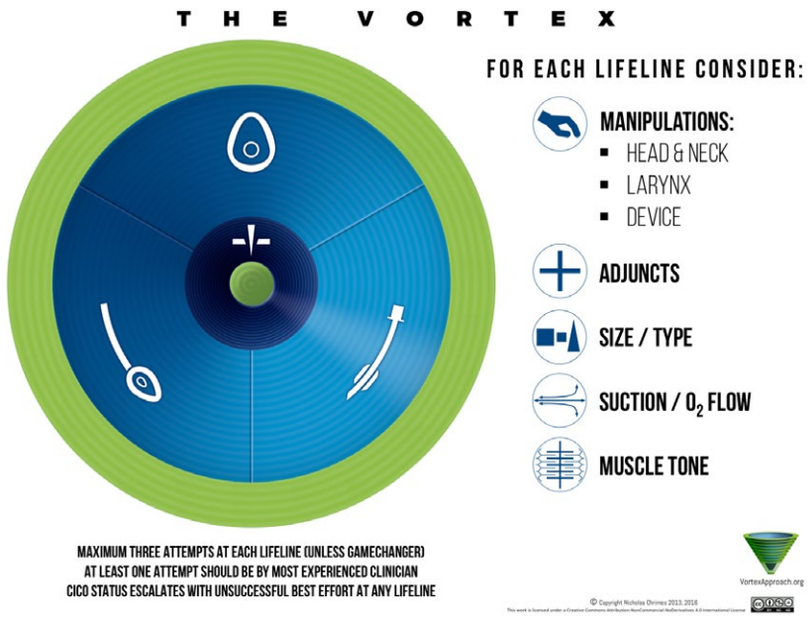
In contrast, the Vortex Approach[5] is based around a "high acuity implementation tool", designed to be used during the high-stakes, time-critical situation of an evolving airway emergency. It is intended to help clinical teams perform under pressure by providing a simple, consistent template that can be taught to all clinicians involved in advanced airway management, irrespective of critical care discipline and whether they are from a medical, nursing or paramedical background. It is also able to be used in any context in which an airway management takes place, regardless of whether the primary intended airway is an endotracheal tube (ETT), a supraglottic airway (SGA) or even a face mask (FM).

The Vortex Implementation Tool

The Vortex Implementation Tool (Figure 1) is based on the premise that there are only three upper airway "lifelines" ("non-surgical" techniques) by which alveolar oxygen delivery can be established and confirmed: FM, SGA and ETT. Completion of a best effort at any of the three upper airway lifelines without being able to confirm adequate alveolar oxygen delivery mandates abandoning further attempts at that lifeline and focusing instead on optimising one of the remaining alternatives. On the circular Vortex graphic this is represented by spiral inward movement. Completion of best efforts at all three lifelines without restoring alveolar oxygen delivery culminates in spiral movement to the central zone of the tool, representing the need to initiate CICO Rescue (emergency front-of-neck airway). Conversely, confirmation of adequate alveolar oxygen delivery using any of the three lifelines, results in outward movement into the circumferential "Green Zone" (see page 6), which provides time to consider and prepare for subsequent airway management options before further instrumenting the airway. The Green Zone is also depicted in the centre of the tool to remind clinicians that, when all three lifelines have been unsuccessful, CICO Rescue can also restore adequate alveolar oxygen delivery and provide these same opportunities.

In contrast to a linear algorithm, the concentric arrangement of the three lifelines on the circular Vortex graphic reflects that airway management can be initiated using any lifeline and, if this is unsuccessful, attempts at the same or alternate lifelines can be implemented in whatever sequence is judged most appropriate in the clinical circumstances. This flexibility in the sequence in which attempts at different lifelines are undertaken, better represents real-world airway management practice than the more rigid sequential progression through upper airway techniques depicted by an algorithm and allows the Vortex to be applied to any context in which airway management occurs.

Figure 1. Vortex.



The Vortex Approach

The Vortex Implementation Tool is the core of the broader "Vortex Approach" which provides an extended array of resources[6] to facilitate all phases of advanced airway care including airway assessment, development of an airway strategy and efficient performance of airway interventions in both the routine and emergency setting. The focus of the Vortex Approach is on providing "implementation tools" designed to be simple enough for real-time use during the process of airway management. This includes a suite of resources designed to facilitate both the preparation and intervention phases of advanced airway care. These adjunctive tools work in an integrated fashion with the primary Vortex tool using the same concepts and language to maximise opportunities to establish alveolar oxygen delivery by:

- Facilitating effective planning for airway management.
- Facilitating efficient best efforts at each of the three upper airway lifelines.
- Encouraging appropriate decision making when adequate alveolar oxygen delivery is achieved via any lifeline.
- Promoting early priming for CICO Rescue as an airway crisis evolves.
- Facilitating rapid recognition of the need for CICO Rescue.
- Facilitating ready access to appropriate airway equipment.

BEST EFFORT AT UPPER AIRWAY LIFELINES

The term "best effort" refers to the circumstance in which all reasonable interventions to facilitate success at entering the Green Zone via a given lifeline have been implemented. Whether or not a given intervention constitutes a "reasonable" contribution towards achieving a best effort represents a balance between its likelihood for success and its potential for harm in a given clinical situation.

The likelihood of success of an intervention is influenced by:

- The intervention: its intrinsic efficacy for addressing a particular problem.
- The problem: the specific challenges impeding entry to the Green Zone in a given patient.
- The clinician: experience and skill set in implementing the intervention.

Repeated interventions to optimise success at a lifeline may contribute to harm by two mechanisms:

- Trauma: repeated airway instrumentation may produce trauma that potentially compromises the ability to enter the Green Zone by alternative means. Airway instrumentation may also produce trauma resulting in patient morbidity beyond airway compromise.

- Time: repeated airway instrumentation consumes time and if unsuccessful may prolong the time to enter the Green Zone relative to exploring alternative options. This potentially increases the duration and severity of hypoxaemia to which a patient is exposed. Even in patients with adequate SpO2, delays to entering the Green Zone consume safe apnoea time and potentially increase the risk of a patient subsequently being exposed to critical hypoxaemia.

Except in the unusual circumstance where an attempt at a given lifeline is considered futile, at least one attempt at each lifeline is usually indicated prior to initiating CICO Rescue. Although desirable, it is not usually feasible to implement all optimisations required to maximise success at a given lifeline and achieve a best effort on this first attempt. Additional factors which might improve the chances of entering the Green Zone may only be identified after initial airway manipulations have taken place. In addition, while some optimisations can be superimposed in an incremental fashion during a given attempt (for example, application of external laryngeal manipulation) others represent alternatives (for example, use of a hyperangulated rather than a Macintosh blade videolaryngoscope) that necessitate an additional attempt. As a consequence, achieving a best effort at a given lifeline typically occurs in a cumulative fashion over a number of attempts, each incorporating additional optimisations that have not previously been implemented. To address the potential for trauma and delays with repeated instrumentation, the Vortex limits the maximum number of attempts to achieve a best effort at each lifeline to *three* but emphasises using the *minimum* number of attempts possible.

To assist with the process of efficiently achieving a best effort over the minimum number of attempts, the Vortex implementation tool (Figure 1) includes a list of five categories of optimisation that apply equally to each of the three lifelines and provide a prompt to consider specific interventions relevant to achieving a best effort at a particular lifeline. Categorising optimisations in this manner is intended to help the entire team to track which interventions have been implemented by the airway operator and to offer suggestions in a structured way.

It is not expected that all the optimisation interventions in a given category are exhaustively implemented for a particular lifeline, as this would be both time consuming and inappropriate in most circumstances. Instead the optimisation headings serve to encourage the clinical team to *consider* all of the options, with the airway operator only *implementing* those thought to be beneficial in a particular context. This structured approach to considering optimisation strategies maximises the opportunities for achieving timely entry to the Green Zone by ensuring that the process of achieving a best effort is:

1. Efficient: by minimising both the time and number of attempts needed to implement all strategies considered to be useful.
2. Rigorous: by minimising the likelihood that potentially helpful interventions are overlooked.
3. Finite: by outlining a set of optimisations that define an endpoint to optimisation of a given lifeline. This promotes team recognition that a best effort at a given lifeline has been completed and, if adequate alveolar oxygen delivery has not been achieved, provides them with permission to move on to an alternate technique.

The goal is to maximise opportunities to enter into the Green Zone in the shortest possible time and with minimum instrumentation of the airway. This makes optimal use of the safe apnoea time and minimises the risk that the patient will be exposed to critical hypoxaemia.

The specific interventions required to achieve a best effort and the number of attempts over which these are employed is thus a context dependent decision, to be made by the airway operator within the confines of the principles set out by the Vortex Approach. In a given set of circumstances this decision will be influenced by the clinical situation and the difficulties being encountered as well as the skill set of, and resources available to, the team managing the airway.

Attempts

In order to meaningfully limit the number of attempts at a lifeline it is necessary to precisely define what is meant by an "attempt". The definition used by the Vortex Approach for an attempt at each lifeline is as follows:

- ETT: the insertion and removal of a laryngoscope from the airway.
- SGA: the insertion and removal of a supraglottic airway from the airway.
- FMV the application and removal of a face mask to the patient's face.

It is not necessary that all attempts in pursuit of a best effort at one lifeline must be completed before initiating the first attempt at an alternate lifeline. Best efforts at multiple different lifelines may be proceeding in parallel, with sequential attempts alternating between optimising different lifelines. This reflects normal clinical practice as well as being the most efficient way to achieve entry into the Green Zone[7].

Declaration

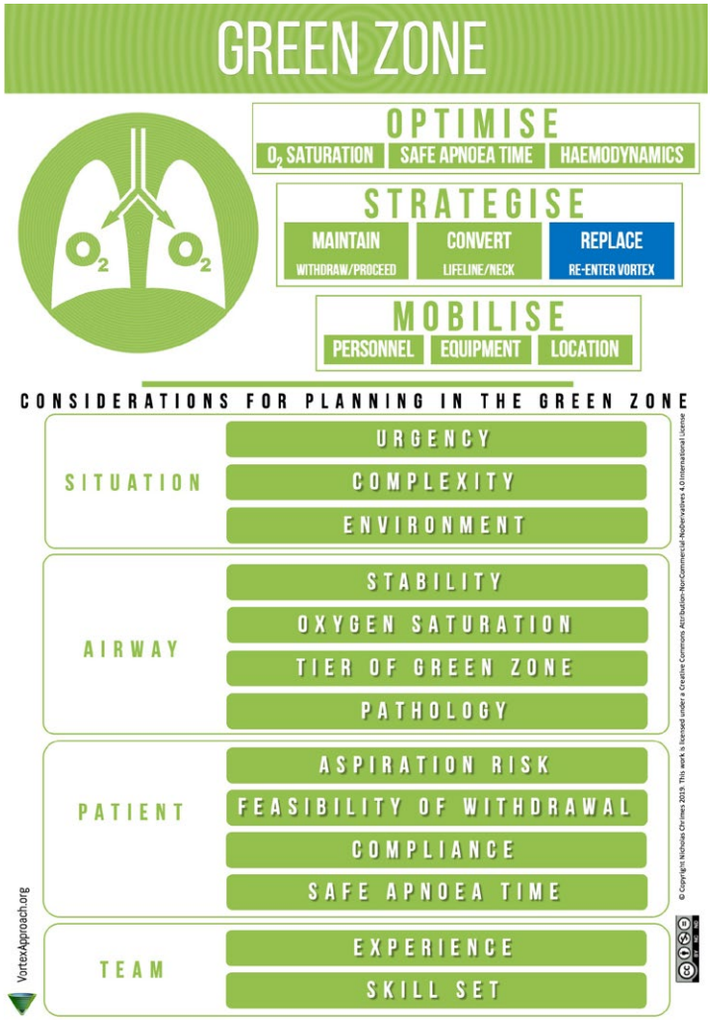
Declaration that alveolar oxygen delivery cannot be achieved by a given technique is a key step in encouraging the team to commit to alternate strategies. Most of the major difficult airway algorithms emphasise the need to make declarations of “failure” at each of ETT, SGA and FM[2-4] in order to facilitate team situation awareness of the need to progress to other techniques. Linking such a declaration to the notion of “failure”, however, with the implications this may carry for the competence of the airway operator, may have the potential to become a psychological barrier to such a declaration being made. Use of the term “best effort” rather than “failure” serves to convey the futility of further attempts at the relevant lifeline while emphasising that the clinician has maximised the opportunities available to them according to anatomical, situational and clinician factors at the time. The expectation is that there are less barriers to a clinician to declaring a best effort at intubation than to declaring failure.

If following a best effort at any lifeline alveolar oxygen delivery has not been restored, then alternate strategies must be exclusively pursued, including CICO Rescue when best efforts at all upper airway lifelines have been exhausted.

THE GREEN ZONE

Entry into the Green Zone via any lifeline removes the imminent threat of critical hypoxia and places the patient in a position of relative safety. The declaration “we’re in the Green Zone” prompts recognition of the opportunity this presents to optimise physiology, strategise further airway management and mobilise resources (Figure 2).

Figure 2. Green Zone.



Identifying the Green Zone

The essential question to be answered to identify whether the Green Zone has been entered is: Can *adequate* alveolar oxygen delivery be *confirmed*?

- Confirmation: real-time confirmation of alveolar oxygen delivery should typically be achieved by ensuring the presence of $ETCO_2$ (when the patient is being ventilated with oxygen) though a rising pulse oximetry (SpO_2) reading also establishes this.
- Adequacy: the adequacy of alveolar oxygen delivery is not defined numerically but is instead assessed by asking "Is the patient likely to suffer harm from hypoxaemia if exposed to this level of SpO_2 for the next 15 minutes?". The absolute SpO_2 value satisfying this criterion will vary according to the context.

Entry into the Green Zone is therefore not synonymous with obtaining a normal SpO_2 measurement. Normal SpO_2 may be maintained by preoxygenation stores despite an obstructed airway and absent alveolar oxygen delivery. As such there is an ongoing urgency to address the situation before the safe apnoea time is exhausted. Conversely following severe desaturation, obtaining an $ETCO_2$ trace accompanied by recovery of the SpO_2 from 40% back to only 85% would clearly confirm the occurrence of alveolar oxygen delivery. Irrespective of the exact value of the SpO_2 reading, provided it is considered “adequate” in context, confirmed alveolar oxygen delivery always represents entry into the Green Zone.

Any time adequate alveolar oxygen delivery cannot be confirmed, the patient is instead described as being “in the Vortex”. This provides a clear conceptual dichotomy by which all patients must either be “in the Green Zone” or “in the Vortex” at any time. After each attempt to establish or optimise one of the airway lifelines, clinicians are encouraged to verbally declare whether they are in the Vortex or the Green Zone. Such a declaration clearly conveys to the team the answer to a critical question in relation to decision making during airway management: If something is not changed, will the patient inevitably become critically hypoxaemic? By highlighting whether the patient remains at risk of imminent critical hypoxaemia, the declaration of whether or not the patient is in the Green Zone facilitates team situation awareness of the urgency and priorities of airway management at any given point in time in a way that may be obscured when focusing solely on the adequacy of saturations or “oxygenation”.

Opportunities of the Green Zone

1. *Optimise:*

Optimisation of patient physiology consists of maximising the oxygen saturation of the blood, extending the safe apnoea time and stabilising haemodynamics:

- Optimising the blood oxygen saturation minimises the *immediate* threat of harm from tissue hypoxia.
- Optimising the safe apnoea time minimises the *future* threat of harm from tissue hypoxia in the event that alveolar oxygen delivery is subsequently interrupted.
- Optimisation of haemodynamics may previously have been overlooked while trying to restore the airway, leading to compromise of oxygen delivery to the tissues.

2. *Strategise:*

Initial strategic options in the Green Zone can be discussed under three broad headings:

- Maintain: maintain the lifeline by which the Green Zone was achieved and use it to either proceed with the indication for which airway management was initiated or withdrawn (“wake” the patient), using the current lifeline as a bridge to provide time for the patient to regain the ability to maintain their own airway.
- Convert: an attempt can be made to convert the current lifeline, without leaving the Green Zone, to a more appropriate alternative that satisfies other secondary goals of airway management. This can either occur via one of the upper airway lifelines (for example, converting a supraglottic airway to an endotracheal tube using an Aintree catheter) or via some form of front-of-neck airway under more controlled circumstances.
- Replace: this option involves a deliberate decision to abandon the lifeline that provided entry to the Green Zone, interrupting alveolar oxygen delivery, with the expectation that it can be restored using an alternate lifeline.

Categorising strategic options in this manner provides a simple format that decreases the likelihood that key alternatives are overlooked.

NAP 4 emphasised that clinicians should develop a strategy rather than a plan for airway management[1]. A strategy can be defined as an integrated series of plans, each a contingency for failure of the preceding one,

concluding with the trigger for initiation of CICO Rescue. Thus, even when the plan is to remain in the Green Zone ("maintain" or "convert" options), consideration should always be given to the possibility that the ability to achieve alveolar oxygen delivery is inadvertently lost. This should include developing plans to complete best efforts at any remaining lifelines and an appropriate level of priming (see below) to perform CICO Rescue. Thus, it is not sufficient to simply plan the next step in airway management while in the Green Zone. In developing a strategy the question that must repeatedly be asked is: What is the plan if that plan fails?

3. Mobilise:

Having developed a strategy, the time provided by restoration of alveolar oxygen delivery can be used to assemble the resources necessary to facilitate the safe management of the patient. Resources include personnel, equipment and the potential to change the location in which airway management is taking place.

- Personnel: this may include seeking the assistance of an experienced anaesthetist, an ENT surgeon, additional medical/nursing staff or even consulting with a remote colleague via phone.
- Equipment: any specialised equipment for both primary and contingency plans should be made immediately available.
- Location: there may be circumstances in which it is desirable to transfer the patient to a more suitable environment such as the operating suite before proceeding with further airway management.

Entry into the Green Zone consistently provides the same opportunities. The scope of the options available to exploit these opportunities and what constitutes an appropriate strategy, however, depends on the context. The context dependent considerations that might influence this are outlined in the lower half of the Green Zone tool. The Green Zone Tool thus prompts the team to consider the key considerations for planning in the Green Zone. The implications of each of these considerations on the decision making process should be apparent to airway clinicians from their training and is beyond the scope of the content addressed by the Vortex Approach.

CICO RESCUE

CICO Rescue is the term used by the Vortex Approach to describe emergency cannula or scalpel cricothyroidotomy/tracheostomy procedures required during can't intubate, can't oxygenate (CICO) events. Unlike many other terms applied to this procedure (emergency surgical airway, emergency front-of-neck access, invasive airway access, infraglottic rescue, and so on) CICO Rescue satisfies the criteria required of such a term[8] in being simple, intuitive, precise, unintimidating (even reassuring) and inclusive of both cannula/scalpel techniques performed on either the cricothyroid membrane or trachea. This enables it to be readily distinguished from non-emergency techniques to access the airway via the anterior neck (for example, surgical tracheostomy, percutaneous tracheostomy) which are inappropriate for the time critical situation of a CICO event.

There is considerable variation in the way the CICO acronym is verbalised by clinicians. In addition to spelling out C-I-C-O, phonetics range across *Kick-Koh*, *See-Koh*, *Chee-Koh*, *Sic-Koh* and *Psy-Koh*. To facilitate clear, efficient communication during an airway crisis, the Vortex Approach encourages consistent pronunciation of the CICO acronym as *Ky-Koh*.

Trigger for Initiating CICO Rescue

According to the Vortex Approach the trigger for initiating CICO Rescue is the inability to confirm adequate alveolar oxygen delivery following best efforts at all three upper airway lifelines. Note that this trigger is independent of the oxygen saturations since, even in the unusual situation where the oxygen saturations remain high following best efforts at all three lifelines, the inability to confirm alveolar oxygen delivery means that eventual desaturation is inevitable. Rather than being a deterrent to its performance, recognition of the need for CICO Rescue while the oxygen saturations remain high should be viewed as advantageous – providing increased time to perform this confronting procedure in a more controlled manner, thereby increasing the chance of success. Conversely, a critically low oxygen saturation is not in itself a trigger to initiate CICO Rescue if best efforts at all three lifelines have not yet been completed. While legitimate opportunities to enter the Green Zone in a timely fashion via the familiar upper airway lifelines remain, these should be given priority, as they are more likely to be successful than resorting to an unfamiliar and more traumatic technique.

Oxygen saturations are therefore not a relevant consideration in deciding the trigger for CICO Rescue – this is always "the inability to confirm adequate alveolar oxygen delivery following best efforts at all three upper airway lifelines". They are, however, a relevant consideration in making the context dependent decision of what constitutes a best effort at each lifeline in a particular situation. This is because the oxygen saturations impact on how much time it is reasonable to invest in optimising each of the upper airway lifelines before declaring

a best effort. When the oxygen saturations are critically low it might be reasonable to have only one attempt at each lifeline before declaring a best effort, even though this means leaving some potential optimisation interventions untried. This is because the incremental benefit of repeated attempts to optimise a lifeline that has already failed is typically low relative to untried alternative lifelines. Thus the time expended on such low yield interventions cannot be justified when the patient is already critically hypoxaemic and alternatives (including CICO Rescue) with a substantially higher likelihood of success remain.

Priming for CICO Rescue

The term "priming" was introduced by the Vortex Approach to refer to an escalation in readiness to perform CICO Rescue that occurs prior to recognition of a CICO situation. This includes activities that occur during an evolving airway crisis in parallel with attempts to enter the Green Zone via one of the upper airway lifelines, not just preparatory activities that take place in the more static setting before the initiation of airway management. Priming is crucial to ensure that airway management teams are poised to perform CICO Rescue, ideally with zero latency, when CICO is declared and minimise the exposure of patients to hypoxaemia.

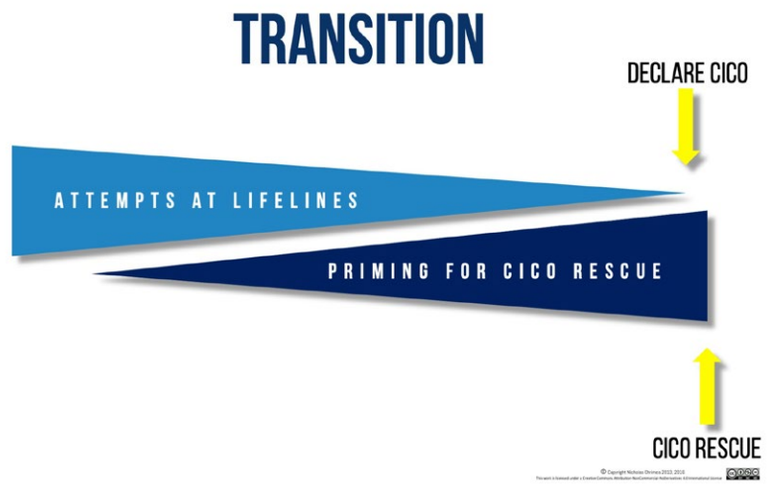
Priming represents a departure from the way in which clinical teams have typically approached readiness for CICO Rescue – which has been to wait until a CICO event is imminent or has already occurred before making any efforts towards getting ready to perform CICO Rescue.

Transition to CICO Rescue

Priming is a key component in the process of "transition" to CICO Rescue encouraged by the Australian and New Zealand College of Anaesthetists (ANZCA)[9]. ANZCA's transition concept emphasies that the shift in focus from attempts to enter the Green Zone via the upper airway lifelines, to achieving this via CICO Rescue, should be a *process* (occurring over a period of time) rather than a *pivot* (occurring at an instant in time).

The Vortex Approach describes transition as *"the phase of care leading up to and including the potential initiation of CICO Rescue"*. Transition is therefore comprised of simultaneous priming for CICO Rescue in parallel with ongoing attempts to enter the Green Zone via the upper airway lifelines (Figure 3). Transition thus commences with the onset of priming and concludes either with entry into the Green Zone via an appropriate upper airway lifeline (typically) or the initiation of CICO Rescue (rarely).

Figure 3. Transition.



CICO Status

While the concept of transition is appealing, effective priming presents two main challenges:

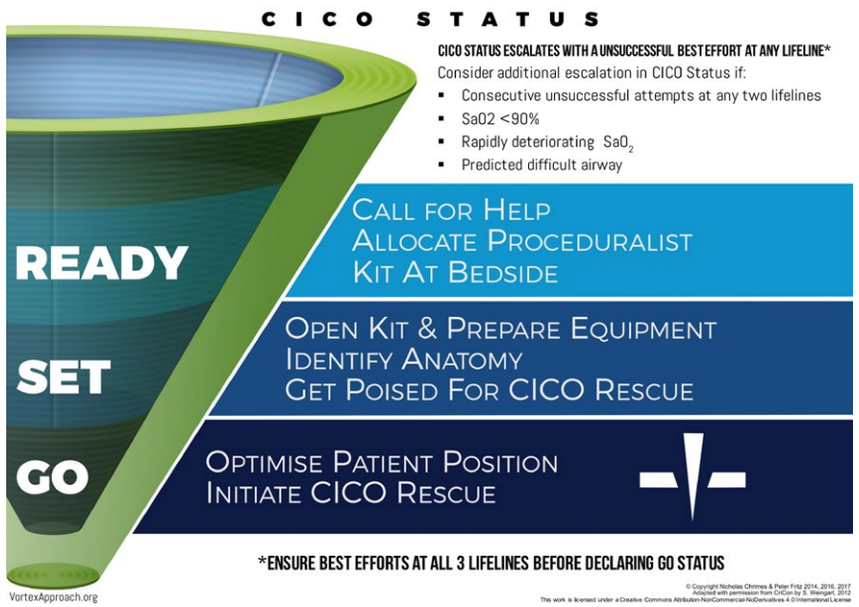
1. Trigger: The onset of an airway crisis is frequently insidious. Even during routine airway management, it is not uncommon for optimisations to be required before entering the Green Zone. The gradual evolution of these routine issues into an airway emergency makes it difficult for clinical teams to identify and declare a clear point of onset for a crisis and thus a trigger to initiate priming.

2. Outcome: To be effective, priming must be initiated early in the management of the challenging airway. Given that CICO events are so uncommon, it would be expected that in most cases the airway will subsequently be successfully managed by one of the upper airway lifelines. Thus initiation of priming will not usually culminate in a declaration of CICO or the need for CICO Rescue.

The above two issues have the potential to create a barrier to effective priming. While the absence of occurrence of a CICO event represents an expected outcome of most episodes of priming rather than a "false alarm", clinicians may be reluctant to initiate priming early, due to concerns about being seen to have panicked or overreacted. As such, a tool is required to facilitate implementation of the process of transition.

While the Vortex tool defines when performance of CICO Rescue is indicated, it does not in itself provide a clear trigger to initiate priming for CICO Rescue. To facilitate effective priming for CICO Rescue, the Vortex Approach uses the CICO Status tool (Figure 4) as an adjunct. This tool helps to address the above issues by linking specific pre-defined priming actions to objectively defined events in the management of the challenging airway in a manner that is integrated with the Vortex model. Using a three-tiered ready-set-go system, the CICO Status escalates with the declaration that a best effort at any lifeline has been completed without providing entry to the Green Zone. Adopting a structured and standardised approach to priming shares the responsibility for escalation with the team, removes the focus on the "anxiety" of an individual clinician and reduces the barriers to timely escalation towards CICO Rescue.

Figure 4. CICO Status.



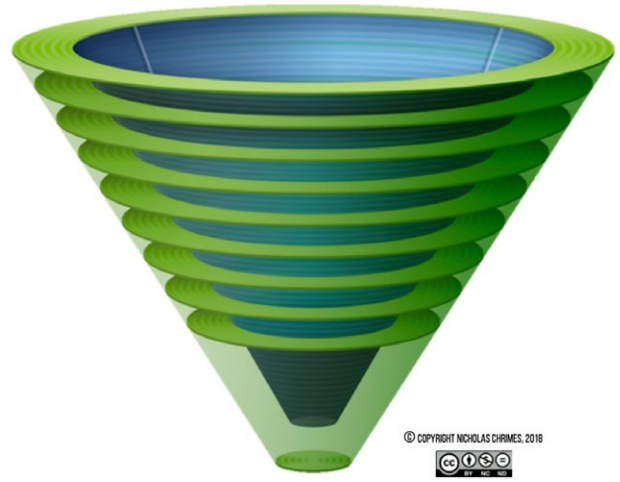
As well as the mandatory escalations with completed best efforts at any lifeline, additional discretionary escalations of the CICO Status may be suggested by members of the team according to other recommended criteria on the tool or their own clinical judgement. In an anticipated difficult airway, where there is perceived to be a high risk of needing to proceed rapidly to CICO Rescue, airway management may even begin with the CICO Status already at SET (the "double setup"). It is also appropriate to consider the need to escalate the CICO Status in any circumstance where previously secured access to the Green Zone has the potential to become compromised, such as during extubation of a high-risk airway.

The declaration of a completed best effort at any lifeline should therefore be accompanied by a request to escalate the CICO Status. If this is not made by the airway operator, other members of the team should feel empowered to insist on this. It is important to note, however, that the CICO Status should not reach GO unless best efforts at all three lifelines have failed to provide entry into the Green Zone. Once the CICO Status reaches SET it should plateau here until a declaration is made that best efforts at all three upper airway lifelines has been unsuccessful.

CONCEPTUAL IMPRINTING

The circular graphic on the Vortex Implementation Tool is intended to represent looking down into a funnel, as illustrated in the lateral three-dimensional image of the Vortex (Figure 5). This three-dimensional depiction of the Vortex is not intended to be referred to during an airway crisis but is used during training to convey and promote retention of additional concepts relating to airway management – a process described as "conceptual imprinting". The Vortex implementation tool is then able to evoke recall of these imprinted concepts without making specific reference to them, which allows it to maintain a simple, low content interface.

Figure 5. Vortex Lateral.



The narrowing of the funnel represents the decreased time and options available with spiral descent deeper into the Vortex. The darker blue at the centre of the funnel evokes recognition of the potential for worsening hypoxaemia and cyanosis if alveolar oxygen delivery is not restored. The sloping surface of the interior of the funnel emphasises that this is an unstable situation and reinforces the need to keep moving forward with attempts to efficiently establish alveolar oxygen delivery via one of the lifelines to avoid a deterioration in tissue oxygenation. In contrast the horizontal surfaces which make up the surrounding Green Zone serve as a reminder that whenever alveolar oxygen delivery is achieved the risk of imminent hypoxaemia has been arrested. The patient is then in a situation of relative safety which provides time to pause and exploit the opportunity to optimise physiology, strategise management and mobilise resources.

CRITICAL LANGUAGE

Critical language refers to standardised communication using specific terms or phrases that are clearly defined, mutually understood and consistently used[8]. The Vortex Approach emphasises the use of critical language to facilitate team situation awareness during airway management. Such terminology is commonplace during cardiac arrest where standardised phrases such as no output, shockable rhythm, stand clear, and so on are routinely used. In contrast, emergency airway management has not evolved an analogous lexicon, leading to duplication and ambiguity of many terms[8], which has the potential to negatively impact on team performance. This has necessitated the Vortex Approach coining idiosyncratic language such as best effort, Green Zone, CICO Status and CICO Rescue to address these deficits.

CLINICAL INTEGRATION

The structured approach to considering optimisation strategies using the five categories of the Vortex for each lifeline can be integrated into the clinical environment[10]. Labelling the emergency airway cart drawers to correspond to the different domains of the Vortex and arranging equipment inside them according to the optimisation categories allows clinicians to use the equipment itself as a prompt to ensure efficient optimisation of the lifelines. In addition, graphics in the drawers can provide visual cues for non-equipment interventions. In this way the airway cart itself becomes an extension of the cognitive tool.

SUMMARY

The Vortex Cognitive Tool is the core element of a broader array of integrated airway resources that include critical language, equipment layout and adjunctive cognitive tools that comprise the Vortex Approach. The Vortex Approach provides a simple, consistent template to prompt team recall and application of technical background material in real-time. Underpinning the effective use of the Vortex Approach is the need for team training to ensure familiarity with the elements required for its successful application. It should not be viewed as an alternative to the major airway algorithms but as a complementary resource, designed to facilitate implementation of the management recommendations outlined by these training tools and improve the performance of clinical teams.

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Managing airway trauma: Applying logic and structure to the anaesthetic decision-making process

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INTRODUCTION

Traumatic airway injuries (TAIs), like other "threatened airway" presentations, are rare. Despite accounting for only 1% of all trauma presentations the mortality rate among these patients is estimated to be well over 20%[1,2]. Exact mortality rates are difficult to gauge as a significant proportion of these patients die at the scene.

Existing guidelines on airway management are (mostly) designed for use in situations of unanticipated difficulty during routine airway management[3,4], and are thus intended to be applied where anaesthesia has already been induced. As such, they are not directly applicable to the situation of a patient presenting with a TAI. Moreover, several authors have emphasised that adhering to these guidelines in the presence of a TAI may be unhelpful[5] or even harmful[6].

There have been a large number of reviews focusing on airway trauma[1,5-11]. These articles comprehensively describe the incidence, aetiology, and common presentations of these injuries, and catalogue the diagnostic investigations and management options available. With a few exceptions, however, these reviews either fail to provide a framework to guide decision-making around airway management or focus specifically on the decisions pertaining to surgical management. The few reviews that do provide a framework or algorithm for anaesthetic decision-making fail to address how extrinsic (non-patient) factors such as equipment available in the emergency department (ED) compared with that in the operating theatres (OT) and the distance from ED to OT impact choices around airway management.

This article attempts to provide a decision-support matrix for the management of TAIs that incorporates both the intrinsic considerations such as patient and airway factors, and the extrinsic considerations such as the situational factors described above and team factors. These factors are then applied in a sequential decision-making process which addresses when and where the airway should be managed, the team composition, and the primary and contingency airway management plans.

Components of the presented decision-support matrix are derived or borrowed from the Vortex Approach[12]. [See "The Vortex Approach to airway management" by Nicholas Chrimes in this edition of *Australasian Anaesthesia*]. Specifically, the table of considerations presented later is a modification of that presented in the Green Zone planning tool, and the contingency plan options are presented as either those available "in the vortex" or those available "in the green zone".

TAIs are comprised of a heterogenous collection of injuries including maxillofacial trauma, blunt and penetrating neck trauma, and inhalational injuries. Tracheobronchial injuries can also result from blunt chest trauma, but due to low survival-to-hospital rates these won't be addressed here. An overview of the presenting features of the various types of TAIs is presented below.

Maxillofacial trauma

Maxillofacial trauma may involve the mandibular/maxillary structures or the mid-face region. These injuries are characterised by copious bleeding which may threaten the airway via aspiration and hypoxia and may complicate airway management. Patients often present sitting erect and spitting out blood in order to avoid choking and asphyxia. Rarely mandibular condylar impaction can restrict mouth opening. Bilateral mandibular fractures may cause the tongue to migrate posteriorly, obstructing the airway. These patients will also present in an erect position. Mid-face fractures are associated with airway disruption along the nasopharynx and with cervical spine injuries[13].

Blunt neck trauma

These injuries are often part of a wider multi-trauma picture, such that urgent airway management may be required due to deterioration secondary to other injuries. The cricoid cartilage and cricothyroid membrane are involved in 50% of blunt airway trauma where the airway is compromised. Thyrohyoid membrane, thyroid cartilage and upper tracheal injuries accounting for the remainder[14,15]. Laryngo-tracheal disruption is a feature in more than half of these patients and complete separation may occur, usually between the cricothyroid membrane and the fourth tracheal ring. Patients with blunt neck trauma may present with cough, dyspnoea, aphonia, stridor, subcutaneous emphysema or haemoptysis but symptoms don't correlate well with location of injury or severity[16,17]. Airway obstruction can be secondary to oedema, haematoma, subcutaneous emphysema, tissue deformity from cartilage fracture, or a combination of these.

Penetrating injuries

Injuries include airway laceration and disruption, cartilage fracture and vocal cord damage, blood vessel damage, pneumothorax and oesophageal perforation. They cause airway compromise through aspiration of blood, oedema, subcutaneous emphysema, haematoma, and pneumothorax. Large penetrating injuries may allow establishment of a definitive airway by direct placement through the wound. Cervical spine injuries are frequently associated with gunshot wounds but less so with other causes of penetrating neck trauma[18].

Airway burns

Thermal injury to the airway is typically seen in patients trapped in an enclosed space for a prolonged period. The main concern is airway obstruction secondary to oedema. Swelling may be immediate or delayed and can be exacerbated by fluid resuscitation. Inhalational injury is a significant cause of mortality in burns patients[19]. Difficulty with airway management and specifically intubation increases with time[20]. Nasendoscopy has been used to predict need for intubation, and can be used serially to assess increasing oedema[21,22].

GOALS OF AIRWAY MANAGEMENT IN TAI

In patients presenting with a TAI the airway may be compromised or complicated by a broad range of pathological processes. Despite this, the goals of airway management in all cases remains the same.

1. To identify which patients with TAIs need their airways secured.
2. To place a cuffed tracheal tube into the lumen of the airway distal to the location of the injury while avoiding hypoxia.
3. To avoid exacerbating a potential or actual airway disruption and/or migrating an endotracheal tube (ETT) outside the airway.
4. To avoid creating or exacerbating subcutaneous emphysema.

INTRODUCING A FRAMEWORK TO GUIDE DECISION-MAKING IN THE MANAGEMENT OF TAIs

With reference to the goals of airway management in the presence of a TAI, as described above, it is understandable why awake airway management techniques such as flexible bronchoscopic intubation (FBI) or performance of a front of neck airway (FONA) under local anaesthetic have been promoted by some as the "gold standard" for the management of patients with TAIs. In reality, performance of awake techniques, especially those involving specialised equipment and/or specific technical skills is only a realistic option under certain circumstances. Hence, over-emphasis on an aspirational ideal is unhelpful. It may even promote dangerous practices whereby clinicians ignore or avoid intuitively safer options in favour of pursuing techniques inappropriate in the given context or attempt dangerous transfers of unstable patients to the operating theatres.

Prior to deciding how the airway is to be managed, it must first be determined when and where the airway can and should be managed. Most, if not all patients presenting with a symptomatic TAI will arrive first to the ED. There they will be assessed and managed by a multi-disciplinary team that, in Australia and New Zealand, will (almost) always include an anaesthetist or anaesthetic trainee. The decision to stay in ED or move to theatre will impact the options available for airway management. Another decision that should precede, and will ultimately impact, the selection of how the airway is to be managed is that of who can and should be involved in the management of the airway. Once a decision has been made on how the airway is to be managed, the final aspect of management to be considered is what are the contingency plans in the event of failure.

They key questions to be addressed are:

1. Where and when should the airway be managed?
2. Who should be involved?

3. How should the airway be managed?
4. What is the plan if that plan fails?

In order to guide the key questions outlined above, a broad array of factors need to be considered. These are outlined in Table 1.

Table 1. Key considerations in patients with TAIs.

Situation factors	Urgency
	Complexity
	Environment/Location
Airway factors	Stability
	O_2 Saturation
	Viable options
	Pathology
Patient factors	Aspiration risk
	Feasibility of waking
	Compliance
Team factors	Experience
	Skillset

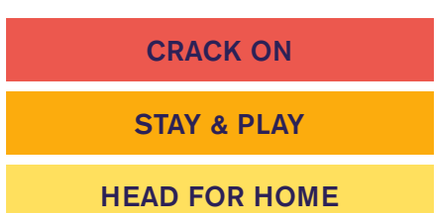
Where and when should the airway be managed?

The decision-making process begins with an airway triage to decide whether the option to move the patient out of the ED and into the operating theatre (OT) is realistic and safe. While the presenting state of the patient will impact this decision-making, important situational factors will also come into play. Many of these factors will be specific to the facility within which that case is taking place and may even vary with time of the day or day of the week. The importance of taking local circumstances such as the distance from the ED to the OT was emphasised in the NAP4 report, where several cases where identified where a transfer between the two locations led to a prolonged period of hypoxia[23]. In smaller hospitals theatre staff may not be immediately available after-hours or on weekends and the consequences of any delay required to have theatres ready to receive a patient with a TAI need to be carefully considered.

In 2016 Mercer and colleagues presented a systematic review of traumatic airway injury management and suggested dividing patients into three groups: no time, some time, and adequate time to allow airway assessment, investigation and intervention[6]. The advantage of this taxonomy is that it utilises the clinical picture at presentation along with an understanding of the pathophysiology and its likely progression to help decide how urgently the airway needs to be managed. It does, however, fail to account for the aforementioned situational factors. There is limited value in advocating a decision-support model that utilises a time-based classification system if the included categories have different management implications across different hospitals, days of the week or times of the day. In fairness to the authors, they were presenting an institution-specific protocol.

For the purposes of developing a transferable, universally applicable approach, an airway triage system is proposed that accounts for both intrinsic and extrinsic factors impacting when and where the airway should be managed. This is shown in Figure 1.

Figure 1. Airway triage categories.



Triage category 1: "crack on"

Patients triaged to this category are those *in extremis*, where the risks of delaying airway management outweigh any advantages gained by waiting for additional personnel or equipment. These are patients obviously too unstable to undergo extensive airway assessment or investigation, let alone be transferred to the OT. It should be noted that the self-selecting nature of these injuries will dictate that relatively few patients will arrive at a trauma department in this state as a direct result of their TAI – most will have either died at the scene or have had their airways managed in-transit[1].

Table 2. Absolute and conditional indications for immediate airway management.

Absolute indications for immediate airway management	Indications for immediate airway management when associated with actual or expected deterioration
Severe hypoxia	Stridor
Airway obstruction from blood or secretions	Respiratory distress
Decreased conscious state	Subcutaneous emphysema
Profound shock	Expanding neck haematoma
Cardiac arrest	Inability to lie flat

It is hard to identify a definitive list of signs or symptoms which indicate a patient should be triaged to the "crack on" category. Some, such those listed in the left hand column of Table 1 are incontrovertible. Others, such as those listed in the right hand column of table need to be interpreted within the context of the presentation. It can logically be argued that the presence of one or more from the list in the right hand column of the table, without evidence of progression, may not necessitate immediate airway management. For example, if a patient with a TAI is recorded as having stridor and a respiratory rate of 32 at the scene of the accident, and then arrives in the ED with her clinical state unchanged, the potential benefits of waiting for additional resources may outweigh the risk of the airway deteriorating further. This example highlights the fact that the process of differentiating patients within the "crack on" category from those in the "stay and play" category requires consideration of both the significance of the presenting sign or symptom and the rate of progression of the underlying pathology.

Triage category 2: "stay and play"

Patients triaged to this category are those where the risks of transferring the patient are deemed to outweigh the advantages inferred by being in the OT environment. These patients are, however, stable enough to permit delaying definitive airway management in order to maximise the likelihood of success. This may involve gathering of personnel and equipment, and performing limited investigations of the airway. Transfer for CT scan is unlikely to be feasible in this cohort of patients but nasendoscopy along with radiographs and ultrasound of the neck are quick to perform and are likely to influence decision-making. In some centres, patients with major airway injuries excluded on nasendoscopy are managed conservatively, despite the presence of voice changes and/or subcutaneous emphysema[8,24].

In the presence of a TAI, a patient would be triaged to the "stay and play" category if displaying signs and symptoms suggestive of major airway injury but without evidence of the rapid progression or deterioration that would demand immediate definitive airway management. Specifically, these are patients with stridor, dyspnoea, subcutaneous emphysema, neck swelling or intolerance of the supine position.

Other injuries may prevent a patient with an otherwise stable TAI from being transferred to the OT. Examples are major haemorrhage or head injury in a multi-trauma patient, and smoke inhalation in burns patients. The signs and symptoms associated with TAIs have been noted to have poor predictive value[16,17], and as such the pathophysiology or mechanism of the injury and/or the impact of patient specific-factors may suggest the need to "stay and play". For example, the underlying airway oedema in patients with symptomatic inhalational thermal injuries is likely to rapidly progress[20]. As mentioned, factors such as distance to theatres, availability of theatres or theatre staff, and equipment available in the ED need also be considered when deciding whether to transfer or not[5,9].

Triage category 3: "head for home"

This category comprises those patients with TAIs who require definitive airway management but are stable enough to permit transfer to the OT prior to airway being secured. As with those in the "stay and play" category, these patients should undergo a comprehensive airway assessment including nasendoscopy, chest and neck radiographs and possibly neck ultrasound. Unlike the "stay and play" patients, these patients should be considered for CT scan. The decision to surgically explore or repair a TAI secondary to blunt laryngeal trauma is largely based on the criteria outlined in the Schaefer classification system[25] or one of its many derivations[14,26]. These criteria include a combination of presenting signs and symptoms, nasendoscopy findings and features on the CT scan. Essentially all symptomatic patients with severe oedema, significant mucosal disruption, vocal cord immobility or displaced laryngeal fractures will require surgical intervention.

Who should be involved with airway management?

Pausing to consider who should be involved prior to commencing airway management in the presence of a TAI is about ensuring both that personnel with the correct skillset and experience are in attendance, and also that roles are clearly allocated and defined. The most senior anaesthetic help available should be deployed for these cases along with a surgeon with tracheostomy and/or cricothyroidotomy skills.

In the "crack on" group of patients, the ability to get additional senior help and an ear, nose and throat (ENT) surgeon or similar, may be restricted to presentations where the presence of airway pathology is recognised and communicated at the time of trauma team activation.

Taking time to consider who should be involved is likely to infer the greatest benefit in the patients falling within the "stay and play" triage category. NAP4 identified several cases with poor outcomes involving non-urgent but complex airway injuries or pathology where the airway was managed in the ED by anaesthetic trainees while senior help had been available[23]. In situations where time is available but the patient is considered too unstable for transfer to the OT, the presence of a senior anaesthetist and an ENT surgeon should be requested. Consideration should also be given to having a capable anaesthetic nurse or technician from OT attend the ED.

Patients in the "head for home" category will be managed in the OT, and the process of explicitly considering who should be involved can be used to overcome the complacency that can arise with the familiarity of the environment and the relative stability of these patients. The anaesthetist should ensure that all team members are present in OT at the outset of airway management, and that all roles are allocated including a "hands-off" team leader.

How should the airway be managed?

There is no consensus on how TAIs should be managed and in many cases authors appear determined to identify and advocate a single best way to manage all presentations, rather than considering the pertinent factors in a structured way to guide decision-making. This is particularly evident with laryngotracheal trauma, where historically awake tracheostomy was advocated by many for all patients requiring definitive airway management[26,27]. Others advocated rapid sequence induction with direct laryngoscopy despite the risk of exacerbating a tracheal tear[14]. More recently some have proposed awake FBI as the method of choice[24] while others suggest any of the aforementioned techniques may have place in the management of TAIs[6,9,10]. The impracticality of a "one size fits all" approach has already been explained. Instead a method for deciding which options are feasible and appropriate in different circumstances should be employed.

In the Vortex Approach patients are considered to be in one of two states based on whether alveolar oxygen delivery is occurring: either "in the vortex" or "in the green zone"[12]. A Green Zone (GZ) tool is provided to guide decision-making in the circumstance where alveolar oxygen delivery has been restored. This tool is discussed later in this paper.

The situation of the threatened airway lends itself to a modified version of this model. Any patient presenting with a threatened airway such as a TAI who is able to maintain their own airway would be considered to be "in the green zone". Assuming that the patient requires definitive airway management, a primary airway plan that addresses the goals of airway management in the presence of a TAI would be selected from within following three broad categories:

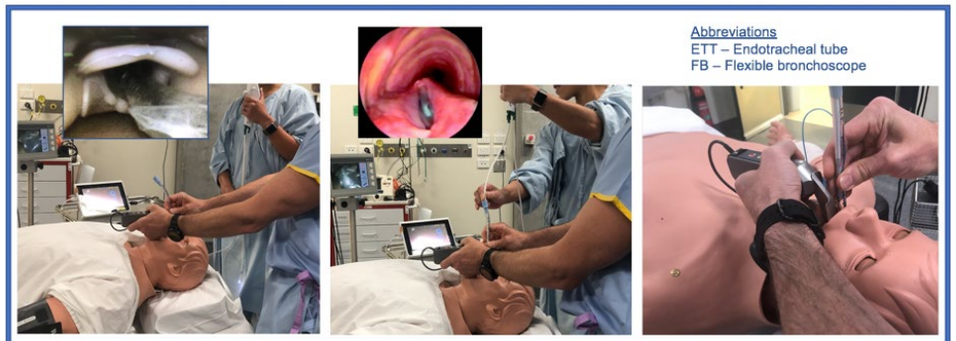
1. AWAKE – securing the airway awake – patient remains within the green zone.
2. SV – securing the airway asleep but with maintenance of spontaneous ventilation – patient remains within the green zone.
3. RSI – securing the airway asleep and apnoeic with rapid sequence induction – patient enters into the vortex.

In other, non-trauma, presentations of threatened airways the use of "holding measures" such as continuous positive airway pressure, high-flow nasal oxygen and heliox (helium-oxygen mixture) have been advocated[28]. While these may intuitively seem worthy of consideration in TAIs where stridor and obstruction feature prominently, the possibility that these may exacerbate surgical emphysema should mandate careful patient selection.

Primary plan options in patients in the "crack-on" triage category

In the patients that have been triaged to the "crack on" category the time-limitations render awake and spontaneous ventilation techniques impractical. In these situations the primary airway plan will constitute a modified RSI with or without manual in-line stabilisation. Recognising that blind passage of an ETT during RSI can exacerbate airway disruptions and lead to migration of the ETT outside the trachea[14], measures to mitigate this risk should be employed. Mercer and colleagues recommend a modification of RSI whereby the concurrent use of videolaryngoscopy (VL) and an flexible bronchoscope (FB) allows negotiation of any airway disruption under direct vision[6]. The steps involved with this technique are explained in Table 2.

Table 2. Steps involved in an FB-assisted RSI.



Step 1	Step 2	Step 3
Following induction of anaesthesia, the primary anaesthetist proceeds to place the bevel of the ETT at the introitus of the trachea, at the vocal cords. The second anaesthetist is poised with the FB.	The second anaesthetist advances the FB into the trachea identifying the location of, and passing beyond, any tracheal tear.	The primary anaesthetist rotates the ETT so that the leading edge of the bevel is furthest from the tracheal tear. The ETT is then gently advanced to a depth where the cuff is well beyond any identified tear.

It should be noted that FBs are not immediately available in the emergency departments of most Australian and New Zealand hospitals. The FB-assisted RSI described above will only be possible in the few hospitals where these are stocked in ED or where a portable FB is mobilised to the ED at the time of the trauma team activation. In the absence of an FB, a smaller than usual ETT should be utilised. Cricoid pressure should be avoided in the presence of a laryngeal injury, as should high flow nasal oxygen delivery which generates a degree of positive airway pressure. Simple apnoeic oxygenation delivered at 10-15 litres per minute via standard nasal cannulae can significantly prolong time to desaturation[29] and should be utilised in these patients.

Regardless of the exact technique used to perform an RSI in these situations, a second clinician should have the equipment ready for, and be poised to perform, an emergency front of neck airway (eFONA); the only viable contingency plan in this situation. This has been described as a "double set-up"[7].

Occasionally with patients in the "crack on" triage category it will be determined that the extent and severity of the airway and facial pathology equate to a very low probability of success with direct or video laryngoscopy during RSI. In these cases immediate eFONA following induction may constitute the primary plan with the highest likelihood of success.

Primary plan options for TAI patients in the "stay and play" triage category

In these patients where some time is available, but management necessarily must occur in the ED, options from within each of the Awake, SV and RSI categories become viable. The patient factor having the greatest impact on choice of technique in these patients is compliance. An awake technique is only tenable in situations where a patient is cooperative, while an SV or RSI techniques will be required in a non-compliant patient.

In a compliant patient where a surgeon is available, and factors such as blood in the airway or a lack of equipment or skills make awake FBI less viable, awake FONA should be the technique of choice. The location of the injury will determine whether cricothyroidotomy or tracheostomy is indicated. It should again be emphasised that neither FBs nor the equipment used for topicalisation are commonly available in Australian and New Zealand EDs. Awake FBI will rarely be a viable option for patients in this triage category and should only be considered where time and/or availability permits its use and the pathology strongly indicates the need for this technique.

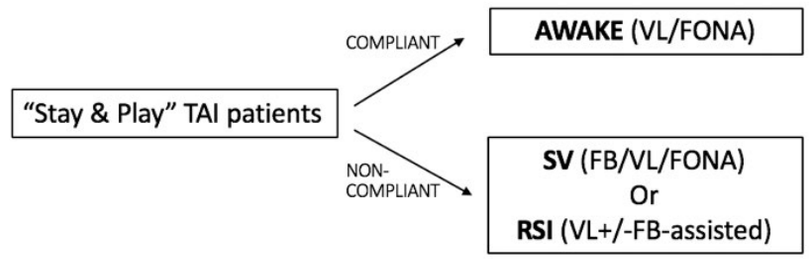
In situations such as severe maxillofacial injury or a penetrating injury to the pharynx or hypopharynx, blood will be a prominent feature but subglottic structures are likely to be intact. In such cases, awake VL or awake surgical airway are the primary plan options with the highest likelihood of success. The skillset and experience of the team should be used to guide which is selected.

In confused or combative patients in this triage category the choice of a SV or RSI technique will be guided by the estimated risk of aspiration (blood or stomach contents) and the anticipated ability of the patient to maintain a patent airway while anaesthetised.

The pharmacological options for inducing anaesthesia while maintaining spontaneous ventilation are limited in the ED. The use of ketamine is advocated by some authors for this situation[7] and has been used extensively to gain control in combative patients prior to RSI[30]. Topicalisation is not required for performance of FBI after induction with ketamine. This technique should, therefore, be considered in the minority of EDs where these devices are available, or where a disposable scope has been mobilised from OT early in the process.

If an RSI technique is utilised, the same modications and precautions described earlier should be adopted. A summary of the options for the primary airway plan in patients in the stay and play category is presented in Figure 2.

Figure 2. Primary plan options in patients in the "stay and play" triage category.



FB, flexible bronchoscope. VL, videolarngoscope. FONA, front of neck airway. SV, spontaneous ventilation. RSI, rapid sequence induction.

Primary plan options in TAI patients in the "head for home" triage category

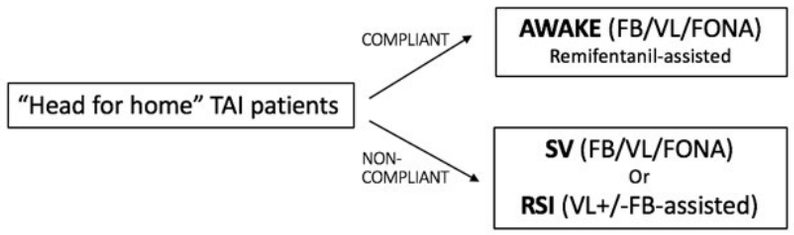
Options from all three of the management categories; awake, SV, and RSI are available to the anaesthetist. The same considerations as those described above for patients in the "stay and play" triage category apply to these patients. Additionally, information from a CT scan may determine the need for a surgical procedure that itself requires specific airway management such as a tubeless field across the larynx.

As with patients in the "stay and play" triage category, compliance will again be the factor having the greatest impact on choice of anaesthetic technique for the primary airway plan. Among cooperative patients the choice of awake FONA, awake FBI or awake VL will largely be determined by airway factors, with equipment availability and team skillset less likely to play a role than with the cohort of patients in the "stay and play" triage category. The availability of target-controlled infusion pumps for the delivery of remifentanil in the OT environment is likely to enhance performance of awake techniques[31].

The small group of combative patients that do make it to theatre, and those that refuse an awake technique, will require either an SV or RSI technique. Aspiration risk and likelihood of the airway remaining patent after induction will again determine this choice. A small proportion of patients may be appropriate for rigid laryngoscopy and bronchoscopy, but concurrent cervical spine injury is common in TAIs, and would be contraindication to these.

The utility of SV techniques using volatile inhalational agents in threatened airway presentations has been questioned[28] and was associated with frequent failure in cases reported in NAP4[32]. An SV technique utilising intravenous anaesthesia has theoretical advantages[28] and target-controlled infusions of propofol have been successfully used to maintain SV in patients requiring airway surgery for subglottic stenosis[33]. The primary plan options in the "stay and play" patient cohort are summarised in Figure 3.

Figure 3. Primary plan options in patients in the "head for home" triage category.



FB, flexible bronchoscope. VL, videolarngoscope. FONA, front of neck airway. SV, spontaneous ventilation. RSI, rapid sequence induction.

What is the plan if that plan fails?

One of the themes that emerged from NAP4 was the frequency with which airway management was embarked upon with only a primary airway plan rather than a strategy comprising both a primary plan and contingency plans to be enacted in the event of the primary plan failing[32]. Even the existence of a viable airway strategy is of limited value unless it is shared with members of the team such that a shared understanding of the steps within the strategy exists.

A useful way to ensure that likely contingencies and the appropriate responses to these are considered is to always ask "What is the plan if that plan fails?" A second, and equally important component to contingency planning in the setting of TAIs, is to also ask the question "What is the plan if the airway is lost now?" This is particularly pertinent in patients triaged to the "stay and play" and "head for home" categories, where a delay to permit optimisation of the environment or a transfer to OT is planned. There are numerous case reports of patients with initially stable TAIs deteriorating suddenly necessitating immediate airway management[34-36].

The options available as contingency plans are usefully delineated by the Vortex Approach[37]. If alveolar oxygen delivery is not occurring due to airway obstruction or the patient becoming apnoeic, the only options available are the three upper airway lifelines of facemask ventilation (FMV), supraglottic airway rescue (SGA) and intubation (ETT), or the last resort of eFONA. If alveolar oxygen delivery is still possible, or is restored via one of the three upper airway lifelines then the options are to either i) maintain oxygenation with the current airway and wake the patient or proceed with surgery, ii) convert the current airway while maintaining alveolar oxygen delivery, or iii) abandon the current airway and move to another modality to achieve definitive airway management. The Vortex Approach cognitive tools designed to prompt recall of these options are presented in the chapter "The Vortex Approach to airway management" by Nicholas Chrimes in this edition of *Australasian Anaesthesia*.

It must be emphasised that the cognitive tools are prompting recall of ALL of the options available, and it is the responsibility of the team to decide which options should be considered as viable and appropriate contingency plans. Clearly some of these options are unlikely to be successful and in fact may make further attempts at securing the airway more difficult. For example, positive pressure ventilation via FMV or LMA is likely to cause or exacerbate subcutaneous emphysema in the presence of an airway disruption. Similarly, performance of eFONA at the cricothyroid membrane may be at or above the level of the injury and therefore unlikely to achieve the goals of airway management in the presence of a TAI.

In some circumstances FMV or LMA may appropriately be incorporated into contingency planning for management of patients with TAIs, but at best these are likely to buy time for the performance of FONA. For this reason the approach being advocated here for all symptomatic TAIs involves immediate mobilisation of personnel and equipment for FONA and an escalation of preparedness such that the procedure can be immediately performed in the event of sudden deterioration or the failure of the primary plan. This is the "double set-up" described earlier, which is analogous to a CICO status of "set" using the Vortex Approach[38].

Where the decision to perform FONA is made while alveolar oxygen delivery is still possible a more precise FONA approach may be adopted. If oxygen delivery has failed, however, akin to a "can't intubate, can't oxygenate" (CICO) situation, a technique that can secure the airway within minutes must employed – eFONA. This distinction needs to be clearly communicated to, and understood by, the team member allocated to this task.

PUTTING IT ALL TOGETHER

A composite decision-support tool for management of patients presenting with a "threatened airway" is presented in Appendix 1. A high-resolution version is available for download via www.sim.scssc.edu.au/threatened-airway-tool. The tool prompts consideration of the key patient, airway, situational and team factors that impact decision-making. It then guides clinicians through the process of answering the four key questions explained above. The tool is designed to provide appropriate guidance for not only patients presenting with TAIs, but also other pathologies found within the heterogenous group of patients that present with imminent airway obstruction: infection, haematoma, tumour and foreign body.

Like all cognitive aids, the "Threatened airway planning tool" requires prior knowledge of its content and an understanding of the concepts and techniques included in the tool. It is designed to both support the decision-making of the individual anaesthetist and promote effective team performance. Clinical performance is likely to be optimised by rehearsal with immersive simulation which utilises the same tools, resources and personnel that will be available in the clinical setting.

The tool is relatively complex and information-dense. As such, it is likely to be of most use in situations where some time is available – patients presenting in the "Stay and play" or "Head for home" triage categories. It is incumbent on the individual practitioners and teams managing emergent patients to have a clear idea of how patients presenting in-extremis – those in the "crack on" triage category, should be managed without needing to refer to a cognitive aid.

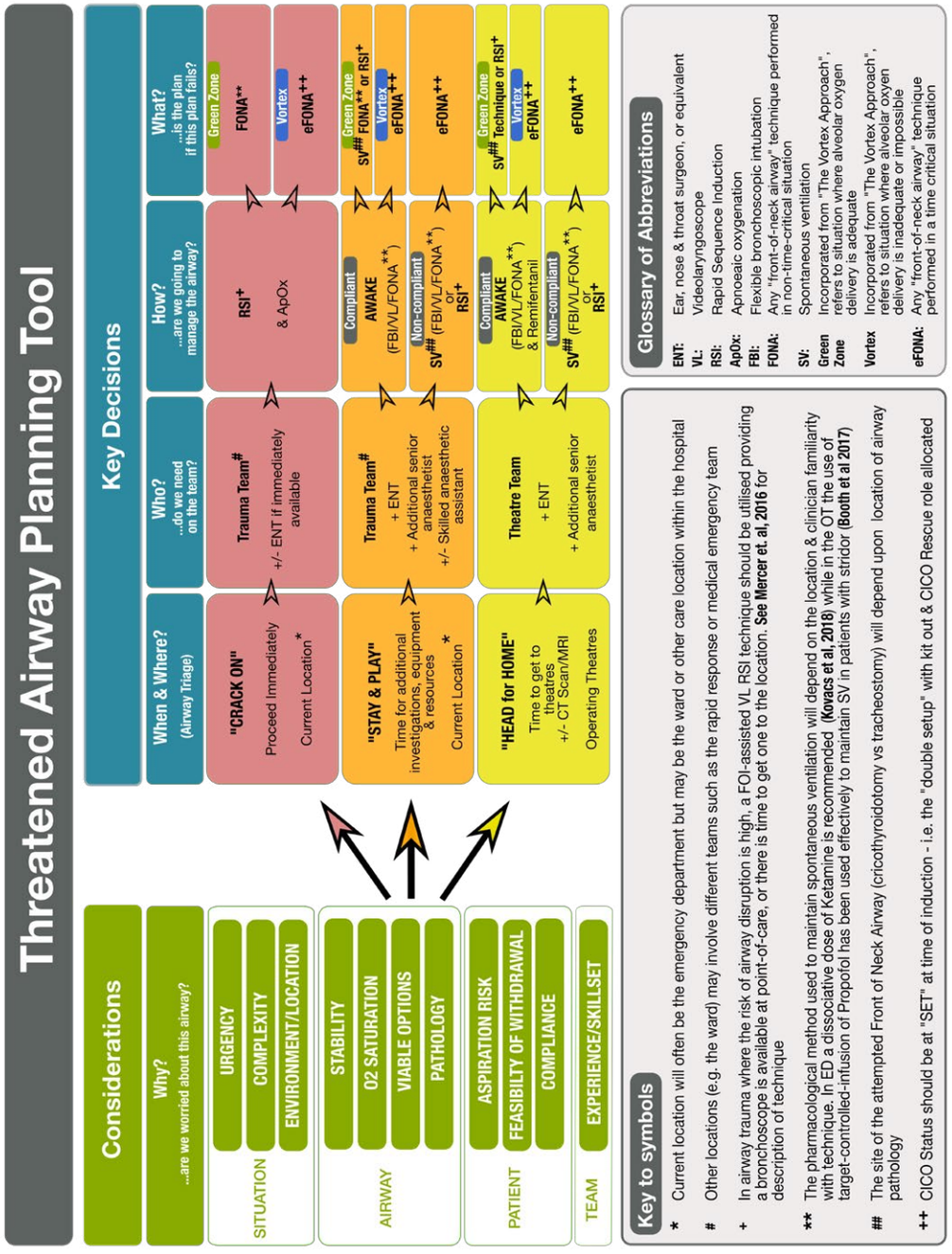
CONCLUSION

TAIs, and other presentations involving "threatened airways" are rare events requiring complex anaesthetic decision-making to optimise outcomes and avoid potential complications. The impact of extrinsic factors such as location, distance to theatre, and team skillset on the available options are often ignored but in fact need to be integrated into the decision-making process. Hopefully the step-wise approach outlined here, along with the accompanying decision-support matrix in the Threatened Airway Planning Tool provide a logical, structured approach to these challenging situations.

ACKNOWLEDGEMENT

I would like to acknowledge Nicholas Chrimes for allowing incorporation of the Green Zone Tool from The Vortex Approach in the Threatened Airway Planning Tool.

Appendix 1. A composite decision support tool for management of the threatened airway.



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Unanticipated difficult airway events: A systematic analysis of the current evidence and mapping of the issues involved using a Bowtie diagram

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INTRODUCTION

Unexpected difficult airways are challenging to study. In the first place they are relatively rare[1] and because of the different causes, clinical set-ups, protocols in place, various levels of preparation by the anaesthetist and different degrees of skill levels, they are extremely hard to analyse and also somewhat difficult to prevent. Although this article will include methods to predict and prevent a difficult airway event, one of the main focus points will be adequate planning in all cases, not just the expected difficult airways.

The principles of data quality were defined by Wang and Strong and it was defined that "high-quality data should be intrinsically good, contextually appropriate for the task, clearly represented, and accessible to the data consumer"[2]. With regard to the intrinsic quality of the data, the highest level of evidence in medicine is believed to be well-conducted and large randomised controlled trials (RCTs) or a meta-analysis of multiple RCTs. However, serious difficult airway events are relatively rare, vary in severity and, during management, seconds count. This makes standardisation and randomisation impossible. Even if this were possible, it would not be ethical to randomise to a single strategy for management. The best level of evidence is therefore case series, case reports and case based audits. The following studies will be used for this review.

The Australian Incident Monitoring Studies (AIMS)[3-5], the National Audit Project 4 (NAP 4) which was conducted in the UK[1] and the Danish Anaesthesia Database[6] have all provided valuable data regarding airway management of patients undergoing anaesthesia. None of these studies were randomised double-blinded trials, which traditionally are considered the gold standard in scientific evidence-based clinical studies.

While there is a large amount of airway data and recommendations available, there is some difficulty summarising the data into a format that is easy to understand, that is consistent and available at the point of care. Therefore, current data sources such as journal articles and long reports do not meet the data quality requirements of easy accessibility to the data consumer and are not clearly represented in terms of the ability to use the information while working. Memorising this information is the current way in which we work and, in some tasks, this is assisted by checklists and crisis management resources.

At this stage, there is no formal classification system which combines hazards, preventive factors, management, and outcomes of airway incidents. A formal classification may aid in a higher level of comprehension and would also aid in the reporting of incidents and consequently in analysing the data acquired. A standardised approach is also important because memory recall is limited, especially while in a crisis. It has been suggested that a visual display of data improves memory and aids the recall of effective strategies put in place[7].

The Bowtie diagram is a risk assessment tool used in high-risk industries. It allows for a visual display of the connection between hazards, preventive measures, management and outcomes of incidents. This article will analyse current evidence and strategies developed for the management of the difficult airway scenario, and then combine them into a Bowtie diagram. This will provide a new and innovative visual learning tool for risk assessment and management of patients with unexpected difficult airways. This review will aim to collate airway management data and guidelines into a simple mapping format and will display this data in a Bowtie diagram.

HISTORY AND DEVELOPMENT OF THE BOWTIE METHOD

The Bowtie method is a risk evaluation tool, which is used to analyse causal relationships. It was developed for industries heavily reliant on safety such as aviation, emergency services and engineering. The method takes its name from the visual shape of the risk-assessment diagram.

The exact origin of the Bowtie method is unclear. Its first published reference was in a hazard analysis course presented by Imperial Chemical Industries, a firm connected to the University of Queensland, in 1979[7,8].

Since then, the Bowtie method gained popularity throughout various industries, as it has proven to be a suitable tool for providing an overview of risk management practices in any kind of scenario.

Bowtie diagrams represent the "fusion" of a "fault" tree and an "event" tree[9,10] linking the cause and effect of decision-making[9]. The fault tree highlights and offers potential to exhaustively analyse all interactions between forces within a complex decision. A simplified version of this method represents the left side of a Bowtie diagram.

Event trees were further developed during nuclear reactor hazard studies in the 1970s[11], which further integrated the probability and frequency of potential adverse outcomes. A modified version of the event tree method describes the right side of the Bowtie diagram, where the functionality of controls is assessed.

These two methods have each been evaluated as separate tools in the assessment of patient safety[12]. The combination of the fault tree method and event tree method created the Bowtie diagram[13].

The Bowtie diagram was applied when considering medication safety in 2009[14] and was found to be an applicable and comprehensive method in determining the type and frequency of adverse effects. Additionally, it was reported that this technique of risk analysis simplified visualisation and understanding of interdisciplinary goals, challenges and managements of risks in each medical subspecialty.

Consequently, intensive care unit studies used Bowtie diagrams for prospective risk analysis on patient transportations and unplanned extubation scenarios. The analysis undertaken was reported as easy to perform as it provided clear visual insight and resulted in several recommendations and positive changes to clinical practice[7,15-17].

THE USE OF THE BOWTIE TO PRESENT THE DATA

A formal classification of the evidence will help to ensure that no items are omitted, and that the information is presented in a structured fashion. However, traditional methods of classification may not be compatible with human memory recall especially in stressful circumstances. It is also believed that images may be recalled better than text or at least might assist memory. It is well known that humans may be unable to recall a fact but the assistance of a trigger, such as a word or an image, will allow the recall of a whole raft of information[7].

Therefore, after formally classifying the information relating to unplanned airway events, mapping these factors into a diagram will assist with recall. A diagram that is ideally suited to this is the Bowtie diagram which has also been proposed as a mapping tool for anaesthetic incident analysis[7]. It has the advantage of containing word triggers as well as being a structured image.

Figure 1. A generic Bowtie diagram.

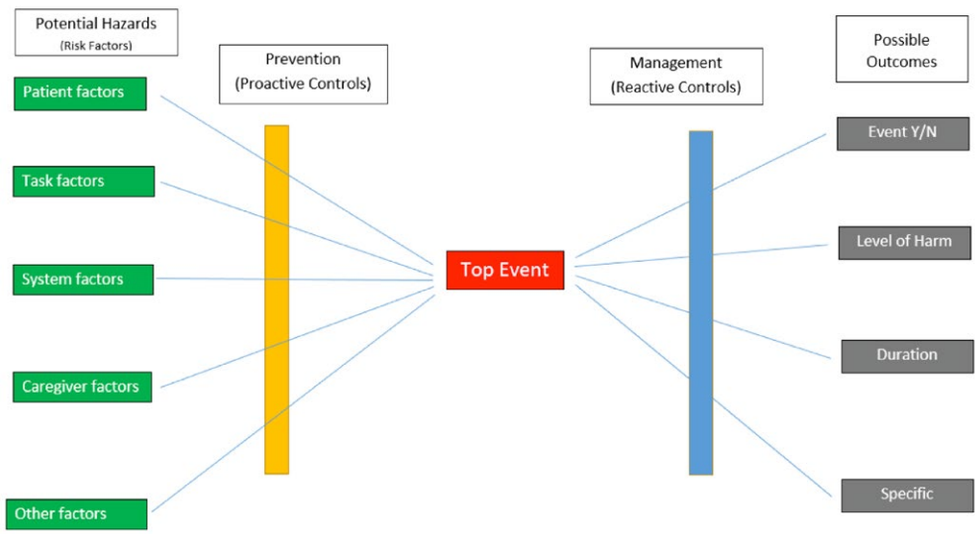


Figure 1 shows a generic Bowtie diagram for medical incidents in general. All the possible causal factors, which are called "hazards" in Bowtie nomenclature are shown on the left-hand side and grouped into one of the five categories shown with a green background. Various methods for prevention will be listed in the yellow section and if possible, barriers devised specific to each hazard. However, in medicine it is often not possible to place a single barrier for each hazard and so the methods for prevention are often listed generically. One method might be, for instance, a checklist in many cases. The "top event" is shown in the middle of the diagram and if this point is reached then methods for management are considered which are shown to the right-hand side in blue. Finally, to the far right several final outcomes are shown with a dark grey background and may vary in the level and the duration of the harm.

AIRWAY FIRE AS AN EXAMPLE FOR SIMPLE BOWTIE MAPPING

Factors involved with airway fires

Fires in the operating theatre are not common but still occur despite apparently adequate precautions to prevent these. A search of the literature revealed that the first report of a fire associated with anaesthesia was during a facial operation in 1850[18,19]. In the latter case, the problem was more to do with the high flammability of ether rather than oxygen. This raises the important question about how fires start, how they are propagated and how they are managed.

In the 19th century the major risk factor was fuel, which was frequently in the form of flammable agents used in anaesthesia. This was largely eliminated in the latter half of the 20th century with the development of non-flammable anaesthetic agents. Recently the major risk factor in anaesthesia has been high levels of oxygen, close to a source of ignition such as a diathermy tip[19,20]. Alcohol containing solutions are also an ongoing risk factor especially with surgical preparation solutions[19].

Mapping the factors into a Bowtie diagram

For a fire to occur there are three basic requirements, which in simple terms are a source of fuel, a source of ignition (heating the fuel to flashpoint) and oxygen (or an oxidant)[18] (see Figure 2). In addition, there may be patient factors, task factors, human factors or other factors that might have contributed to the occurrence of the fire. Preventative measures include separation of the three components required for a fire to occur. In order to extinguish the fire, one or more of the above components must be removed.

Classifying the factors involved with airway fire during anaesthesia:

Risk factors (hazards)

- Fuel
- Oxygen or an oxidising agent
- Source of ignition

Prevention

- Separation of fuel, oxygen and ignition sources

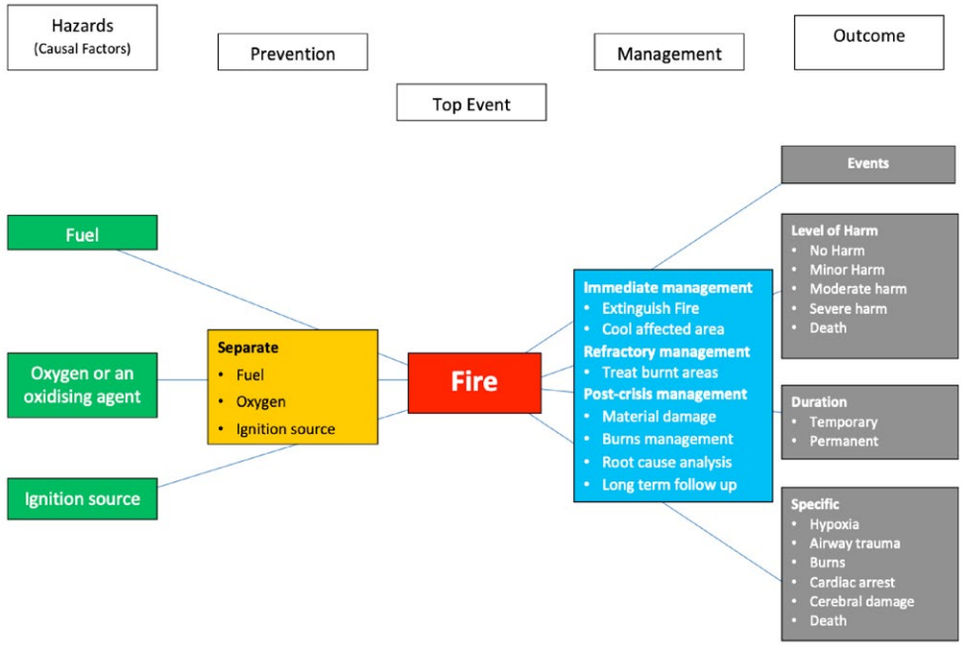
Management

- Put out the fire
- Cool any affected tissues
- Treat any burnt areas
- Long term follow-up

Outcomes

- No harm
- Minor effects
- Temporary harm
- Permanent harm
- Death

Figure 2. A simple Bowtie as an example for “airway fire”.



MAPPING COMPLEX AIRWAY EVENTS

The airway fires example is a simple one to path via a Bowtie diagram. It is possible to use this diagram in a conceptual way to map complex airway events.

Oxygenation and ventilation after induction of anaesthesia are most commonly applied via facemask ventilation, laryngeal mask insertion and ventilation and, or endotracheal intubation. Each of these techniques also serves as a rescue technique, should one or the other method fail.

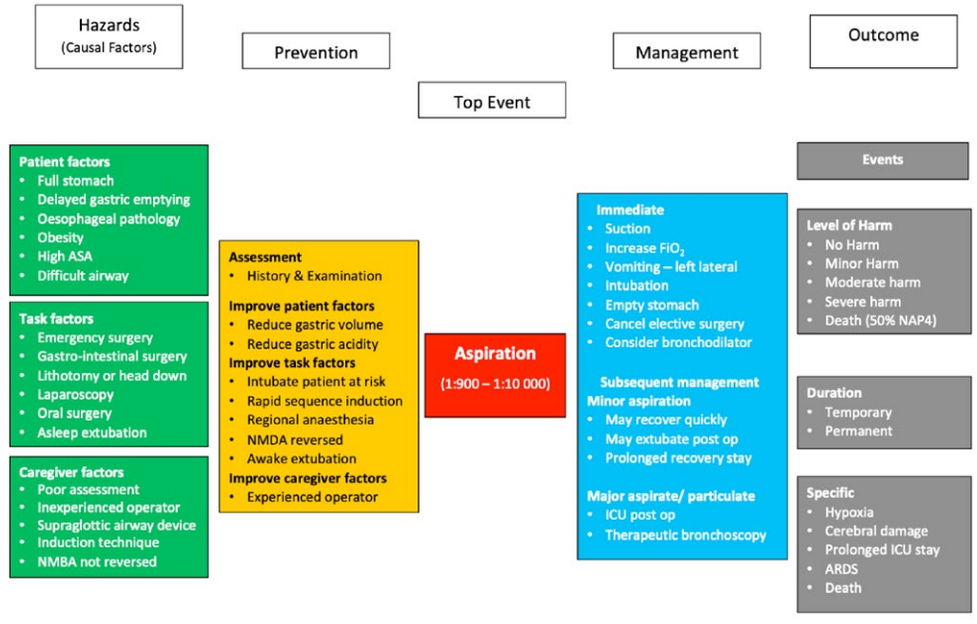
The incidence of difficult facemask ventilation has been described as 0.5-1.5%[21] and the incidence of impossible facemask ventilation as 0.15%[22]. Failed laryngeal mask insertion has been reported as above 1%[23] and the failed intubation occurs in around 1 in 1000 cases[1,24]. The feared “can’t intubate, can’t oxygenate” (CICO) scenario occurs in approximately 1:20,000 anaesthetic procedures[1].

More than 50% of anaesthesia-related deaths were found as a consequence of aspiration in NAP4[1] and 23% of all cases reported to NAP 4 involved aspiration as either the primary or the secondary event. Patients who were not affected by mortality suffered significant morbidity and prolonged ICU stays with aspiration quoted as the commonest cause of brain damage (53% NAP 4)[1].

BOWTIE DIAGRAM FOR ASPIRATION

Pulmonary aspiration has been quoted to affect 1:900 to 1:10,000 anaesthetics, depending on patient population and risk factors[25]. Prevention of aspiration remains a cornerstone of anaesthetic practice. NAP4 provided evidence that aspiration often occurred as a consequence of incomplete patient assessment and failure to modify the anaesthetic technique[1]. The incidence of aspiration under anaesthesia has been shown to be significantly higher in patients with higher ASA requiring emergency surgery[25].

Figure 3. Bowtie aspiration.



Risk factors aspiration (hazards)

The predisposing risk factors for aspiration are many and can be classified in patient factors, task factors, and caregiver factors. Aspiration might occur, not only at induction of anaesthesia, but also during maintenance (NAP4) and during emergence, with up to 20% of aspiration occurring after extubation[3,27]. More than 100 ml residual gastric volume in the stomach is recognised to increase the risk for pulmonary aspiration. Individual risk factors for this to occur vary, but include inadequate fasting times, upper and lower gastrointestinal pathologies, systemic diseases, recent trauma and opioid use. Caution and preventative measures are required in pregnant, very sick and obese patients. Certain surgical techniques and emergency procedures have a higher incidence of regurgitation and aspiration. Inadequate anaesthetic assessment and inexperience are factors that in turn may lead to inadequate planning or choice of a suitable airway device.

Figure 3 shows patient factors[3,27], task factors and caregiver factors.

Prevention and risk reduction strategies

A variety of guidelines has been developed and multiple strategies have been recommended to reduce the risk of aspiration[28]. Adequate preoperative fasting times, nasogastric aspiration and the use of prokinetic medications are techniques used to reduce gastric volume. Preoperative administration of antacids, H2 histamine antagonists or proton pump inhibitors will reduce gastric acidity and therefor might cause less damage to the respiratory system in case of aspiration. Anaesthetic risk factors may be reduced with appropriate intubation and extubation strategies. Neuromuscular monitoring confirming full reversal of the neuromuscular blocking agent in combination with an awake extubation in the lateral position has been recommended as a safe extubation technique for patients at risk[28].

Prevention and risk reduction strategies are also outlined in Figure 3.

Management

If aspiration occurs, then immediate management is directed to reduce further soiling of the lungs and to maintain oxygenation. Subsequent management is directed to supportive treatment and organ support and depends on the severity of the aspiration.

Immediate and subsequent management strategies are also outlined in Figure 3.

Outcome

Aspiration has been described as the single largest cause of death during anaesthesia and was accountable for 26% of all airway events and 50% of all airway deaths in NAP 4[1]. The cause of death was hypoxia in all cases, which often occurred days later in ICU. Half of the surviving patients enjoyed a quick recovery whereas the other half required prolonged ICU stays, prolonged intubation and ventilation and suffered from ARDS.

BOWTIE DIAGRAM FOR FAILED INTUBATION

The incidence of failed intubation has been described as 1 in 1000-2000 cases in the elective general population. In the emergency settings the incidence is higher and has been quoted as 1:250[24,29,30]. Failed or difficult intubation was the primary event in one third of all NAP4 reports[1] and accounted for more than half of tracheal intubation related cases. The majority of these cases happened in the operating theatre, with some progressing to a "can't intubate, can't oxygenate" scenario.

Figure 4 outlines risk factors (hazards) for failed intubation.

Analyses of the Danish database[6], NAP4[1] and the first 4000 incidents reported to AIMS[5-6] have produced important information in regard to risk factors for difficult or failed intubation[1]. ENT, head and neck abnormalities and procedures have been identified as a cohort with a high-risk of failed intubation[1]. A patient who suffered from a failed intubation in the past has been reported as having a 22-fold increase in the likelihood of failing again[6].

It has been observed that 70% of anaesthetists planned and continued with a routine induction, even when a difficult intubation was anticipated[31]. More than 60% of these cases progressed to a "can't intubate, can't oxygenate" situation and outcome was commonly poor.

Procedures performed in remote or unfamiliar areas, where equipment and assistance availability are limited, are at high risk of complications[1].

Patient factors[1,6,24], task factors[1,6,24,31,32], caregiver factors[1,4,5] and system factors[1,6,24,31] are also outlined in Figure 4.

Prevention and risk reduction strategies

Major national airway societies have developed guidelines for the management of the difficult airway based on scientific evidence, audits and expert opinions[33-36]. Emphasis is on prevention of airway incidents, preparation for the unexpected difficult airway, team preparation and equipment availability before induction of any patient[37]. Pre-oxygenation is considered a routine manoeuvre before any induction[33-37]. Regular staff trainings and familiarisation with basic and advanced airway equipment are highly recommended[33-36].

Multiple screening tests for predicting difficult intubation exist and application of these has become routine practice of an anaesthetic assessment[1]. When performed in isolation, the predictive value of these tests has been considered poor[38] but predictability is thought to increase by combining multiple tests and investigations[6,38-45] including innovative techniques like nasendoscopy, virtual endoscopy and ultrasound assessment[46-48].

Appropriate equipment, skilled help and exit plans need to be immediately available before any anaesthetic intervention[33-36]. The aim is to develop a strategy of airway management techniques with the goal to maintain oxygenation and subsequently restore ventilation in the anaesthetised patient.

Prevention and risk reduction strategies for failed intubation are outlined in Figure 4.

Management of failed intubation

Practitioner's performance is influenced by environmental, technical, system and human factors[49,50]. Cognitive performance deteriorates with stress and fixation error has been demonstrated as a common issue in the management of failed intubation causing significant harm to the patient[1,24,33,51,52].

Complex and rigid algorithms may not be cognitively accessible during times of stress. Cognitive aids are increasingly being used in crisis situations[53-56]. They do not compete with existing airway algorithms but are designed to complement and facilitate their implementation in real time[53-56].

The primary goal in a failed intubation situation is to restore and maintain oxygenation without causing further harm to the patient.

Figure 4 outlines management strategies in case of a failed intubation.

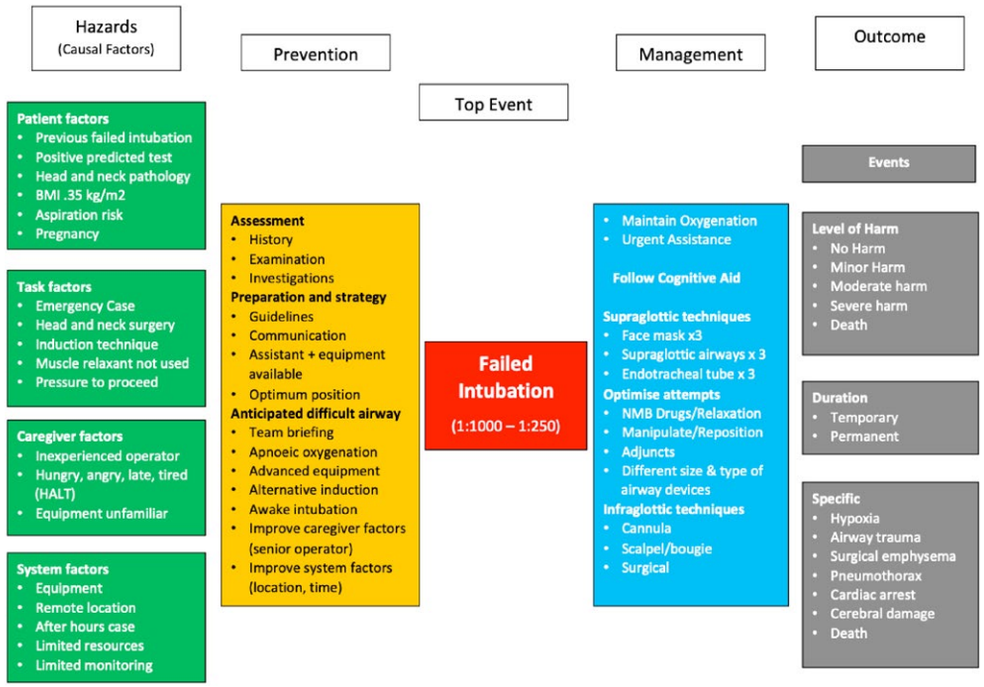
Outcome

Outcomes can be divided into generalised outcomes as per Agency for Healthcare Research and Quality (AHRQ)[57] scale and specific outcomes.

The AHRQ scale is a standardised scale describing the type and severity of the incidence, including the duration of harm. Specific outcomes are varying depending on the type of incidence.

Both scales can be included in the Bowtie diagram (Figures 1-4).

Figure 4. Bowtie failed intubation.



Final Outcome NAP 4[1]

One hundred and thirty-three airway events were reported during anaesthesia in the course of NAP 4. The final outcome was death in 16 of these cases, of which 9 were caused by aspiration. Three patients suffered from permanent hypoxic brain damage, 6 patients made a partial recovery and 106 patients made a full recovery. Two patients passed away due to other causes. One hundred and three patients suffered moderate harm and 5 patients severe harm.

WebAIRS airway data

At the time of writing this article, there were 7205 incidents from 194 sites reported to the web-based anaesthetic incidence reporting system (webAIRS) in Australia and New Zealand. The majority of these events are related to airway and respiratory issues, accounting for more than thirty per cent of all incidents[58].

CONCLUSION

An abundance of data relating to difficult airway management is available. Unfortunately, the data is often not displayed in a format that is easy to follow, practical to use or immediately accessible at the point of care. Most anaesthetists are familiar with current guidelines and recommendations, but it might be difficult to recall the information in an acute crisis.

In its current form, the information is sequential and not necessarily in a logical sequence. In order to easily recall all the information that might be required to assess, prevent and manage an event, it is necessary to group the information into risk factors, principles for prevention, management (should prevention fail), and then the possible outcomes that might result. A Bowtie diagram has the potential to group and summarise the important aspects of airway management and act as a memory jogger. It is also a living document that can be revised as necessary, rather than being set in stone (or paper). It is suitable for display in a web page and could be constructed in such a way as to provide links for more detail if required for each section.

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Flexible bougies, introducers and bronchoscopes – Key adjuvants in the Age of Videolaryngoscopes

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INTRODUCTION

Direct laryngoscopy (DirectLS), which is designed to align the airway for a relatively straight path to endotracheal tube (ETT) placement, will allow many anaesthetists to blithely enjoy an almost perfect tracheal intubation record even if a completely "direct" view of the larynx is not obtained. However, the patient who has a difficult airway can present without warning, producing anxiety-provoking and potentially dangerous outcomes due to the limitations of DirectLS.

Indirect laryngoscopy using a videolaryngoscope (VideoLS), a modified laryngoscope that is fitted with a video camera to provide a view of the larynx, provides significant advantages over DirectLS. These have been well described and include improved laryngeal visualisation for novices[1] and for teaching, reduced number of failed tracheal intubations especially in patients with difficult airways, reduced laryngeal /airway trauma and reduced cervical spine movement[2-4].

There are many VideoLS available. They can be divided into "channelled" or "non-channelled" devices; referring to the ability to preload an endotracheal tube (ETT) within the device. They can also be divided broadly into the Macintosh "style" non-hyperangulated blade devices, or hyperangulated (approximately 60°) blade devices. Commonly used hyperangulated blade devices in Australasia include "GlideScope®", "Karl Storz C-MAC® (D-blade)" and "McGrath™". A more detailed review of types and preferences for use are found in previous issues of *Australasian Anaesthesia*[5,6].

Whereas successful tracheal intubation with experienced anaesthetists is often quicker with DirectLS[7], hyperangulated blade VideoLSs are recognised in teaching hospitals as ideal choices of VideoLS for supervised anaesthesia training in tracheal intubation, allowing inexperienced operators to gain proficiency rapidly compared to DirectLS[8]. The hyperangulated blade VideoLS is also recognised as the best VideoLS design for achieving successful tracheal intubation when a patient with a truly difficult airway is encountered[9,10]. Additionally, hyperangulated blade VideoLSs are being adopted as the tool of first choice for operators in the ICU and the emergency department, where emergent airway scenarios lead to a high incidence of difficulty. While the hyperangulated blade VideoLS is an excellent device for tracheal intubation, it still has not eliminated all problems related to tracheal intubation.

This review will focus on descriptions of emerging techniques relating to the hyperangulated non-channelled blade VideoLS. Specifically, it will address two important aspects related to the hyperangulated blade VideoLS.

1. The important clinical problem of the occurrence of anterior impingement of the ETT upon the tracheal rings (tracheal impingement) in patients where the trachea forms an acute angle with the line of sight (the so-called "anterior larynx")[11]. This is a common, but not sole, cause of the "can see can't intubate" problem when using a hyperangulated blade VideoLS.
2. The evolving role of the hyperangulated blade VideoLS in patients with extremely difficult airways in which an awake bronchoscopic tracheal intubation has traditionally been considered to be the gold standard for safety and efficacy.

In addressing these two issues, this review will outline key adult tracheal intubation studies which have been published in large numbers since the hyperangulated blade VideoLS has attained widespread clinical use. It will not cover all of the extensive retrospective review, manikin study, correspondence opinion, and case report literature in this area as each of these have significant limitations in terms of extrapolating lessons. Especially problematic among the large number of manikin or "bench" studies is a lack of transferability to the difficult or emergent tracheal intubation[12], as well as editorial comment that has questioned the scientific value of these studies and the commercial interests promoting them[13]. Unfortunately, it is extremely difficult to design a prospective study comparing devices or techniques in actual clinical scenarios. This, combined with heterogeneity within and between studies, means that it has been difficult to make recommendations about hyperangulated blade VideoLS, explaining a lack of didactic directives in difficult airway management protocols. Addressing this lack of direction, ANZCA has been proactive in this area with its policy document: *PS56 Guidelines on Equipment to Manage a Difficult Airway During Anaesthesia*[14]. The document dating back to 2012 includes hyperangulated blade VideoLS among a large number of possible devices for the management of the difficult airway. While not dismissing the many other historically successful techniques available, the list of equipment can be bewildering for those without explicit expertise. It is likely that a future version of this document will address a global trend to earlier recourse to the hyperangulated blade VideoLS and acknowledge a heuristic learning process within hospital anaesthetic departments confirming the enormous functionality of these devices.

TRACHEAL IMPINGEMENT: THE PROBLEM AND SUGGESTIONS

The role of stylets

The stylet is a popular device to aid with the passage of the ETT, once the glottis has been viewed. Stylets may be completely rigid, malleable or flexible and are inserted into the ETT to assist guiding the ETT towards the glottis. A rigid stylet has a shape which cannot be altered by bending or shaping. A malleable stylet is able to be pre-formed into a desired shape within an ETT. A flexible stylet has a mechanism enabling flexion of the shaft or the tip of the stylet, controlling the angle at which the tip of the loaded ETT enters the trachea. The firm nature of the stylet not only allows the ETT to be accurately directed, it can be used to displace or elevate supraglottic structures. Unfortunately this may be partly responsible for tracheal intubation induced trauma including palatal damage[15,16] and subglottic injury[16]. All stylets are prone to the problem of the ETT impinging upon the anterior tracheal wall after entering the trachea at an acute angle.

The "GlideRite®" stylet (Verathon, Bothell, WA) (Figure 1a) is a rigid stylet preformed to mimic the curve of the GlideScope® (Verathon, Bothell, WA). There have been studies comparing the GlideRite® with other malleable stylets[17,18]. The stylets used in these studies have various tip to shaft angles; ranging from 60° to 90°[19,20]. "J" and "Z" shaped stylets have also been described in communications[21]. Unfortunately, the particular angle of stylet which demonstrates superiority over another may depend upon the setup of the manikin, the technique of blade insertion, and the previous experience of the operator, a fact confirmed by a comparison review paper elaborating upon the trials[22]. It may well be that each variation of stylet angle may suit a particular operator and a homogeneous group of patients.

PRACTICE POINT: **The GlideRite® stylet is a justifiably popular option when using the GlideScope®. Other stylets are equally useful, with the exact curve dependent upon the hyperangulated blade VideoLS chosen and past experience. Find a stylet variation which suits the patient position and the hyperangulated blade VideoLS insertion style preferred by you.**

A flexible stylet is an innovation which attempts to address the inherent variation of tube insertion angle required to atraumatically enter the glottis, while still maintaining sufficient rigidity to direct the tube when using the hyperangulated blade VideoLS. The Parker Flex-It® directional stylet (Figure 1b) (Parker Medical, Highlands Ranch CO), the Truflex™ Articulating Stylet (Figure 1c) (Teleflex, Netanya Israel) and a surgical instrument: "goldfinger"[23] each provide the ability to flex the ETT to enter an anterior larynx but cannot retroflex if the tube impinges on the tracheal wall (Figure 1d).

There have been several studies evaluating the Flex-It® stylet including two clinical studies. The first study compared a preformed Rusch® malleable stylet (Teleflex Medical, Bannockburn IL) with the Flex-It® flexible

stylet in a group of 80 patients and found the malleable stylet slightly superior in terms of speed and ease of use[24]. Unfortunately, the study methodology, not being a cross-over design, did not eliminate a learning effect that may have affected the result. The second clinical study compared the GlideRite® stylet with the Flex-It® and found the Flex-It® was superior in terms of time and ease of use, additionally consistently reducing symptoms associated with minor trauma[25]. The third, a manikin study, looked at five different simulated situations ranging from normal to difficult. The main differences were found in the simulated pathological airway situations of "swollen tongue" and "swollen pharynx", where the Flex-It® stylet produced a higher rate of successful tracheal intubation[26].

The Truflex™ is a similar design metal articulating stylet with a preshaped curve and the ability to flex up to 60°. A clinical study demonstrated a preference by experienced anaesthetists compared with the malleable Portex® stylet[27].

Another flexible stylet that can be used with a hyperangulated blade VideoLS, the "Rapid Positioning Tracheal intubation Stylet" RPiS™ (Airway Management Enterprises, LLC), has been developed but has only been tested in a pilot study comparing it with the GlideRite® stylet. The advantage of this stylet is that it can flex and retroflex unlike the aforementioned models[28]. It is otherwise rigid apart from the tip and it is designed to protrude beyond the end of the ETT, allowing for a clearer field of vision as the stylet tip enters the glottis. The protruding tip however can be lost to vision as the tube approaches the glottis thus presenting the possibility of trauma.

PRACTICE POINT: **Flexible stylets may become your first choice over a rigid or malleable stylet with potentially an easier entry into the glottis, but can present the same potential problems of traumatic insertion and anterior tracheal wall impingement when using a hyperangulated blade VideoLS.**

Figure 1a. GlideRite® stylet.
Source: Verathon.com

Figure 1b. Flex-It® directional stylet.
Source: Bomimed.com

Figure 1c. TruFlex™ stylet.
Source: Truphatek.com

Figure 1d. TruFlex™ stylet inside an endotracheal tube.
Source: Truphatek.com

Bougies and flexible intubating introducers

A bougie (or intubating introducer/catheter) is a thin, semi-rigid device that is placed in the trachea and used as a guide for the subsequent passage of the ETT, rail-roaded over it. Its smaller diameter and greater manoeuvrability compared with a styletted ETT make it especially useful in patients with a reduced oropharyngeal space. Unfortunately, unlike the plethora of studies looking at stylets, there are fewer comparative studies for bougies. One manikin study with novice emergency trainees, comparing a malleable stylet curved into a J-shape, with bougie curved to 60°, failed to find a significant difference in speed or ease of tracheal intubation in both easy and difficult airway scenarios[29]. Another manikin study with experienced anaesthetists using the hyperangulated VideoLS looking at six different tracheal intubation strategies with bougies and stylets, showed no practical difference in either standard or difficult tracheal intubation setups[30]. This study demonstrates some common methodology problems: with six different tracheal intubation strategies, two different manikin settings, multiple comparisons and an unblinded observer, a meaningful result was unlikely. Another clinical study in routine cases showed a faster tracheal intubation time and less haemodynamic changes with a standard bougie compared with a stylet angled to 60° using a CMAC® D-blade hyperangulated blade VideoLS[31].

With little direction from the literature, trying to make some practical sense of this is difficult. But we can be guided by the same principles evolved from the stylet, particularly in the two clinical scenarios stated at the start of this article: the patient with an acute angle created by the hyperangulated blade VideoLS which aligns the ETT tip perpendicularly with the anterior tracheal wall, creating impingement or trauma, and the patient with deforming pathology creating awkward angles challenging any tracheal intubation strategy.

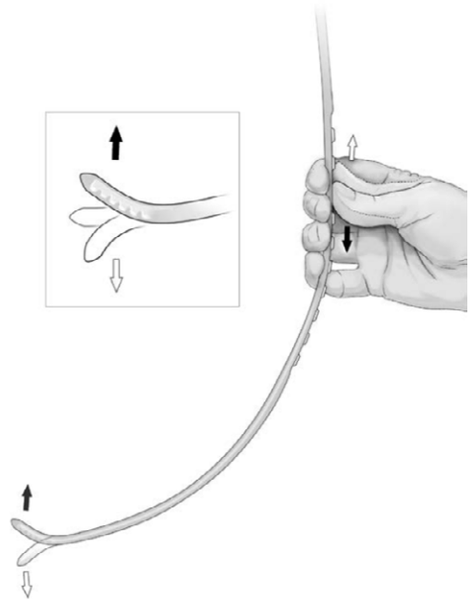
A brief report in 2009 suggests the use of a flexible tipped bronchial blocker to act as a tube introducer, overcoming these angulation and aforementioned space issues[32]. The authors had previously used a fibreoptic bronchoscope in a similar fashion but suggested a simpler option should be developed. Since then several articles have been published describing flexible tipped bougies including two devices conceived and developed by Australian anaesthetists. The "D-Flect®" bougie (Specialist Airway Solutions, Brisbane, Queensland, Australia) is similar to the widely used Frova® intubating introducer (Cook Medical, Bloomington, Indiana, US) in dimensions, yet differs in that the distal tip can be flexed by an assistant pulling upon an internal wire mechanism (Figure 2a). A study with experienced operators and a difficult airway manikin with a fixed hyperangulated blade VideoLS view showed a significant improvement in time and insertion success with the D-Flect® bougie compared with the Frova® intubating introducer[33]. The most recently developed "Flexible tip bougie" (FTB) (Construct Medical, Melbourne, Victoria, Australia) has a fixed preformed curve with a soft silicone tip which can be both flexed and extended via a slide mechanism incorporated into the shaft (Figure 2b). This ability to extend may help overcome the tracheal impingement problem often leading to the "can see but can't intubate" scenario. There has also been a manikin study with the FTB demonstrating superiority in both time to tracheal intubation and ease of tracheal intubation[34]. This study involved anaesthesia, intensive care and emergency medicine fellows intubating a difficult airway manikin using a C-MAC® (D-Blade) and importantly included some observational data regarding ease of use. Important to note is that neither the "D-Flect®" nor the FTB have an internal channel for supplementary oxygenation, unlike the Frova®, and the FTB cannot be bent into a more acute curve if desired. Nasal tracheal intubation using a "gum elastic bougie first" and GlideScope® technique has been described and found to be less traumatic, with less need to use Magill's intubating forceps, than a "reinforced ETT first" nasal technique[35]. It should be noted that if the FTB is used with this technique, the slide mechanism may be partly or wholly within the nostril as the tip passes the glottis making further extension of the tip impossible.

The flexible bronchoscope has a similar flexible tip utility with the additional benefits of vision beyond the vocal cords and a channel for insufflation or suction. Descriptions of successful use of the flexible bronchoscope as a tube introducer in combination with hyperangulated blade VideoLS abound[36-40] but invariably involve a second anaesthetist, which is undoubtedly the major drawback and definitely a deterrent to everyday use. Additionally, it is more costly to use and often harder to access and set up quickly if required. Most recently a well conducted clinical trial compared GlideScope® tracheal intubation with a malleable stylet against GlideScope® tracheal intubation with a flexible bronchoscope acting as a flexible tipped tube introducer (without bronchoscopic vision)[41]. One hundred and sixty patients, predicted to have a difficult tracheal intubation by strict criteria, were randomised to either method, prior to induction of relaxant general anaesthetic. The findings were conclusive: improved first-attempt tracheal intubation success, decreased airway injury and decreased time to tracheal intubation when the bronchoscope was used like a flexible bougie. It is an impressive study despite the well-recognised problem of a discrepancy between predicted and actual difficult tracheal intubation, and the failure to specify the exact curvature of the malleable stylet in that group. It is likely that the authors were unaware of the FTB at the time of publication as they suggest encouraging the design of a flexible guide without optical fibres as a cheaper option with a similar utility.

PRACTICE TIP: Consider the use of a flexible tip bougie (or bronchoscope) when there is limited oropharyngeal space (making the bulk of a styletted ETT problematic) or there are multiple angles to be negotiated, for example, pharyngeal or base of tongue tumours. A flexible tip bougie is helpful to eliminate the anterior tracheal wall impingement problem in the "can see can't intubate scenario".

Figure 2a. D-Flect® bougie, seen here with the C-MAC® (D-blade), with a distal tip can be flexed by an assistant pulling upon an internal wire mechanism.
Courtesy of Dr Anton Booth

Figure 2b. Flexible-tipped bougie.
Source: © Beth Croce, bioperspective.com



Endotracheal tube types: Does correct ETT choice get the job done?

Assuming correct placement of a bougie or a flexible bronchoscope, the final challenge in VideoLS tracheal intubation is to avoid "tube hang-up" at the glottis. It is likely, but not proven, that this is more common with the hyperangulated blade VideoLS than the direct laryngoscopy technique or the non-hyperangulated blade VideoLS. The Seldinger technique over a bronchoscope or introducer, has been associated with complications and challenges, particularly anatomical obstructions and tissue trauma. At the supraglottic level the obstruction is most commonly the arytenoid cartilages[42], whereas at the subglottis level, the obstruction is usually the anterior tracheal wall[43].

Modifications to the ETT have been made over the years to overcome these obstructions. An example is the Parker Flex-Tip® (PFT) tracheal tube (Parker Medical, Eaglewood, Colorado, US) (Figure 3a). The PFT tube is characterised by a flexible, hemispherical, posterior-facing bevel with a soft curved tip. This tip closely wraps around introducers more than other tubes, decreasing the chance of anatomical obstruction. The PFT tube avoids the "step-up" that exists between the introducer device and ETT's outer diameter, which can lead to ETT impingement at the level of the laryngeal inlet or vocal cords. The PFT tube has been associated with decreased time to tracheal intubation, and has been favourably compared with standard ETTs in failed tracheal intubation situations[44]. Similarly designed ETTs that wrap closely around an introducer are the LMA® Fastrach™ ETT (Uxon, UK) (Figure 3b) and the BlockBuster® tube (Tuo Ren Medical Instrument Co Ltd, China) (Figure 3c). Studies using the LMA Fastrach® ETT for bronchoscopic tracheal intubation found that the incidence of resistance at the laryngeal inlet was reduced by about 40%[45,46]. The BlockBuster® ETT is a straight reinforced tube with a long flexible tip, and a posterior facing bevel. A study comparing this to the standard ETT and the Mallinckrodt reinforced tube (Covidien, Ireland) demonstrated shorter tracheal intubation time and reduced subglottic mucosal injury[16].

Another variant is the Endotrol® tracheal tube (Medtronics, Minnesota, US) (Figure 3d). It is a single-lumen ETT, and enables the operator to have directional tip control by pulling the ring loop. This feature allows it to negotiate the glottis without the use of an introducer device. In a study comparing the use of Endotrol® ETT with a standard ETT preloaded with a non-malleable stylet, the authors found that the Endotrol® tube was associated with longer tracheal intubation times and a subjective increase in difficulty of use[47].

PRACTICE TIP: **When using a bougie or a bronchoscope with a hyperangulated blade VideoLS, consider a tube where the tip lies in close contact to avoid hang-up. If extreme difficulty is predicted or encountered make this tube selection a priority, either downsizing or choosing a "rounded end" variety. This is more important than any intrinsic flexion features of the tube itself.**

Figure 3a. Parker Flex-Tip® endotracheal tube.
Source: Parkermedical.com

Figure 3b. LMA Fastrach®.
Source: lmaco.com

Figure 3c. BlockBuster® endotracheal tube.
Source: Touren.com

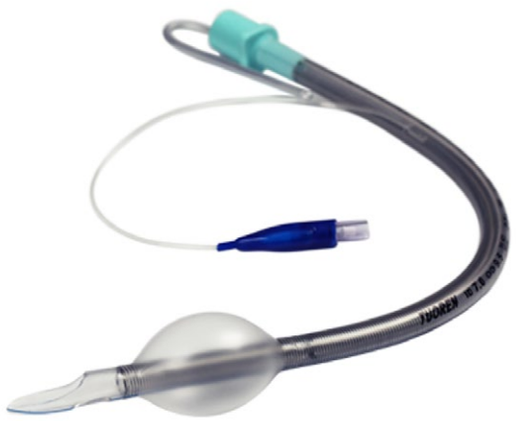
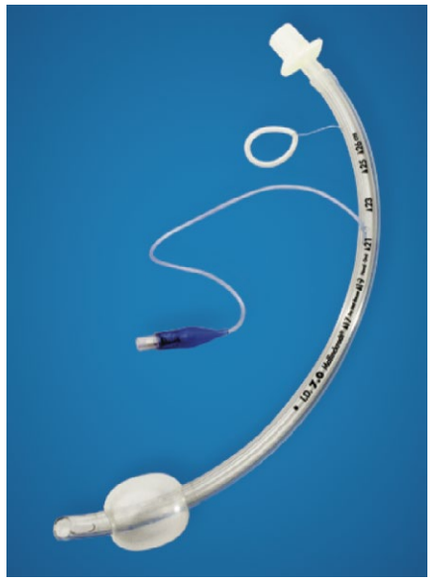


Figure 3d. Endotrol® endotracheal tub.
Source: Medtronic.com



Physical manoeuvres: fine tuning the approach

Surprisingly, the head position may not be as critical when using the hyperangulated blade VideoLS compared with DirectLS. A prospective trial by Mendonca et al found no difference between sniffing and neutral head positioning[48]. A previous multivariate regression analysis of prospective data from a large 1100 patient study did find that a more neutral head position led to fewer difficult tracheal intubations. However, the study was not designed to test this outcome and the head position was not randomised[49].

Reverse camber loading of the ETT upon a stylet refers to inserting the stylet so that the curve is opposite that to the ETT curve. When the stylet is held at the glottis, the ETT will theoretically feed off the stylet, down the trachea. A clinical study comparing several techniques, in 200 patients with a low risk of a difficult airway, showed that reverse camber techniques, when using a hyperangulated blade VideoLS, did not improve time to tracheal intubation[19]. A single case report suggested that a sharp rotation of the ETT preloaded with an angulated stylet may align the ETT tip with the trachea when the passage is difficult due to an acute angle at the glottis[50]. This idea has not been followed up with any prospective studies, perhaps due to the evolution of flexible devices and concerns over trauma to the larynx.

Several authors have suggested that obtaining the "best view" may not correlate with ease of tracheal intubation. Most elegant of these explanations comes from Sorbello and Hodzovic who suggest that a shallower insertion of the blade into the oropharynx; so that the tip of the hyperangulated blade VideoLS reaches the base of tongue, instead of the vallecula, may lead to a better angle for ETT passage[51]. Other manoeuvres are aimed to solve the reduced working space within the oropharynx, especially in those patients with reduced mouth opening. One author suggests inserting the tube prior to the hyperangulated blade VideoLS[52] and another suggests inserting the hyperangulated blade VideoLS much further to the left side than usual, in cases where access is limited[53].

The use of these tricks may be employed when, despite optimum conditions, tracheal intubation fails. Second and subsequent attempts at tracheal intubation should include modification of several factors which existed during the first unsuccessful attempt.

PRACTICE TIP: **Practice using the hyperangulated blade VideoLS regularly, even if not required. The technique varies considerably from DirectLS and familiarity will make emergent use easier if needed. Regular use of the hyperangulated blade VideoLS guarantees appropriate levels of experience with "tricks".**

THE ROLE OF THE HYPERANGULATED BLADE VIDEOLS IN PATIENTS WITH EXTREMELY DIFFICULT AIRWAYS

Airway challenges including extremes of anatomy, tumours, radiotherapy and oedema continue to feature in morbidity and mortality data reports. The DirectLS and the awake bronchoscope remain excellent stand-alone techniques for tracheal intubations in patients whose airways range from uncomplicated to challenging. However, it is the area of difficult tracheal intubation where a hyperangulated blade VideoLS in combination with innovative thinking will probably dominate. Multiple references show the benefits of utilising the flexibility of a videobrochoscope to navigate the curves associated with a difficult tracheal intubation, while simultaneously having the more proximal view provided by the hyperangulated blade VideoLS[37,40,54]. A case report featuring the FTB being used with a hyperangulated blade VideoLS[55], even highlights the technique of using the hyperangulated blade VideoLS for awake airway assessment, prior to proceeding with relaxant general anaesthesia. Further to this, with adequate topicalisation, experience is accumulating with these techniques in awake patients, thus adding an even greater margin of safety. This evolving area of interest is well covered in a previous edition of *Australasian Anaesthesia*[56]. Even with the "gold standard" awake bronchoscopic tracheal intubation, the addition of the hyperangulated blade VideoLS offers several advantages compared with the bronchoscope alone. It can temporarily restore space, improving ventilation and creating clearer vision with the ensuing bronchoscope[57]. It can allow suctioning of blood and secretions under direct vision and allow direct observation of the glottis as the bronchoscope passes the vocal cords to be followed by the railroaded ETT. Some have attempted to compare the bronchoscope and the hyperangulated blade VideoLS head to head. The authors consider it best to assess each clinical case on its merits and have them both available to be used separately or together[58,59].

PRACTICE TIP: **An airway emergency is not the best time to try a new technique; explore the growing utility of the hyperangulated blade VideoLS in combination with a bronchoscope or flexible bougie in controlled circumstances. In a crisis enlist help early from a colleague. Two anaesthetist techniques are proven to be advantageous and so too is having the video screen visible to all involved.**

CONCLUSION

The hyperangulated blade VideoLS allows an indirect approach to the larynx; we now can look around corners, allowing a clear view of the larynx in situations where this was impossible with DirectLS. This major advance has not been matched, with some notable exceptions, by advances with our primary adjuncts; stylets, bougies and introducers. Nor, perhaps more importantly, by alterations of our techniques. This review has highlighted techniques that can be used to overcome the clinical problem of tracheal impingement that can occur with the hyperangulated blade videoLS, as well as the important emerging role that the hyperangulated blade videoLS may play in the management of patients with extremely difficult airways.

It may be deduced from the evidence given that a hyperangulated blade VideoLS used with a flexible bougie, introducer or bronchoscope may provide the final common pathway to successful oral tracheal intubation in nearly all patients. It is however still too early to mandate this in difficult airway algorithms. The hyperangulated blade VideoLS is an essential tool to improve tracheal intubation success in a variety of difficult situations. To realise the advantages of this equipment, the anaesthetist must practice with it, with regular use being reasonable initially to gain familiarity. Only then will the full scope of this review's recommendations for stylets, bougies, introducers and adjuvant techniques become immediately apparent.

Further reading

Previous reviews of this subject have been found in the anaesthesia, emergency medicine and nursing literature[1,22,60] and some elements which have previously been touched upon will be reiterated. We also acknowledge previous VideoLS reviews in past editions of *Australasian Anaesthesia* which have made mention of some of these reports[5,6,56].

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Breathing/ Ventilation

Hyperbaric medicine
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Hyperbaric medicine

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INTRODUCTION

Hyperbaric medicine dates back to 1662, when British physician and clergyman Nathaniel Henshaw, theorising that acute conditions would respond to elevated atmospheric pressures, and chronic conditions would respond to reduced pressures, attempted to use alterations in atmospheric pressure to achieve therapeutic outcomes[1]. Henshaw constructed a chamber (a sealed room in this case) which was manually compressed and decompressed with a pair of large organ bellows[2]. It is unlikely that it reached pressures of any clinical significance. At this time air had not been broken down into its constituents; compressed air was used without the addition of oxygen.

It wasn't until the industrial revolution, in the 1800s, that pressure-related diseases were first noticed. In 1839 a French mining engineer, M Tigres, designed an apparatus to use compressed air to push back underground water from encroaching in coal mining operations, which allowed dry excavation[3]. This pneumatic caisson was first put to the test in 1841, at Challones, and was deemed a success. A short note from Tigres at the time reported that two workmen who had spent seven hours in compressed air then suffered joint pains (one in the left arm, the other in the left shoulder and knees) approximately half an hour after exiting the apparatus[4].

Caissons were subsequently used in bridge building, to build underwater piers and abutments to anchor bridges, and workers on these were exposed to pressures as high as 3.7 atmospheres. In 1859 in the UK, one of the early caissons was used to build a bridge at Saltash, and all 25 workers suffered DCS; two with paraplegia, one with hemiplegia, and one coma.

In the USA, the Eads Bridge was completed in 1874 to span the Mississippi River, and was one of the next to utilise a caisson, although this had not been the plan from the outset. Part way through construction, on a trip to Europe, James Eads, a talented layman who had designed the bridge, witnessed caisson use and determined it would be the best way to construct the mid river piers and east abutment. Caissons were then built and were ready for use by October 1869. This was a significantly more ambitious undertaking than the European bridges built with caissons prior to this time as the caissons were larger, the river beds deeper, and the rivers more treacherous. Problems soon arose. The first men were sent to hospital in February 1870 after working at 23 metres. An early publication reported that the first effect of pressure on men was an "occasional muscular paralysis" of the lower limbs, rarely accompanied by pain, which "usually passed in a day or two"[5]. On March 19 1870, however, a worker collapsed dead after a two-hour shift. Another man died the same day. Three days later, 20 "bridge cases" were sent to the hospital; five of these died. A physician by the name of Jaminet was employed in late March 1870, following 11 deaths, and was tasked with interrupting the epidemic. In total there were 119 severe cases, and 14 deaths from decompression sickness (DCS) among workers on the Eads Bridge[6], which was finally complete in 1874.

The construction of the Brooklyn Bridge began in May 1870, and was completed in 1883. Lessons had been learned from the tragedies of the Eads Bridge project. The use of caissons had been planned from the outset. An onsite physician (Andrew Smith) was employed from the start. Jaminet and Smith (who coined the term "Caisson Disease") attempted to control rapid decompression, obtained standard decompression schedules, negotiated for rest rooms and elevators to limit excessive post-exposure exertion. They reduced workers' exposure by shortening shifts. They identified high-risk workers and excluded them from compressed air work.

On construction of the Brooklyn Bridge bedrock was reached at approximately 23 meters beneath the surface. Two men died after working at 24 meters; one immediately after leaving the caisson, the other was found unwell in the lock and died hours later. A third fatality occurred in a man who had worked at 25 metres who felt unwell leaving the caisson and died when he reached the entrance of his boarding house. Work was discontinued that day, and the decision was made to build it on a spit of sand rather than persisting with the dig into bedrock[7]. The total number of cases of DCS among workers on the Brooklyn Bridge was 110, with only the three deaths.

Later, incidents of decompression sickness began to emerge from the diving world, and finally, the aviation world[8].

In an article in 1879, French Surgeon Fontaine was the first to describe adjunctive uses of hyperbaric oxygen therapy. He built a mobile, operating room which could be pressured, where he demonstrated that pressurised patients were not as cyanotic after the use of nitrous oxide for induction of anaesthesia as compared to those anaesthetised at atmospheric pressure[9].

In 1908, the issue of "safe decompression" was solved by Haldane and published in the *Journal of Hygiene*. He also suggested at that time that hyperbaric oxygen treatment (HBOT) might be useful in the treatment of "the bends"[10].

In the post-WW1 period, the main area of hyperbaric medicine interest was in diving and diving related areas. However, a number of somewhat questionable practitioners spruced its uses for a range of maladies.

In 1928 Professor of Anaesthesia, Dr Orville Cunningham, erected the "Steel Ball Hospital", a compressed air, five-storey, 20-metre diameter hyperbaric chamber which could reach three atmospheres. He treated patients with a wide variety of illnesses. His theory was that a cryptic anaerobic organism caused multiple human diseases. He was censored by the American Medical Association in 1930 for lack of scientific evidence of benefit, and his hospital was subsequently deconstructed for scrap metal during World War II[11]. In Amsterdam in the 1950s, Dutch surgeon and engineer Ite Boerema was looking for a way to prolong time of circulatory arrest for cardiac surgery. He used porcine studies to determine that life could be sustained with a haemoglobin of 0.4% of normal, in animals breathing oxygen, pressurised to three atmospheres; levels that were not compatible with life in normobaric conditions. In essence he determined that oxygen supply is possible without blood cells. Subsequently there was a rapid increase in clinical and experimental studies, and many chambers were built around the world, in which cardiac surgery was performed.

In 1962 the Harvard School of Public Health donated a hyperbaric chamber to Boston Children's Hospital, where a new approach of paediatric heart surgery was established. More than 120 infants with congenital heart defects (who were too small to be put on an oxygenator for surgery) were operated on in the chamber. Cardiac surgery was performed in the chamber until 1974, when innovations such as heart-lung bypass made it safe to operate on infants in normal operating rooms.

HBOT has been used for many years, for a range of purposes, including many purposes for which the scientific foundations were weak. In 1967 The Undersea and Hyperbaric Medicine Society (UHMS) was founded to promote sharing of data and research between dive medicine communities, and later came to include the clinical practice of Hyperbaric Medicine. The European Underwater and Baromedical Society (EUBS) was founded in 1971, as was the South Pacific Underwater Medicine Society (SPUMS) in Australia, to facilitate the study of and provide information on all aspects of underwater and hyperbaric medicine. In 1976 the UHMS developed a committee to oversee the development of an evidence-guided list of indications for the use of HBOT, and is also one of the primary sources of scientific information for diving and hyperbaric medicine physiology worldwide.

Medicare funding for HBOT became available in 1984 in Australia, and has been guided by The Medical Service Advisory Committee (MSAC) since 1998. Medicare has a list of indications for HBOT, approved for funding, which are supported by evidence of their safety, clinical effectiveness and cost-effectiveness.

Accredited training in hyperbaric medicine is offered in many of the hyperbaric units around Australia. SPUMS offers the Diploma in Diving and Hyperbaric Medicine (DipDHM) and since 2017 ANZCA has offered the ANZCA Diploma of Advanced Diving and Hyperbaric Medicine (Dip Adv DHM). The training component of the DHM diploma may be started prior to completion of specialist qualification (FANZCA, FACEM or FCICM), but will only be awarded after completion.

THE PRESENT

Hyperbaric chambers

There are two main types of hyperbaric chambers. A multi-place unit is a larger chamber, capable of accommodating multiple patients at one time, as well as an inside-nurse or attendant (see Figures 1 and 2). During pressurisation patients typically wear a soft silicone neck seal (or a chest seal for example in tracheostomy patients), and once the chamber has reached the predetermined pressure a clear plastic hood is connected, which has in and out-flow tubing to deliver 100% oxygen and remove expired gases. The patient breathes 100% oxygen while at pressure, except during short intervals, called air-breaks, in which the oxygen hood is removed. Air breaks are given to reduce the likelihood of oxygen toxicity (and to allow time for the patient to use the bathroom/stretch their legs). At times a mask may be used to deliver oxygen to the patient instead of a hood. With appropriate hyperbaric-rated equipment, it is also possible to treat ventilated critically ill patients (such as those with necrotising soft tissue infections).

A monoplace unit is a small chamber, designed for a single patient only. The technician remains outside of the chamber. The entire pressurised chamber is flushed with oxygen, and with air for air-breaks. Alternatively, a mask set up can also be used to deliver air or oxygen to the patient in the monoplace, in which case the chamber itself is only pressurised with air. An example of a treatment table used at our institution is shown below.

Table 1. A typical treatment profile used at The Alfred, Melbourne.

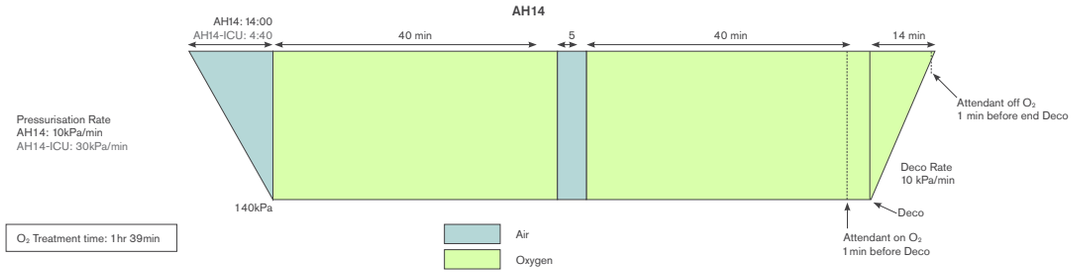

Figure 1. Photograph of a rectangular multiplace hyperbaric chamber (background) and control panel (foreground). Supplied by Fink Engineering.

Figure 2. Photograph of the inside of a rectangular multiplace hyperbaric chamber showing the fire deluge system, communications apparatus, internal surveillance, entertainment, medical lock, gas supply ports, view port, environmental control systems. Supplied by Fink Engineering.

A. The Physics of Hyperbaric Oxygen

There are a variety of ways to describe pressure. Atmospheric pressure, as recorded at sea level, is the downward pressure exerted by the weight of the atmosphere above. This is referred to as 1 atmosphere (ATM). This is equivalent to a column of 33 feet (fsw) or 10 metres (msw) of sea water, or 760 millimeters of mercury (mmHg). It is also equivalent to 1.47 psi, 1.01 bar, or 101.3 kilopascal (kPA). Of these, kilopascal is arguably the most frequently used unit in hyperbaric practice.

Hyperbaric Oxygen Treatment (HBOT) is the delivery of oxygen at pressures greater than one atmosphere absolute. Typical, frequently used treatment pressures range from 100 to 180kPA dependent on indication and table used. This pressure refers to the pressure within the chamber, in addition to atmospheric pressure, that is, 2-2.8 ATA absolute. With reference to diving, 100 kPA would be the equivalent of diving to approximately 10 metres of sea water. The actual pressure the diver, or patient, is exposed to at 100kPA is 2 ATA; 1 ATA exerted by the atmosphere above sea level, and 1 ATA exerted by the 10 metres of sea water, or 100kPA of compressed air.

The mechanics of hyperbaric oxygen are based on several basic physics principals.

Henry's Law states that "the amount of gas dissolved in a given type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid". Increased pressure in the chamber therefore causes more oxygen to be dissolved into the plasma than would be seen at atmospheric pressure. In a person breathing air at atmospheric pressure the arterial oxygen tension is approximately 100mmHg, and that of venous blood is 55mmHg. By contrast, when breathing 100% O_2 at three atmospheres, arterial oxygen tension is approximately 2000mmHg, and venous oxygen tension is approximately 500mmHg. This is sufficient oxygenation to support tissue function without a contribution from haemoglobin.

Boyle's Law states that as pressure increases, the volume of a bubble/airspace decreases. This is particularly relevant to treatment of decompression illness (caused by nitrogen bubbles), and CAGE (cerebral arterial gas emboli). It is also the crux of a relatively common complication of hyperbaric oxygen therapy; middle ear barotrauma, which occurs when the middle ear is unable to be adequately ventilated during pressurisation, resulting in a reduction of volume of the air space, which can cause stretching and tearing of the structural elements of the tympanic membrane[12].

Boyle's Law:

p1v1 = p2v2

Charles' Law explains the increase of temperature within the chamber during pressurisation and decrease during decompression. Typically, hyperbaric chambers now have air temperature control to control for these changes.

Charles' Law:

[p1v1]/T1 = [p2v2]/T2

B. Physiologic effects of Hyperbaric Oxygen Treatment:

Increased oxygen delivery plays a major role in the treatment of decompression injury, arterial gas emboli, wound healing, acute crush injury, ischaemic grafts and flaps, arterial occlusions and in severe blood loss anaemia. There is much overlap of the mechanisms within the following headings.

Wound healing

HBOT can enhance wound healing, and prevent amputations, when used as an adjunct therapy in certain types of non-healing wounds[13].

HBOT provides increased access of oxygen via plasma to damaged tissue to restore hypoxia within the wound. Anti-infective effects and anti-inflammatory effects (which will be discussed in separate sections below) contribute, as well as stimulation of angiogenesis, vasculogenesis and mobilisation of stem cells. These latter effects are triggered by HBOT via mechanisms both within the wound itself, and via bone marrow mediated mechanisms:

a. synthesis of growth factors *within the wound itself* enhance angiogenesis and increase vasculogenesis by improving the recruitment and function of endothelial progenitor cells (EPCs). These growth factors include:
   i. vascular endothelial growth factor (VEGF)-A which is synthesised by macrophages and is stimulated by oxidants and by NO (which itself has been shown to be elevated by HBOT). VEGF-A is increased by HBOT in experimental wounds[14,15].
   ii. other factors including basic fibroblast growth factor, transforming growth factor b1, angiopoietin-2 and platelet-derived growth factor, which have also been shown to be increased by HBOT.

b. mobilisation of *bone marrow* EPCs which differentiate into vascular channels by a NO-dependent mechanism. This is supported by a study by Thom et al involving patients who received 20 hyperbaric treatments for osteoradionecrosis (ORN) prophylaxis and were found to have a fivefold increase in circulating endothelial progenitor cells[16].

Augmentation of free radical synthesis by HBOT is likely responsible for both these processes.

In summary, HBOT enhances the mobilisation of endothelial progenitor cells (EPCs) from bone marrow, which exhibit better growth potential, and it enhances recruitment of progenitor cells to ischaemic and diabetic wounds, which then heal faster[17].

Hyperbaric oxygen-induced angiogenesis and fibroplasia also promotes healing in patients with delayed radiation injury, which is useful as radiation damaged tissue does not spontaneously revascularise due to the unique wounding pattern.

Reduced volume of gas bubbles

Decompression illness occurs as the result of dissolved nitrogen coming out of solution and forming bubbles in the diver's blood. When diving (that is, at increased ambient pressure), more nitrogen is absorbed than at atmospheric pressure. On ascent, this nitrogen must come out of solution. If ascent is too rapid, if decompression is omitted, or when insufficient off-gassing of nitrogen occurs for another reason, then it comes out of solution and forms bubbles. These bubbles can affect joints, skin, spinal cord, lymphatics, brain, inner ear, and other areas.

Arterial gas embolism (AGE) is a potentially catastrophic event which occurs when gas bubbles either enter into or form within the arterial vasculature and occlude blood flow. They are classically the result of either a rapid ascent from diving or of inadvertent injection of air into the vascular system during medical procedures. A rapid ascent from diving, particularly without expiration of the expanding gas in the lungs, can lead to overexpansion of the lung and pulmonary barotrauma. If there is rupture of the pulmonary vascular mucosa, gas can directly enter the pulmonary veins. Gas entrained into or formed within the venous system may also cause AGE. If the pressure in the right atrium exceeds the pressure in the left atrium, and a patent foramen ovale is present, then right-to-left flow occurs, and with it, shunting of gas bubbles. Approximately 30% of the population

have a patent foramen ovale. Venous bubbles may also overwhelm the mechanisms in the lungs that normally prevent arterial gas emboli[18,19]. Animal studies suggest that either a large bolus of gas (20mL or more) or small continuous amounts (11mL/min) introduced into the venous system may generate intra-arterial bubbles[20].

Iatrogenic AGE can occur during a range of procedures, across a range of medical specialties. Air may enter an extracorporeal-bypass circuit during cardiac surgery, or be incompletely removed from the heart after cardioplegic arrest. It may enter the cerebral circulation, particularly in upright neurosurgical procedures. It can enter via ECMO or dialysis circuits, or via intravascular catheters. AGE can occur as the result of caesarian section, following gas insufflation during endoscopic and laparoscopic surgery, and during arthroscopy, arthroplasties, and spine surgery in prone patients. There are many other documented cases of air emboli across a wide range of specialties[21].

HBOT directly reduces the size of these bubbles by raising the ambient pressure, and further shrinks the bubble size by creating an enormous diffusion gradient for oxygen into and nitrogen out of the bubble. The improvements in oxygen-carrying capacity of plasma and in the delivery of oxygen to tissues offsets the embolic insult to the microvasculature. HBOT also reduces the post-injury inflammation commonly seen post air emboli.

Peripheral vasoconstriction occurs as a result of decreased nitric oxide (which is effectively scavenged by reactive oxygen species produced during hyperbaric hyperoxia) and this results in a reduction of blood flow, without compromising oxygen supply in this context. This allows capillaries to absorb extra fluid, leading to decreased oedema, which assists further by reducing the diffusion distances of oxygen to cells.

This effect is useful in the treatment of crush injury, compartment syndrome, thermal burns and threatened flaps and grafts.

Osmosis: Oxygen acts as an osmotic agent in its own right. Hypoxia results in cellular Na/K pump failure with a subsequent loss of intracellular fluid into third spaces. If even low levels of oxygen can be delivered then this can be prevented, stopping the worsening of oedema. The reduction in oedema and subsequent reduction in tissue pressure, allows the re-establishment of venous flow, thus breaking the triad.

Modulation of ischaemia-reperfusion injury with HBOT occurs by decreased production and increased degradation of reactive oxygen species.

HBOT decreases pro-oxidant enzyme expression. Hypoxia-inducible factor-1 alpha (HIF-1 alpha), p53 and caspase-3 mediated apoptosis are down-regulated. A reduced inflammatory response has been demonstrated by VEGF, COX2 and neutrophil counts in studies of ischaemic flaps in HBOT; that is, HBOT does not exacerbate ROS-mediated tissue injury.

Neutrophil-endothelial interactions are transiently inhibited (while in the absence of ischaemia there is no observable effect on this interaction), and lipid peroxidation is reduced[22]. Animal studies have shown that a decreased neutrophil adherence to ischaemic venules is observed with elevated oxygen pressures (2.5 ATA).

HBOT increases antioxidant enzyme expression. Scavengers are produced to destroy oxygen radicals[20], reducing reperfusion injury.

These effects are useful in the treatment of ischaemic wounds, CO poisoning, crush injury and compartment syndrome.

Studies suggest that the maximal beneficial response to HBOT occurs during the ischaemic phase and may be time-dependent.

Infection control: *Antimicrobial effects* of HBOT are useful in necrotising soft tissue infections, gas gangrene, osteomyelitis, life or limb threatening infections. HBOT is directly toxic to anaerobic bacteria, but also exerts an antibiotic effect on aerobic bacteria, by raising O2 tension in tissue, which increases the ability of leucocytes to kill bacteria. It has bacteriostatic and bactericidal effects on Clostridia, Escherichia coli and Pseudomonas[23].

Additionally, HBOT has a synergistic effect with at least some antibiotics, including linezolid, vancomycin, *teicoplanin*, ciprofloxacin and imipenem, as well as aminoglycosides, cephalosporins, sulfonamides, and amphotericin[13,24-27].

Clostridial *alpha*-toxin production is inhibited by HBOT in gas gangrene[28].

a. Current UHMS indications[29]
   - Air or gas embolism
   - Arterial insufficiencies
     – Central retinal artery occlusion
     – Enhancement of healing in selected problem wounds

   - Carbon monoxide poisoning
   - Clostridial myonecrosis (gas gangrene)
   - Compromised grafts and flaps
   - Acute traumatic ischaemia
   - Decompression sickness
   - Delayed radiation injuries (soft tissue and bony necrosis)
   - Sudden sensorineural hearing loss
   - Intracranial abscess
   - Necrotising soft tissue infections
   - Refractory osteomyelitis
   - Severe anaemia
   - Thermal burns

b. Absolute contraindications
   i. Untreated pneumothorax: intrapleural air may double or triple in volume on decompression as normal atmospheric pressure is approached.
   ii. Premature infants: due to susceptibility to retrolental fibroplasia, resulting in blindness
   iii. Bleomycin: a chemotherapy agent used to treat a variety of tumours, which has been associated with irreversible restrictive lung disease. Oxygen breathing, even several years after the use of bleomycin, can cause severe interstitial pneumonitis leading to pulmonary fibrosis, and severe lung damage can occur.
   iv. Disulfiram (Antabuse): blocks production of superoxide dismutase, a protective antioxidant which is the body's major protection against oxygen toxicity
   v. Cisplatin: HBOT may increase the cytotoxic effect of the drug in tissues, ultimately impeding wound healing

c. Relative contraindications
   i. Pregnancy
   ii. Asthma
   iii. Thoracic surgery
   iv. Emphysema with CO2 retention
   v. Upper respiratory tract infections
   vi. History of middle ear surgery or disorders
   vii. History of seizures
   viii. Fevers
   ix. Congenital spherocytosis
   x. Optic neuritis

d. Complications of HBOT
   i. Claustrophobia
   ii. Hypoglycaemia
   iii. Middle ear barotrauma
   iv. Sinus squeeze
   v. Oxygen toxicity seizure
   vi. Progressive myopia – typically reverses completely in days to weeks.
   vii. Cumulative pulmonary oxygen toxicity
   viii. Pulmonary barotrauma +/- air embolism
   ix. Exacerbation of congestive heart failure in patients with severe disease, due to:
      a. Sinus bradycardia from stimulation of vagal activity and stimulation of a further measurable, non-oxygen dependent bradycardia that is associated with hyperbaric pressures.
      b. Systemic vasoconstriction causing increased afterload.
   x. Increased rate of maturation of cataracts with very long courses of HBOT.

THE FUTURE

There have been difficulties over the years in conducting large trials in hyperbaric medicine. Many contributing factors, including unit size, small patient numbers within each clinical indication alongside difficulties in creating sham treatments, are commonly reported. These challenges have, unfortunately, led to delays in the progression of high-level research in the field.

In recent times, efforts within the field of Diving and Hyperbaric Medicine have increased towards defining minimum patient quality and outcome datasets for both hyperbaric specific outcomes as well as linkage with other disease-specific datasets. A regional registry throughout Scandinavia is actively collecting data. Registry development in the USA and Australia and New Zealand is progressing well.

Areas of keen interest for future research include the effects of hyperbaric oxygen on necrotising soft tissue infections, on ulcerative colitis and on the modulation of radiation treatment, with studies currently under way.

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Circulation

Perioperative management of heart transplantation

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INTRODUCTION

The first heart transplant was performed more than 50 years ago, with the recipient surviving for 18 days[1]. Survival after heart transplantation was poor in the decade following due to a lack of effective immunosuppression therapy, limited surgical experience, and opportunistic infections. The development of endomyocardial biopsy in the 1970s[2] and approval for the use of Cyclosporine[3] in 1983 led to vastly improved outcomes. In recent years, the use of ventricular assist devices to improve cardiac output and end organ dysfunction while on the transplant waiting list, together with a deeper understanding of the immunological processes leading to rejection, have improved the median survival of a heart transplant recipient to 12 years[4].

In 2018, 129 heart transplants were performed in Australia and 20 in New Zealand[5]. The chances of encountering a heart transplant recipient requiring non-cardiac surgery are increasing, given both improved survival, and the cumulative total of more than 5000 cardiac transplants per year occurring worldwide[6]. An understanding of the physiological differences following heart transplantation and how the transplant process works is therefore important for all anaesthetists and intensivists. In this article we will discuss patient demographics, perioperative management for the transplant itself and also the management of heart transplant patients for non-cardiac surgery.

Table 1. Demographics of heart transplant recipients in Australasia 2016 in patients >18 years of age[5,6].

5121 transplants worldwide, Australasia = 149.
76% male, 24% female.
Mean time on "active waiting list" = 150 days (Range: 113-226 days)
58% New York Heart Association (NYHA) III, 11% NYHA IV.
8% on inotropic support.
43% with Ventricular assist device (VAD)
Mean age of recipient = 45 years, mean age of donor = 35 years.

PREOPERATIVE ASSESSMENT

Patient characteristics

Patients presenting for heart transplant are a diverse group with a variety of underlying pathophysiological processes to be considered in the preoperative anaesthetic work-up (see Table 1 and Figure 1). Patients are generally referred via a cardiology specialist to the transplant service but acute cases may present via intensive care and be expedited onto the urgent list.

Figure 1. Graphical representation showing proportion of patients in each disease group who undergo transplant[7].

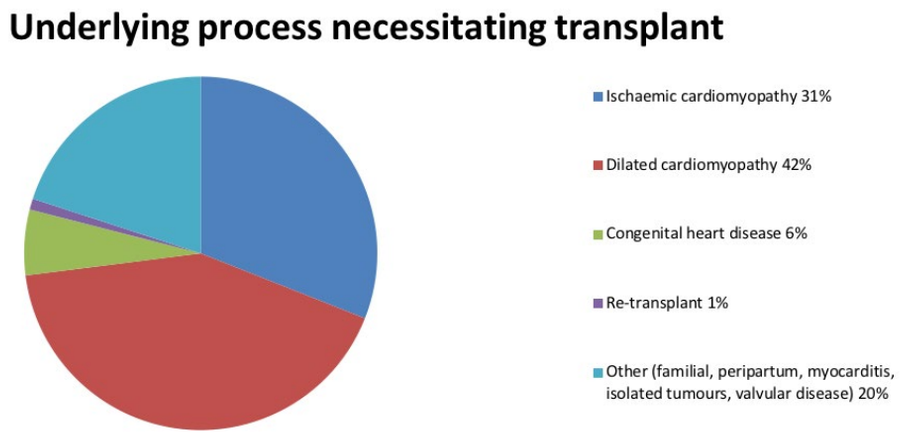

Table 2. Indications and contraindications for heart transplant[8,9].
**Australasian guidelines are referenced here but are subject to constant expansion and review.*

Indications[7]	Contraindications[9]
Clinical indications: ▪ Severe functional limitation (NYHA III / IV) ▪ Arrhythmias refractory to management or recurrent, appropriate shocks ▪ Refractory angina ▪ Overall failure of medical +/- resynchronization therapy *Parameters:* ▪ VO_2 peak <12ml/kg/min ▪ Severe LV systolic dysfunction ▪ HFSS (heart failure survival score) medium to high risk ▪ Seattle heart failure survival model at 1 year <80%	*Relative** ▪ Chronic kidney disease (CrCl<40ml/min) ▪ Liver disease (Bilirubin >50mmol/l) ▪ FEV1 <1 litre ▪ PASP >60mmHg (or PVR >4.0 woods units) post reversibility ▪ Psychological issues; non-compliance, lack of social support, learning difficulties (relative contraindications) Absolute* ▪ Uncontrolled diabetes (HbA1C >59mmol/mol) secondary organ involvement or microvascular complications ▪ Raised BMI >30kg/m2 ▪ Substance abuse (6 months abstinence from illicit drugs, smoking and alcohol are required) ▪ Active or recent malignancy (impacting post-transplant survival) ▪ Chronic infections – HIV, HBV/HCV with liver complications ▪ Active systemic infection

The timing of transplantation is important for maximal benefit, too early may unnecessarily use a scarce resource and put patients through early risks and an arduous recovery process that they may not see maximal benefit from. If allowed to wait too long, end-organ dysfunction may develop and outcomes following the transplant are more likely to be poor. As heart failure progresses to biventricular failure, pulmonary and hepatic congestion occurs together with cardiac cachexia and reduced renal perfusion and creatinine clearance. For these reasons much energy has been placed into trying to establish who will benefit the most, and at what time, from a heart transplant. A summary of the relative indications and contraindications for heart transplant can be seen in Table 2.

Priority status for heart transplant

The Transplantation Society of Australia and New Zealand have guidelines for the urgency of transplantation in order to prioritise those that need transplants first[9]. Patients expected to survive only days or weeks without a transplant are placed onto the "urgent list" with the expectation that the patient will either die or receive a transplant within two weeks. These tend to be patients on mechanical support or who have developed a life-threatening complication whilst on mechanical support or inotropes.

Adjuvant therapies and devices

Aside from a routine anaesthetic assessment, it is important to identify the underlying pathology necessitating transplant, together with therapy up until this point. Centrally administered inotrope infusions; typically dopamine, milrinone or levosimendan may be used in the bridging phase to transplant and the doses and duration of therapy should be noted. Pre-exposure to inotropes can result in blunted responses when required intra-operatively[10]. A small subset of patients may also be established on intravenous pulmonary vasodilators such as prostacyclin[11].

Almost half of patients on the waiting list have been established on a ventricular assist device (VAD) prior to transplant in Australasia. This has been one of the major changes in the transplant population demographic in recent years[5,12]. VADs provide mechanical support to the heart by draining blood from the left ventricular apex, passing it through the VAD pump creating blood flow which can be axial (propeller in a pipe) or centrifugal (magnetised internal impeller) providing non-pulsatile blood flow to the aortic root. VADs are currently used as a bridge to transplant in Australasia whereas in the United States they can be used as destination therapy.

VAD implantation may improve end organ perfusion and allow for improved conditioning of the patient prior to a transplant becoming available, with increases in VO_2 peak and 6-minute walk test being demonstrated[13]. The aim is to improve renal function, allow moderate exercise and to improve body weight while on the waiting list. The steady improvement in VAD technology is one factor contributing to improved survival of patients on the transplant waiting list[14] together with improved outcomes 1-year post transplant. VADs are not free from complications including right ventricular failure, thrombosis, mechanical malfunction and driveline infections.

Patients with a VAD in situ should have the implantation documentation reviewed together with the current settings recorded. The fact that a sternotomy has already been performed confers an increased risk of bleeding and difficulty in establishing tissue planes for the surgeon. VADs are also associated with altered coagulation status due to anticoagulation medications to prevent device thrombosis and an acquired von Willebrand deficiency due to shear forces on plasma proteins as they pass though the pump.

Worldwide a small proportion of patients (1.2%)[15] present for urgent transplant after being placed onto veno-arterial (VA) extra-corporeal life support (ECMO). These tend to be patients for whom a VAD is not feasible due to logistical issues; often those with profound and rapid deterioration such as with acute myocarditis or those with pre-existing congenital heart disease for whom anatomical factors preclude the use of a VAD. This cohort on VA ECMO support has an understandably higher early mortality in the first 6 months when compared to patients presenting via other avenues for transplantation[15].

Psychological assessment

When considering suitability for transplant, psychological assessment and evaluation is imperative. Patients following transplant undergo a taxing regime of immunosuppression therapy, clinic visits and medical interventions with strict adherence being of paramount importance if rejection is to be avoided. Factors such as alcohol or substance abuse, absence of a stable social support network, depression, previous overdose attempts or suicidal intentions are all considered and have been associated with adverse outcomes and as such may be contraindications to transplant[16].

Right heart catheterisation

End stage left heart failure leads to chronically elevated left atrial pressures which in turn results in elevated pulmonary vascular pressures and eventual biventricular failure. Secondary pathological alterations to the pulmonary vasculature are thought to result from increased shear stress and hypoxia affecting the endothelial wall lining the pulmonary vessels. This results in compensatory dilation and thickening of the pulmonary veins,

interstitial oedema due to endothelial cell dysfunction and alveolar haemorrhage. The net result from these processes is increased pulmonary vascular resistance[17].

The presence of increased pulmonary vascular resistance is associated with worsened outcomes as the transplanted heart is untrained to cope with a high right ventricular afterload[18]. It is vital to identify and treat patients with pulmonary hypertension prior to listing for transplantation. The diagnosis and severity of pulmonary hypertension is assessed with right heart catheterisation (RHC)[19]. Measured and derived values from RHC are summarised in Table 3.

PVR is determined by pressure difference divided by blood flow (Poiseuille's Law), and in this instance is the difference between mean pulmonary artery pressure (PAP) and mean left atrial pressure (LAP) divided by cardiac output (CO). LAP is derived from the pulmonary arterial wedge pressure (PAWP) – when a balloon is wedged in the pulmonary artery, this forms a contiguous column of blood with the left atrium. The resulting PVR is given in Wood Units (WU), a conversion factor of 80 is then applied to give a value in dynes.sec.cm^{-5} to allow comparison between the common notation for systemic vascular resistance (SVR).

$$PVR = \frac{MPAP - PAWP}{CO}$$

During the RHC procedure PAWP is taken as an average of 3 readings at the end of normal expiration which coincides with functional residual capacity; the time when intra and extra thoracic pressure is equalised. This measurement is then used to derive PVR.

Transpulmonary gradient (TPG) is calculated as the difference between MPAP and LAP (as estimated by PAWP). This number is useful for diagnosing "out of proportion" pulmonary hypertension in patients with left ventricular failure or mitral disease where the backstream MPAP is higher than would be expected for a given LAP and "pre-capillary" pulmonary hypertension coexists[20]. The gradient responds to changes in cardiac output but has proven a useful predictor of post-transplant survival with values of <11mmHg associated with improved outcomes at 1 year and values of >15mmHg being of concern[21].

Patients with PVR >2.5 Woods units and a TPG >15mmHg are at a threefold risk of right heart failure and early mortality following transplantation as the donor heart is unsuited to generating high right sided pressures. This group should undergo a "vasoreactivity test"[19]. Pulmonary artery vasodilators are administered to assess for reversibility of PVR during the RHC procedure and patients are then placed onto a pulmonary vasodilator trial for 6-8 weeks prior to reassessment. The most studied drug is sodium nitroprusside (SNP) although milrinone, nitric oxide, prostaglandins and sildenafil have all been employed. Successful reversibility is defined as values of <2.5 WU and TPG <15mmHg with systolic blood pressure maintained above 85mmHg. If the pulmonary hypertension is reversible then equivocal outcomes can be obtained once heart transplant takes place[22].

Table 3. Measured and derived values from a right heart catheterisation study.

Measured values	Derived values
Cardiac output (CO) ▪ Obtained via thermodilution technique ▪ Averaged from 3 readings ▪ May be inaccurate if shunt is present	Cardiac index (CI) referenced to body surface area
SvO_2	Transpulmonary pressure gradient (TPG) ▪ MPAP – PAWP
Pulmonary arterial pressure (PAP) ▪ Systolic (PASP), diastolic (PADP) and mean (MPAP)	Diastolic pressure gradient ▪ DPAP-PAWP
Pulmonary arterial wedge pressure (PAWP) - averaged over 3 readings at end expiration	Pulmonary vascular resistance $PVR = \frac{MPAP - PAWP}{CO}$
Right atrial pressure (RAP)	
Right ventricular pressure (RVP)	

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) is an objective investigation that may be used in the pre-operative workup of patients being considered for heart transplantation. The two most commonly cited values for decision-making are VO_2 peak and the VE/VCO_2 slope.

Patients with severe heart failure and preserved exercise capacity defined as peak VO_2 > 14ml.kg^{-1}.min^{-1} have been shown to have equivocal 1 and 2 year outcomes compared with those who undergo transplant. This value helps guide the timing of transplant intervention[23]. The downside of using peak VO_2 as the sole basis for prognostication is that it may be limited by effort or symptoms which stop the test prematurely. VO_2 peak is also a "per kilogram" measurement and can underestimate performance in patients with increased body mass index (BMI) and is negatively affected by beta-blocker therapy[24]. Australasian guidelines advise consideration of heart transplantation if peak VO_2 is less than 12ml.kg^{-1}.min^{-1} if receiving beta-blocker therapy[9] with one American study advising a cut-off of 14ml.kg^{-1}.min^{-1} if not taking or unable to tolerate beta-blocker therapy[25].

Ventilatory efficiency as defined by CPET is the ability to increase minute ventilation (V_E) in response to increased CO_2 production (VCO_2) and is graphically represented by the V_E/ VCO_2 slope. This has been shown to be the strongest CPET predictor of mortality in a longitudinal study looking at outcomes in patients with severe heart failure[24]. In heart failure an excessive ventilatory compensation is generated in proportion to the degree of ventilation/perfusion (V/Q) mismatch and an increased gradient of the V_E/VCO_2 slope is seen. Ventilatory efficiency validity appears to be independent of beta-blocker therapy, sex, age and even VO_2 peak in predicting mortality[26].

Table 4. Characteristics of the ideal donor[29-31].

Gender match
Racial match
Absence of renal impairment (as defined by Blood Urea Nitrogen: Creatinine ratio >30)
Short ischaemic time (< 4 hours)
Young age of donor < 50 years
Non-smoker
Low PVR in the donor
Structurally normal heart without hypertrophy, valvular abnormalities or coronary artery disease
LVEF > 45%
Body size match, ideally within 20-30% of the recipient's body size.
Absence of underlying chronic infection (for example, HIV, hepatitis)
Papworth physiological criteria = MAP > 60mmHg, Cardiac index > 2.4L/min/m2, CVP 4-12mmHg, SVR 800-1200 dynes.cm-5

Ideal donor characteristics

It is useful to consider what an "ideal" donor organ would be, acknowledging that many of these features will not be present in real-world donors and compromise is necessary. These characteristics are summarised in Table 4. Supply and demand mismatch has led to expanded limits for these criteria in the international literature as donor hearts of sufficient quality for transplant are a scarce resource due to the decreasing incidence of stroke, brain trauma and other causes of brain death. Research is still required to fully elucidate exactly which donors should be considered unsuitable and which are "marginal".

The neurogenic storm during brainstem death may have important consequences for myocardial performance. Prior to brain death, autonomic activation may lead to profound vasoconstriction, increased afterload, redistribution of blood volume and arrhythmias[27]. In fact, 40% of brain-death donors have echocardiographic evidence of impaired cardiac function[28]. Following the catecholamine storm a period of vasoplegia often develops, with associated end-organ hypoperfusion that may further impair myocardial function.

Ischaemic time

The ischaemic time refers to the time from when the heart is removed from the donor until the time at which it has been reperfused in the recipient. This can be divided into the warm and cold ischaemic times. Warm ischaemic time refers to aortic cross clamp application until cooling for storage added to the time taken from

rewarming the heart and then anastomosing it into the recipient. Cold ischaemic time refers to from when cold cardioplegia solution is employed until warm reperfusion solution is administered prior to implantation.

The ideal "total" ischaemic time is under 4 hours although this can potentially be extended if the donor is of a young age. An ischaemic time of over 6 hours is an independent risk factor for poor outcome (although isolated cases in the paediatric population have shown good outcomes with ischaemic times exceeding 8 hours[32]). Some centers utilise a "heart in a box" technology which allows for perfusion of the heart with warm, oxygenated and nutrient-enriched blood during transit to extend the time the heart remains functional once explanted. This method was shown to be non-inferior to standard cold-storage techniques in the PROCEED-II trial with perhaps future potential to transfer hearts over larger distances, increasing potential donor numbers in remote locations[33].

INTRAOPERATIVE MANAGEMENT

Pre-induction

Most patients are receiving oral anticoagulants; either due to presence of a VAD or for prevention of myocardial thrombus associated with low cardiac output. These agents require reversal immediately prior to starting surgery due to the risk of thrombus with prolonged interruption. Reversal is achieved according to local policies generally with prothrombin complex concentrate and/or consideration of vitamin K and fresh frozen plasma.

Continuation of pulmonary vasodilators is critical during the perioperative phase in patients with elevated PVR to reduce the risk of right heart failure and facilitate weaning from CPB. Some patients may have a long term central venous catheter in situ through which these medications or other inotropes are administered and it is routine practice in our hospital to remove these during the transplant, siting all infusions and inotropes on newly inserted central venous access lines, due to the risk of infection.

Discussion with the transplant team to coordinate administration of immunosuppression medications in the perioperative phase is essential. Patient factors such as weight and creatinine clearance can necessitate adjustment of dosing. Immunosupression regimes differ regionally but usually include a steroid (for example, methylprednisolone) and an immunosuppressant (for example, mycophenolate, azathioprine or an anti-TNF alpha agent). Antibiotic prophylaxis reflects local susceptibilities as well as pathogens that may have been identified on bronchoscopy of the donor.

Invasive monitoring including arterial line, central venous access, pulmonary artery (PA) catheter and urinary catheter are used. Siting of arterial lines can be challenging in VAD patients and ultrasound assistance should be employed early. Central venous lines should be positioned on the left side where feasible; the right side being reserved for future myocardial biopsy sampling. Some anaesthetists advocate siting central venous lines with the patient awake under local anaesthetic infiltration, in order to titrate inotropes during the induction phase, although this is not universal practice. Most transplant recipients have an implantable cardiac defibrillator (ICD) and this should be interrogated and reprogrammed immediately prior to surgery with anti-tachycardia and defibrillation functions disabled, and a backup pacing mode set to optimise cardiac output. External defibrillator pads should be placed once the defibrillation function has been deactivated.

The goal of anaesthesia induction is to preserve biventricular performance as much as practicable. An approach that uses judicious administration of induction agents while paying careful attention to maintenance of systemic vascular resistance (SVR), normoxaemia and normocarbia is recommended. Patients with end stage heart failure have a fixed stroke volume that is highly preload dependent. A suggested approach would be midazolam 1-5mg (slowly titrated) followed by fentanyl 2-4ug/kg, propofol 0-1mg/kg and a non-depolarising muscle relaxant with fast onset to prevent hypoventilation and a rise in $PaCO_2$. In haemodynamically-compromised patients etomidate may be preferred, although it is likely the dose and speed of administration is the most relevant factor as all induction agents have been successfully described in the literature. Nitrous oxide should be avoided due to the risk of increasing PVR.

Transoesophageal echo should be sited[34] and a decision made whether to place a PA catheter prior to transplantation or to wait until after the donor heart is in situ. Cerebral oximetry using near infra-red spectroscopy (NIRS) can be used to assess for regional tissue oxygen saturation variation in the brain as a surrogate for brain perfusion. Processed electroencephalogram (EEG) is used at our institution to monitor depth of anaesthesia and is continued during the period of cardiopulmonary bypass (CPB).

Timing of induction should coincide with a decision from the retrieval team that the donor heart is suitable for transplant. An experienced team will then judge the likely time taken for recipient anaesthesia induction, siting of lines and obtaining surgical access to coincide with organ arrival, thus minimising ischaemic time.

During surgery

Heparinisation prior to cardiopulmonary bypass should be achieved in the usual manner. Be mindful that patients with a VAD device in situ will have had a sternotomy already and this will increase the risk of bleeding. Cardiopulmonary bypass (CPB) is generally achieved via right atrial cannulation and the PA catheter should be withdrawn prior to this stage. If a VAD is in situ then the outflow graft should be clamped and the device turned off before cannulation of the aorta. Minimal surgical handling of the heart is essential before cannulation to avoid dislodging thrombus that may have formed due to chronically low cardiac output. Progressing with surgery to the point where cardiopulmonary bypass is about to commence may be prudent if the heart is in transit to the operating theatre to minimise ischaemic time. Optimal timing requires constant communication between the retrieval and recipient teams and is usually managed by specific processes and a coordinator.

Bleeding is a common intraoperative complication and cross-matched blood should be immediately available with appropriate cytomegalovirus (CMV) compatibility according to the donor and recipient CMV status. Use of tranexamic acid as routine antifibrinolytic therapy is employed at our institution together with cell salvage once weaned from CPB.

Surgical technique varies but is usually a midline sternotomy followed by isolation of the great vessels including aorta, SVC, IVC and pulmonary artery, with cannulation of the SVC and IVC to facilitate venous drainage to the CPB circuit. Surgery can then proceed via one of three methods: biatrial, bicaval and total transplantation.

The bicaval technique is now the most commonly employed approach and involves resection of the entire right atrium leaving the SVC and IVC to be re-anastamosed to the donor right atrium. A cuff of left atrium is generally left attached to the pulmonary veins allowing for reconstruction of the donor heart with the remnant of recipient left atrium[35]. This approach involves five suture lines and has been shown to improve perioperative mortality, reduce incidence of pacemaker dependence and improve valvular function[36]. Total transplantation involves eight separate suture lines and is now rarely used, while the older biatrial technique has been associated with bradycardia, SA node dysfunction and aortic valve dysfunction.

Separating from cardiopulmonary bypass

When separating from cardiopulmonary bypass, the transoesophageal echocardiograph is essential and aside from the usual considerations, the following areas should be examined:

1. LV function, including regional wall motion abnormalities and septal motion.
2. RV function, focused on dilatation and free wall motion abnormalities.
3. Anastamoses sites, for air.
4. Air in the LV apex.
5. Flow through pulmonary veins to assess for occlusion or stenosis as evidenced by turbulent flow, or increased velocities.
6. Tricuspid valve, for tricuspid regurgitation, assessment of tricuspid regurgitation (TR) jet and tricuspid annular plane systolic excursion (TAPSE) as part of a comprehensive right heart assessment.

Weaning from bypass can be challenging. Donor factors such as ischaemic time, inotrope dependency and ejection fraction can result in poor graft performance. Recipient factors such as raised PVR, bleeding, prolonged CPB time and subsequent vasoplegia can all hamper weaning[37].

Titration of inotropes should be considered according to the pharmacodynamic differences observed in the transplanted heart (see Table 6). A balance needs to be achieved between filling the new heart, which is preload dependent, and avoiding over distention of the right ventricle, which will worsen right ventricular performance. The most common reason for early failure to wean from CPB is right ventricular failure and this is especially likely in the context of raised PVR in a naïve right ventricle. Optimising ventilation and reducing PVR with nitric oxide or phosphodiesterase inhibitor may help. Weaning from CPB may be impossible in some cases and institution of VA-ECMO or placement of an intra-aortic balloon pump or VAD should then be considered. A strategy for this should be discussed with the surgical and intensive care teams in advance of commencing the transplant.

Having separated from bypass, the PA catheter should then be refloated and calibrated to direct further inotrope and fluid management. The goal for the first 24 hours in the intensive care unit should be to protect and optimise RV function. This is achieved by the pneumonic "protect RV":

P = pH optimization, especially avoiding acidosis

R = Reduce PVR (milrinone, nitric oxide, sildenafil, epoprostenol)

O = Oxygenation, avoid hypoxia

T = Temperature, avoid hyper/hypothermia

E = Euvolaemia

C = Central venous pressure (CVP) – watch for sudden rises suggestive of RV failure

T = Tamponade – have a high suspicion and low threshold for treatment

R = Rate – pace at 80-100bpm

V = Ventilation – normal $PaCO_2$

COMPLICATIONS

Primary graft dysfunction

Primary graft dysfunction (PGD) is the major cause of death within 30 days following heart transplant surgery and by definition begins within 24 hours of implantation occurring in 9-12% of cases[38].

PGD is defined as low cardiac output state (cardiac index <2.0l/min/m^2) occurring within 24 hours of surgery with no other secondary cause being identified[39]. PGD is subdivided into RV (45%) biventricular (47%) or LV (8%) failure and severity is graded according to inotrope dependence and need for mechanical support[40]. Primary graft dysfunction is thought to be multifactorial in nature with initial injury to the heart during the process of brain death, subsequent ischaemia-reperfusion injury during transport and re-implantation together with cytokine release and a systemic inflammatory response all playing a role.

Treatment options include intra-aortic balloon pump, insertion of VAD or VA ECMO. One study showed 89% of patients successfully weaned from ECMO[41] who required it post heart transplant and this is the therapy of choice for primary graft dysfunction in our institution.

Secondary graft dysfunction

Secondary graft dysfunction is an umbrella term used when a cause for graft failure has been identified. It includes hyperacute rejection, rejection due to pulmonary hypertension and graft failure due to surgical complications, for example, uncontrolled bleeding. Hyperacute rejection is a rare complication mediated by anti-donor antibodies seen in the recipient[42] and carries a 70% mortality risk but the incidence has fallen with ABO-compatibility testing, human leukocyte antigen (HLA) matching, gender and race matching and aggressive early immunosuppression therapies.

Cardiac allograft vasculopathy

Cardiac allograft vasculopathy (CAV) is an accelerated form of intimal hyperplasia developing along the entire length of transplanted coronary vessels. It differs in its pathophysiology from typical atherosclerosis seen in the non-transplanted heart and is the leading cause of death at 1-3 years following cardiac transplant[43]. CAV is progressive and affects arteries, arterioles, capillaries and occasionally veins of donated vessels only with any remnant recipient vessels being spared. Luminal hyperplasia initially occurs in the intima and then progresses to fibrosis of the media with flow limitation to distal myocardium.

Development of CAV is multifactorial and still poorly understood. It involves an immune-mediated component, with other non-immune factors such as hyperlipidaemia, insulin resistance and homocysteinaemia exaggerating progression. The clinical course can be unpredictable and may manifest as arrhythmias, congestive cardiac failure or sudden cardiac death.

Diagnosis of CAV is challenging as heart transplant patients do not exhibit the classic clinical symptoms of myocardial infarction due to denervation. Suspicion should be raised if new regional wall motion abnormalities (RWMAs) or diastolic dysfunction are identified on echocardiography or new arrhythmias, especially ventricular in origin, develop.

Intravenous ultrasonography (IVUS) is the gold standard investigation and looks at coronary artery wall structure internally (as opposed to purely diameter with angiography) by utilising a specialised ultrasound probe. This investigation is limited to larger coronary vessels and is both expensive and time consuming hence is only available in specialist centers. IVUS should be employed if angiography yields no positive findings and clinical suspicion remains high for CAV[44].

Endomyocardial biopsies

Endomyocardial biopsies are performed regularly during the first-year post-transplant to assess for evidence of graft rejection demonstrated as interstitial monocytic infiltrates within the myocardium or myocardial necrosis. Biopsies are carried out as a day-case procedure under local anaesthetic normally via the right internal jugular vein. Risks include tricuspid regurgitation due to leaflet damage or inadvertent biopsy of the tricuspid chordae and pericardial effusion due to myocardial perforation.

Other complications

Ten per cent of patients require a permanent pacemaker (PPM) after transplant[45]. Ventricular arrhythmias necessitating implantation of an ICD were required in 1.5% of transplant recipients in one retrospective study[46]. Moderate to severe tricuspid regurgitation complicates 10-30% of post-operative courses and is associated with decreased transplant performance and need for further annuloplasty surgery.

Nephrotoxicity secondary to calcineurin inhibitors (cyclosporine or tacrolimus) is commonly seen and more likely if coexisting diabetes mellitus or pre-transplant renal impairment exists. The burden of regular angiograms can cause contrast nephropathy which can also lead to renal impairment.

Improved survival post-heart transplant has resulted in increased duration of immunosuppression therapy and subsequent increased incidence of malignancy. More than 10% of heart transplant recipients develop a de novo malignancy in the first 1-5 years, an excess of 3-4 times that seen in the background population[47]. Skin cancers of squamous and basal cell carcinoma types are seen with 100-fold increased incidence when compared to controls. Squamous cell carcinoma has an increased propensity for metastasis when compared to basal cell carcinoma and rigorous screening is required for early detection and treatment to occur. Other solid organ tumours are seen at a slightly increased rate[48] although some studies show that incidence is now almost equivocal to the normal population as a result of modern immunosuppression regimes. Lymphoma is more common following heart transplant especially in younger recipients in the 18-35-year-old demographic with a prognosis of under 30% survival at 5 years[49].

HEART TRANSPLANT RECIPIENTS PRESENTING FOR NON-CARDIAC SURGERY

Physiological differences

When heart transplant recipients present for non-cardiac surgery it is useful to consider the physiological changes that occur following transplantation, these are summarised in Table 5.

Surgical dissection of the parasympathetic supply to the heart via the vagus nerve as well as sympathetic supply via the stellate ganglion occurs in the transplanted heart. At the sinoatrial (SA) node inflow and outflow innervation is lost and the SA node reverts to a “default” rate of 90-100 beats per minute due to loss of the predominating parasympathetic tone seen in normal hearts. Atrial contraction is asynchronous and atrial filling is impaired, especially in the left atrium. Intrinsic means of increasing cardiac output become more important following transplantation with the Frank-Starling relationship predominating in regard to increasing stroke volume. The transplanted heart is said to be more “preload dependent” for this reason.

Loss of somatic innervation to the pericardium and myocardium means that the sensation of angina in response to myocardial ischaemia is lost. Over the first few days following heart transplant myocardial stores of catecholamines are depleted and so autonomic control is reduced. Alpha and beta receptors remain intact but respond only to systemic stimulation from circulating catecholamines in an attenuated manner, resulting in blunted responses to exercise, pain and hypovolaemia[50]. Maximal heart rate, heart rate variability and contractility are all reduced but coronary autoregulation remains intact[51].

Re-innervation can occur slowly with sympathetic innervation occurring at 6-8 months and parasympathetic innervation redeveloping to variable extent at 1-3 years post-transplant. Reinnervation is heterogenous, partial and unpredictable and tends to occur in the left ventricle first with the right ventricle later, if at all[52].

Arrhythmias can develop in the transplanted heart with conduction delays being most common. Despite native atrial tissue remaining in the transplanted heart the suture line at the transplanted left atrium means that conduction cannot occur but a double P-wave can sometimes be seen on ECG. Suture lines predispose to heart block and are more likely with a bi-atrial surgical technique. Ventricular arrhythmias are less commonly encountered and can be a marker of acute rejection or CAV and should prompt urgent investigation.

Table 5. Physiological differences in the transplanted heart.

Physiological parameter	Normal heart	Transplanted heart
Heart rate	60-70	90-100
Heart rate response to exercise	Increases	Blunted, slower increase
Cardiac output during exercise	Normal	Reduced
Blood pressure	Shows diurnal variation	No variation seen
Somatic innervation	Present, angina in response to ischaemia	Absent

Physiological parameter	Normal heart	Transplanted heart
Preload	Reflex tachycardia in response to drop in preload	Unable to generate tachycardia Reliance on preload and slow rise in circulating catecholamines to increase CO in response to hypotension
Preload dependence	Normal	Increased
Afterload	Reflex tachycardia and increased stroke volume (Anrep effect) in response to increased afterload	No HR response to changes in afterload, that is, decreased SVR from GTN, SNP, neuraxial blockade
Coronary autoregulation	Normal	Remains intact
ANP production	Not affected	Not affected
First degree heart block	Not normally present	Increased Incidence
Double P-wave	Not present	Donor and recipient SA node
Arrhythmias	Not normally present	Common, may be transient. Heart blocks common. 25% develop AF/ atrial flutter. Ventricular arrhythmias may be a sign of vasculopathy or rejection.
Right bundle branch block	Not normally present	5-10%
Bradyarrhythmias	Not normally present	10% require PPM
Carotid sinus massage		No effect
Valsalva		No effect

Pharmacological differences with the transplanted heart

Pharmacological management of heart transplant recipients requires awareness of the different pharmacodynamic effects that commonly used drugs will have. These key differences have been summarised in Table 6. Only drugs which act directly on the heart will be effective; those which act via indirect mechanisms involving the autonomic nervous system will be ineffective unless reinnervation has occurred which can be variable. Direct-acting chronotropic agents are required to stimulate heart rate (for example, isoproterenol or dobutamine) and the effects of adrenaline and noradrenaline can be variable depending on intrinsic stores or catecholamines and degree of reinnervation. Cautious titration is the safest approach to avoid exaggerated effects.

Table 6. Pharmacological differences in the transplanted heart.

Drug	Effects in transplanted heart
Dopamine	Similar response in transplanted heart
Noradrenaline	Exaggerated effect due to increased adrenoreceptor density
Adrenaline	Exaggerated effect due to increased adrenoreceptor density
Metaraminol	Effective, no reflex bradycardia
Phenylephirine (direct vasoconstrictor)	Effective, no reflex bradycardia
Epherdrine	Decreased effect (indirect mechanism)
Dobutamine	Exaggerated effect
Digoxin (mixed direct and indirect)	Inotropic effect remains intact, conduction effects on AV node likely to be absent
Isoprenaline	Effective

Drug	Effects in transplanted heart
Adenosine	Exaggerated bradycardic effect
Atropine	No effect. Ineffective in bradycardic emergencies
Glycopyrollate	Ineffective
Neostigmine	Bradycardia may develop especially if >6 months post-transplant
Lignocaine	Effective
Beta-blockers	Effective but caution as heart is reliant on circulating catecholamines to increase cardiac output
Calcium channel blockers	Effective but exhibit significant negative inotropy

Other considerations

Besides physiological and pharmacological differences, heart transplant patients also have a plethora of other issues to consider when presenting for non-cardiac procedures and surgery. An accurate medication history is important as immunosuppression and steroids are routine therapies, together with anticoagulants, statins and antihypertensives.

A full panel of bloods should be taken including liver function and renal function tests to assess for end-organ impairment that may result from graft dysfunction or adverse medication effects. Recent echocardiogram results, ECG and an assessment of exercise capacity and cardiopulmonary reserve are required in the pre-operative workup. Six-minute walk tests and CPET can be useful investigations to get objective data for perioperative planning together with documentation of NYHA score and overall assessment of exercise capacity.

Details of when the transplant was performed, at which institution, and any complications in the subsequent months and years should be reviewed. It is important to obtain an accurate idea of cardiac performance and whether graft rejection is present or has been an issue in the past.

Venous and arterial access can be difficult and the right internal jugular vein should be avoided where possible to facilitate future myocardial biopsy sampling. Patients may be receiving anticoagulants and may have a permanent pacemaker or ICD in situ which should be interrogated prior to any surgical procedure. In the intraoperative period great care should be taken with aseptic technique given the immunosuppressed state of the patient, particularly when siting central venous catheters and arterial lines. Fluids should be administered judiciously during surgery bearing in mind that the transplanted heart is pre-load dependent and unable to increase ejection fraction or heart rate considerably in the event of a sudden loss of intravascular volume. If there is any doubt as to the clinical condition of the patient then liaison with cardiology services and discussion with a transplant center is advised.

CONCLUSION

With increasing frequency of heart transplantation, and improved survival rates following transplantation, the number of patients with heart transplants is increasing. Improvements in immunosuppression, patient selection for transplant, optimisation with preoperative VAD implantation and postoperative care have led to post-transplant survival in excess of 10 years for most patients. With increased survival comes the increased likelihood of patients presenting for non-cardiac surgery and thus a sound knowledge of the heart transplantation process and the physiological and pharmacological changes that occur afterward are important to ensure a safe transit through the perioperative process.

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Preventing vascular damage during central venous catheter insertion via the internal jugular vein

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INTRODUCTION

Central venous catheters (CVCs) are utilised widely in the critical care environment, however their utilisation is not without risk. Significant morbidity and mortality can result from complications relating to their insertion, creating a healthcare burden in patient quality of life, hospital days and cost. Internationally, closed claim data suggest that the majority of mechanical complications associated with CVCs are vascular injuries, and most often, preventable[1-3]. Relevant injuries include arterial injury, venous injury, and subsequent bleeding and haematoma. Safe vascular access is integral to anaesthetic and critical care practice, and the diligent application of evidence-based prevention measures aims to reduce future morbidity. Strategies to prevent, recognise and manage vascular complications in reference to internal jugular vein (IJV) catheterisation will be discussed.

ARTERIAL INJURY

Inadvertent arterial puncture with a small needle (18-gauge or smaller) occurs in 4.3-9.3% of landmark based CVC placements in reported series[4,5], and in 1.8% of placements using real-time ultrasound guidance[6]. In the majority of cases these are easily recognisable secondary to pulsatile flow and the bright red colour of oxygenated blood, however recognition may be difficult in infants, hypotensive or hypoxaemic patients, and in time-pressured emergency situations. While a small needle puncture appears harmless in the majority of cases, puncture of the carotid artery may cause stroke[7]; a local haematoma or false aneurysm may cause skin and soft tissue pressure necrosis, upper airway compression or compression neuropathy; and if the needle also traverses a vein, there is potential for arterio-venous fistula formation. Arterial dissection, thrombosis, embolus and unintentional catheterisation may cause distal ischaemic damage, with particular relevance to the carotid artery. Accidental arterial catheterisation has a reported incidence of 0.1-1%, and may result in haemorrhage, pseudoaneurysm, stroke or death[8].

VENOUS INJURY

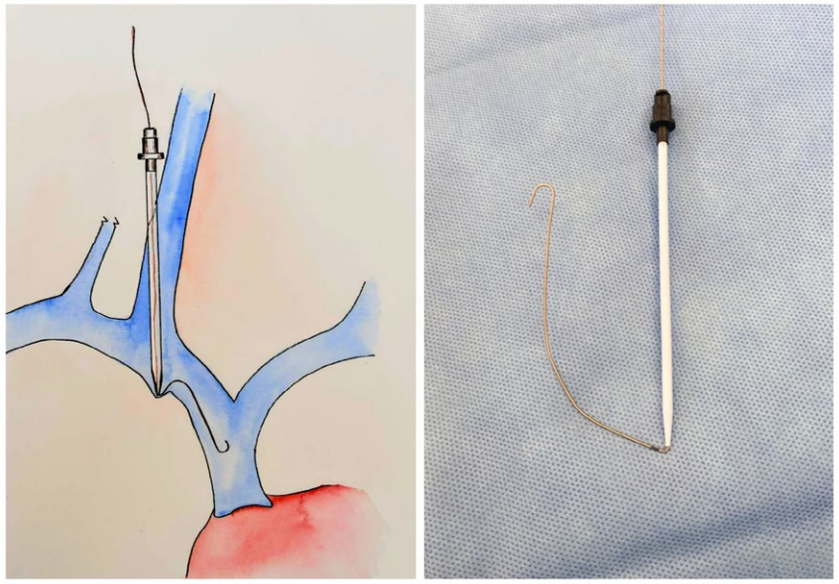
While most emphasis is placed on preventing arterial injury during CVC placement, potentially life-threatening injuries to the superior vena cava, mediastinal vessels and right atrium have been reported. Venous injury may manifest as a localised haematoma, or as bleeding or extravasation into the mediastinum, pleura, peritoneum, pericardium or other space. This may cause haemodynamic compromise, cardiac tamponade or haemothorax[1,9].

The proposed mechanism for venous injury is that the guidewire becomes trapped against the wall of the vein, and subsequent advancement of a dilator or catheter tears or perforates the vessel wall (Figure 1). Such linear lacerations can lead to catastrophic haemorrhage. Whilst catheter placement in the right atrium has previously been favoured due to lower rates of thrombosis, the risk of atrial perforation has changed recommendations

such that the atrial-caval junction is now a preferred target position[10]. Catheter placement in the right atrium can also cause local myocardial irritation and supraventricular arrhythmias, which if unrecognised, can cause significant haemodynamic compromise.

Haematoma formation has been reported in up to 4.7% of all catheter placements[11]. While this is most often non life-threatening, the pleural space and mediastinum are potential spaces where hidden haemorrhage can occur. Communication with the pleural cavity from a perforating vein (or artery) can lead to a rapidly developing, life-threatening haemothorax. Similarly placed small fluid collections can also be a source of infection, with potential abscess formation. Haemothorax should be considered as an important differential diagnosis if blood cannot be aspirated from an attempted internal jugular or supraclavicular catheter.

Figure 1. Guidewire impingement upon the posterior wall of the vein, with subsequent damage to the vessel wall on advancement of a dilator or catheter.



PREVENTING VASCULAR COMPLICATIONS

Factors associated with fewer mechanical complications include increased operator experience, considered site selection, optimal patient positioning, fewer insertion attempts, ultrasound guidance and pressure monitoring.

Operator experience

As with most medical procedures, the level of experience of the proceduralist influences the risk of complications[12]. A prospective cohort study using a landmark technique revealed that operators who had previously inserted more than 50 CVCs were more likely to be successful at inserting subsequent CVCs, with fewer complications[13]. Recognition of the importance of adequate operator experience has prompted many hospitals to require that a certain number of successful CVC insertions be performed before an operator can practice without supervision.

A guideline from the United Kingdom's National Institute of Clinical Excellence (NICE) in 2002 recommended that all those involved in placing CVCs using 2-dimensional (2D) ultrasound undertake appropriate training to achieve competence[14], and in 2012 an international consensus task force was convened to provide evidence-based recommendations for training and insertion of CVCs[15]. They concluded that safe insertion and management of central venous devices requires standardisation of education, simulation practice, and supervised insertions. Education should include didactic or web-based teaching covering insertion procedures, infection prevention, complications, and the care and maintenance of devices, alongside laboratory model utilisation and simulation practice. Detailed competencies and assessment methods are outlined in the Anaesthesia and Intensive Care Medicine Curricula from the Royal College of Anaesthetists, with formal training in the form of courses, simulation labs and apprenticeship models[16].

Defining a competent practitioner in objective terms is, however, difficult. Competence is often determined after performing a predetermined number of procedures, or after subjective assessment by a practitioner who is deemed competent. Other more objective systems have been suggested, using global rating scales or checklists[15]. As such, the 2012 task force[15] recommend that clinical competence be determined by observation during clinical practice using a global rating scale, rather than by the performance of a target number of procedures. Notably, assessment of CVC insertion suits a checklist format, being a sequential and predictable process. Each component of the skill can be performed, observed and assessed, and the practitioner deemed competent when they complete all components proficiently. An example of such a checklist is included in Appendix 1.

Insertion attempts

The incidence of mechanical complications after three or more insertion attempts is reported as six-fold greater than after one attempt[17]. Seeking assistance if an operator is unable to insert a catheter after three attempts seems prudent, with consideration of an alternative insertion site.

Site selection

Catheter insertion site should be based on clinical need, alongside practitioner judgement, experience and skill[18]. Internal jugular and subclavian venous catheterisation carry similar risks of mechanical complications (Table 1, from McGee et al[12]), however subclavian catheterisation is comparatively more likely to be complicated by pneumothorax and haemothorax, whereas internal jugular catheterisation is more likely to be associated with arterial puncture. Haematoma and arterial puncture are common during femoral venous catheterisation, yielding a higher overall complication rate than both subclavian and internal jugular routes, however the rate of serious mechanical complications is low for all three routes. Given that mechanical complications are most likely during catheterisation at the femoral site, however, the internal jugular or subclavian venous route should be chosen unless contraindicated[12].

Table 1. Frequency of mechanical complications, according to the route of catheterisation.
Reproduced with permission from McGee[12].

Complication	Frequency (%)		
	Internal jugular	Subclavian	Femoral
Arterial puncture	6.3-9.4	3.1-4.9	9.0-15.0
Haematoma	<0.1-2.2	1.2-2.1	3.8-4.4
Haemothorax	NA	0.4-0.6	NA
Pneumothorax	<0.1-0.2	1.5-3.1	NA
Total	6.3-11.8	6.2-10.7	12.8-19.4

Patient positioning

Where clinically appropriate and feasible, central venous access in the neck should be performed with the patient in the Trendelenburg position. Non-randomised studies indicate a greater diameter and cross sectional area of the IJV in this position compared to supine positioning[18]. Trendelenburg positioning additionally creates positive venous pressures in the spontaneously breathing patient, thereby reducing the risk of air embolism. Avoidance of greater than 45-degree head rotation is also recommended in order to minimise overlap of the IJV with the closely related carotid artery[19,20].

Guidance and verification of needle, wire and catheter placement

Verification of correct venous placement of a CVC may be considered as a two-step process, with confirmation of the introducer needle within the target vessel first, before subsequent confirmation of venous placement of the introducer cannula or wire prior to dilation and catheterisation.

a. Needle insertion

Methods to confirm needle placement within a vein include observation of blood flow from the needle, blood gas analysis or use of real time ultrasound. The traditional method of observing the colour and pulsatility of blood from the needle hub is unreliable[21]. Measurement of blood gases to assess the degree of oxygenation is limited by potential arteriovenous shunting, and the impractical delay required for a result. Real time ultrasound guidance is a practical, reliable alternative.

Real-time 2D ultrasound guidance is superior to landmark-guided techniques, and is recommended whenever equipment and experience are available, particularly for CVC insertion into the IJV[22]. Dynamic ultrasound allows visualisation of the vein and assessment of compressibility (patency) and expansion of the vein in the Trendelenberg position, the absence of which is a surrogate marker for central venous stenosis or occlusion. Real-time ultrasound imaging additionally avoids blind seeker needle use, and allows the anatomical relations of the IJV to be defined; local pathology to be identified; and aids guidance of needle movement. Meta-analyses confirm superiority of ultrasound guidance to the landmark technique for first insertion attempt success rate, access time, overall successful cannulation rate, and reduced complications (namely arterial puncture, haematoma and haemothorax) with the IJV approach[23,24]. The pooled results of one meta-analysis indicated a rate of arterial puncture with ultrasound use of 37/2009 (1.8%), compared to 196/2018 (9.7%) when landmarks are used[6]. Randomised controlled trials additionally report fewer insertion attempts with real time ultrasound for both the IJV and subclavian vein approach, ranging from 1-1.75 attempts with ultrasound to 1.9-3.12 attempts using landmark techniques[25-29]. Puncture needle ultrasound visualisation may also be enhanced by using an 18G micropuncture needle with an echogenic tip.

Two Cochrane analyses confirmed a benefit of using ultrasound for IJV CVCs, but not for femoral or subclavian routes[30,31]. The advantage of ultrasound guidance for the subclavian approach is diminished by anatomical interference from the clavicle, however the latter result may rather reflect a lack of adequate studies rather than an inherent failure of ultrasound at other sites. As such, guidelines for safe vascular access from the Association of Anaesthetists of Great Britain and Ireland recommend routine use of ultrasound for all routes of access, and numerous national guidelines similarly recommend the use of ultrasound during CVC placement, including those from NICE in the United Kingdom[14], the American Society of Anesthesiologists[18], and the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists[32].

b. Guidewire insertion

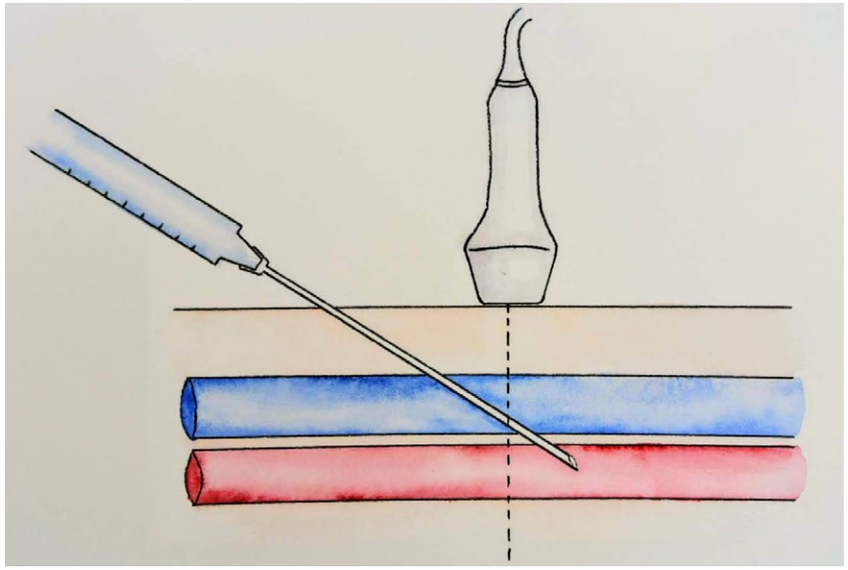
Techniques to confirm intravenous location of the guidewire (and introducer cannula) and avoid arterial placement include blood gas analysis, ultrasound visualisation of the wire in the target vessel, pressure monitoring, fluoroscopy, transoesophageal echocardiography, and chest radiography.

Ultrasound

Blood gas analysis via an introducer cannula is limited as described previously, but may be considered in conjunction with additional measures. While the value of ultrasound guidance is well established in the literature, and should be adopted to check guidewire placement, it does not eliminate the risk of arterial puncture. There are numerous reports of inadvertent large bore arterial catheterisation despite the use of ultrasound guidance[33-36]. Reasons this may occur include:

- Failure to visualise the needle tip with a short axis ultrasound view: whilst the shaft of a needle may be imaged in the vein, the needle tip can unknowingly be in the adjacent artery. Accurate needle tip location is a skill that requires multiple ultrasound views and considerable operator skill (Figure 2).
- Inadvertent migration of a needle into the artery during syringe manipulation or guidewire insertion. Use of a non Luer lock syringe allows easier removal of the syringe from the needle compared to a Luer lock syringe, minimising needle movement. While a guidewire-through-syringe option is available to further minimise needle movement, the authors do not recommend this technique, as pulsatile flow from an arterial puncture may be missed.
- Veno-arterial guidewire placement: the guidewire may pass through the posterior wall of the vein into an adjacent artery, which may not be appreciated on ultrasound imaging. This is particularly relevant for the subclavian and brachiocephalic arteries which lie deep to the clavicle, and may not be easily visualised with ultrasound, and in the low internal jugular approach.

Figure 2. Out-of-plane IJV needle insertion. Needle shaft is visualised in the vein, while the needle tip has inadvertently advanced into the neighbouring carotid artery.



Ultrasound guidance can be best utilised to identify the exact location of the relevant vein, enabling fewer and more accurately directed needle punctures, expediting reliable venous cannulation. Complimentary use of pressure monitoring can then be utilised to further minimise the risk of arterial catheterisation, by confirming venous wire placement prior to dilation of the vessel.

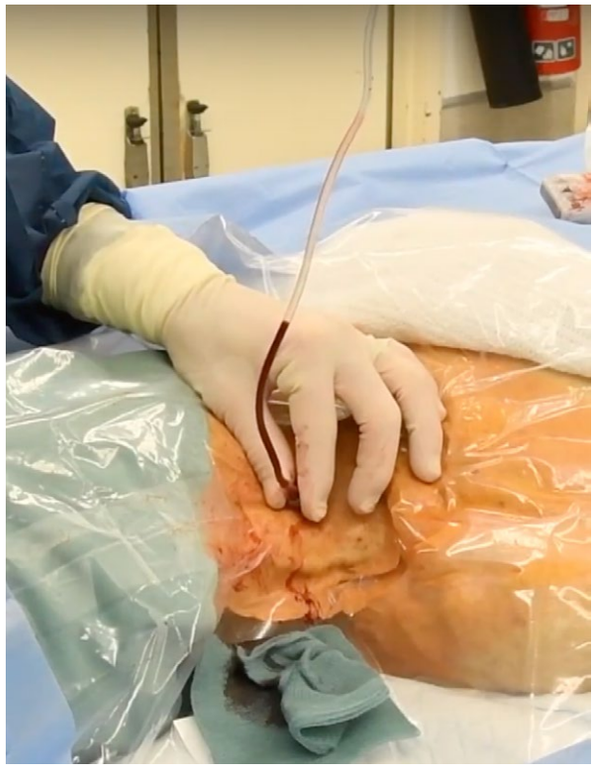
Pressure monitoring

Pressure measurement is a highly reliable method for distinguishing artery from vein, and can be used alone, or in combination with ultrasound guidance to confirm guidewire placement and thereby prevent subsequent inadvertent arterial catheterisation[37,5,4]. Methods include column manometry, connection to a pressure transducer via sterile tubing, or utilisation of a single use pressure transducer device. In a series of over 1700 CVC insertions, Ezaru et al[37] and Jobes et al[5] reported that without pressure monitoring, reliance upon colour or pulsatility would have resulted in an arterial catheterisation rate of 0.8%, with 14 arterial punctures identified only by pressure monitoring. Similarly, Oliver et al[4] correctly identified all arterial punctures using pressure transduction in a series of 1172 CVC insertions (incidence of 9.3%), with no arterial catheterisations as a result.

Column manometry is a simple, inexpensive technique, whereby a length of sterile tubing is connected to the hub of the introducing needle or cannula and partially filled with blood (Figure 3). This can be achieved either by holding the tubing below the level of the heart, or by aspiration. Use of a cannula minimises the risk of inadvertent needle movement when connecting the sterile tubing directly to the insertion needle, and is the technique of choice. The cannula can be inserted directly over the insertion needle (a modified Seldinger technique), or over the guidewire (Seldinger technique), and the guidewire removed. After the tubing is partially filled with blood, it is held vertically above the patient, and the blood/air interface will settle at the level of hydrostatic pressure in the vessel cannulated. If the vessel is venous, the blood/air interface will fall indicating a low pressure system. If the vessel is arterial, the blood will rise to the top of the tubing and overflow. If the level does not change, the test is equivocal, and the sterile tubing can be handed to an assistant to connect to a manometer for pressure measurement, waveform analysis and/or blood gas sampling.

We recommend that column manometry be the second step, after use of ultrasound, in confirming that the guidewire (and introducer cannula) is in a venous location, prior to dilation of the vessel and subsequent insertion of a large bore catheter.

Figure 3. Tube manometry to confirm venous pressure prior to dilation of vein. A sterile length of tubing is connected to a cannula, partially filled with blood, held vertically above the patient, and the blood air interface allowed to settle.



Fluoroscopy and echocardiography

Fluoroscopy can be utilised to identify the anatomical location of the entire course of a guidewire, offering an advantage over ultrasound, which is limited to the vascular insertion point. Indeed, direct visualisation under fluoroscopy is likely the optimal method to minimise the risk of vessel or atrial injury, observing the course of the guidewire and subsequent real time advancement of the CVC, with confirmation of tip position[21]. If a CVC rests against a vessel at an angle greater than 40 degrees, the risk of perforation increases[38], and this can be ascertained via fluoroscopy or plain chest radiography. Given that the location of the wire is inferred indirectly using knowledge of the different location and course of adjacent arteries and veins, however, errors may still occur[21], and evidence in the literature is insufficient to assess its efficacy in this setting[16]. Fluoroscopy may, however, prove useful to confirm line patency and position via digital subtraction angiography where uncertainty exists. Limited availability and time pressures limits widespread utilisation of fluoroscopy in the critical care environment at present.

Careful attention to guidewire resistance during guidewire insertion is mandatory. Resistance to guidewire advancement can result from:

- Wall dissection or “through and through” wall puncture.
- Retrograde advancement toward the brain.
- Central venous stenosis.
- Tracking of the wire into the subclavian or azygos veins.

Abnormal wire placement increases the risk of venous injury with subsequent advancement of a CVC, and the guidewire should be removed in such cases where resistance is encountered, or fluoroscopy utilised to further clarify guidewire position. Additional strategies to avoid and identify entrapment of the guidewire are encouraged. Ensuring that the guidewire can be moved back and forth freely during insertion of the dilator or CVC is suggested. Rotation of the dilator during insertion to prevent impingement on the guidewire is also recommended in order to minimise trauma to the posterior vessel wall.

Similarly, where trained operators and availability allow, transoesophageal echocardiography is an alternative technique that can be used to correctly identify the presence of a guidewire in the superior vena cava or right atrium in a mid-oesophageal bicaval view, with case reports indicating utility in this setting[16].

PROPOSED OPTIMAL TECHNIQUE

In summary, the proposed optimal evidence based technique for IJV cannulation is as follows. The patient is placed in the Trendelenburg position, with <45 degree head rotation, optimising IJV filling and reducing overlap with the adjacent carotid artery. Real-time 2D ultrasound is then utilised to identify the anatomy of the target vein and surrounding structures, and allow guidance of needle depth and angulation. By following the position of the needle tip in short access at all times, the risk of arterial puncture is minimised. Upon venous cannulation, the needle is immobilised at the skin with a pincer grip, bracing the medial aspect of the steadying hand on the skin surface, allowing the guidewire to be advanced gently via a Seldinger technique, minimising the risk of inadvertent needle advancement from the target vein. The introducing needle is then carefully removed, and real time ultrasound utilised to verify the position of the guidewire within the target vessel. Alternatively, a cannula over needle technique can be utilised in a modified Seldinger technique, whereby the cannula is advanced directly over the inserting needle into the vein, and the guidewire subsequently inserted via the cannula. Prior to dilation with an introducer, complementary use of pressure monitoring, through column manometry via an introducer cannula, is utilised to confirm venous placement of the guidewire. Arterial blood gas sampling may optionally be incorporated at this stage if desired. The guidewire is re-inserted, and the dilator advanced cautiously over the guidewire with gentle rotation, ensuring free movement of the wire within the dilator at all times. Risk of impingement of the guidewire on the posterior wall of the vein is thereby minimised. Insertion of the CVC over the guidewire follows, and all lumens aspirated and flushed to identify an inadvertent CVC insertion through the wall of a vein (where one or more orifices no longer reside in the target vessel). This video illustrates this technique: https://www.youtube.com/watch?v=77hS_2Evwjs&t=1s.

Chest X-ray or fluoroscopy is then used to confirm the position of the distal CVC in order to minimise longer term complications such as vessel wall erosion or atrial rupture. Real time ECG guidance may be incorporated, however the need for specialised equipment limits the utility of this tool. Table 2, adapted from Ho et al[39], summarises this process.

Table 2. Insertion process for CVC. Adapted with permission from Ho et al[39].

Step during CVC insertion	Prevention strategy	Rationale
Identification of target vessel	Position: ▪ Trendelenberg. ▪ Avoid neck rotation >45 degrees. Use real-time 2D ultrasonography to identify anatomy of target vein and surrounding structures.	Identify anatomical variations and relative position of carotid artery.
Accessing the vein	Real-time ultrasound imaging to follow needle tip during insertion, and guide needle angulation and depth: 1st line – cannula. 2nd line – needle.	Minimise risk of arterial puncture. Cannula will not perforate a vein if accidentally moved. Needle may be technically less challenging to insert for inexperienced operators.
Guidewire insertion	Use pincer grip to immobilise needle at insertion site while bracing the medial aspect of the steadying hand on the skin surface. Advance guidewire gently, stop if resistance.	Minimise inadvertent needle movement and subsequent displacement from target vein.

Step during CVC insertion	Prevention strategy	Rationale
Two step verification of venous location	Ultrasound confirmation of venous guidewire position at least 5-10cm distal to insertion point. Column manometry: insert access cannula over guidewire, remove guidewire, perform column manometry via sterile tubing, re-insert guidewire. Consider blood gas analysis. Transoesophageal echo or fluoroscopy may be utilised where available.	Minimise risk of inadvertent through and through guidewire insertion into an adjacent artery. Confirm venous wire placement prior to vessel dilation.
Vessel dilation	Anchor guidewire appropriately during introduction and removal of dilator. Ensure free movement of guidewire during advancement of dilator. Rotate dilator during advancement.	Avoid inadvertent withdrawal of guidewire from vein into dilator and subsequent damage to posterior wall of vein. Avoid impingement of guidewire on posterior wall of vein.
CVC placement check	Check all lumens of CVC aspirate and flush freely. Chest X-ray or fluoroscopy.	Detect inadvertent CVC insertion through wall of vein (where one or more orifices no longer reside in target vessel). Determine position of distal CVC to minimise longer term complications, for example, vessel wall erosion, atrial rupture.

MANAGING ARTERIAL INJURY

Inadvertent arterial injury should be suspected in any case where there is:

- Excessive bleeding during insertion of the guidewire or introducer.
- Retrograde flow within catheter/infusion sets.
- Activation of high-pressure alarms on infusion pumps.
- Abnormal catheter passage on chest x-ray.
- Arterial waveform upon pressure transduction.

Needle puncture

Removal of a small 22- or 25-gauge needle from a carotid artery, with application of pressure to prevent haemorrhagic complications, is a common management approach that is likely inconsequential in the majority of cases[8]. Many cases are likely underreported in both the patient's medical record and in the literature. Complications of this approach appear infrequent, with few reports of major morbidity. External compression for 5 to 10 minutes, with clinical assessment of bleeding and haematoma, followed by appropriate imaging to exclude significant complications is suggested. Postoperative embolic stroke has been described in patients with significant carotid atherosclerotic disease whose carotid artery puncture under general anaesthesia was managed with removal and compression. Following a literature review and case series, Guilbert et al[8] suggest postponing elective surgery for certain patients, such as those with carotid atherosclorotic disease, more than one arterial puncture, or in the presence of haematoma, with 24 hour neurological follow up.

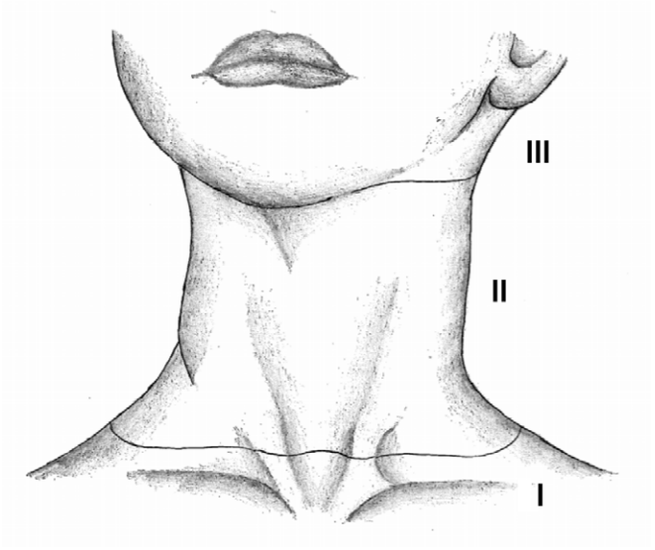
Arterial catheterisation

While diligent use of ultrasound guidance and pressure monitoring should minimise the incidence of inadvertent arterial catheterisation, knowledge of the appropriate management of such a complication is vital. Options include:

- Removing the catheter and applying pressure ("pull and pressure").
- Direct surgical repair.
- Endovascular repair.

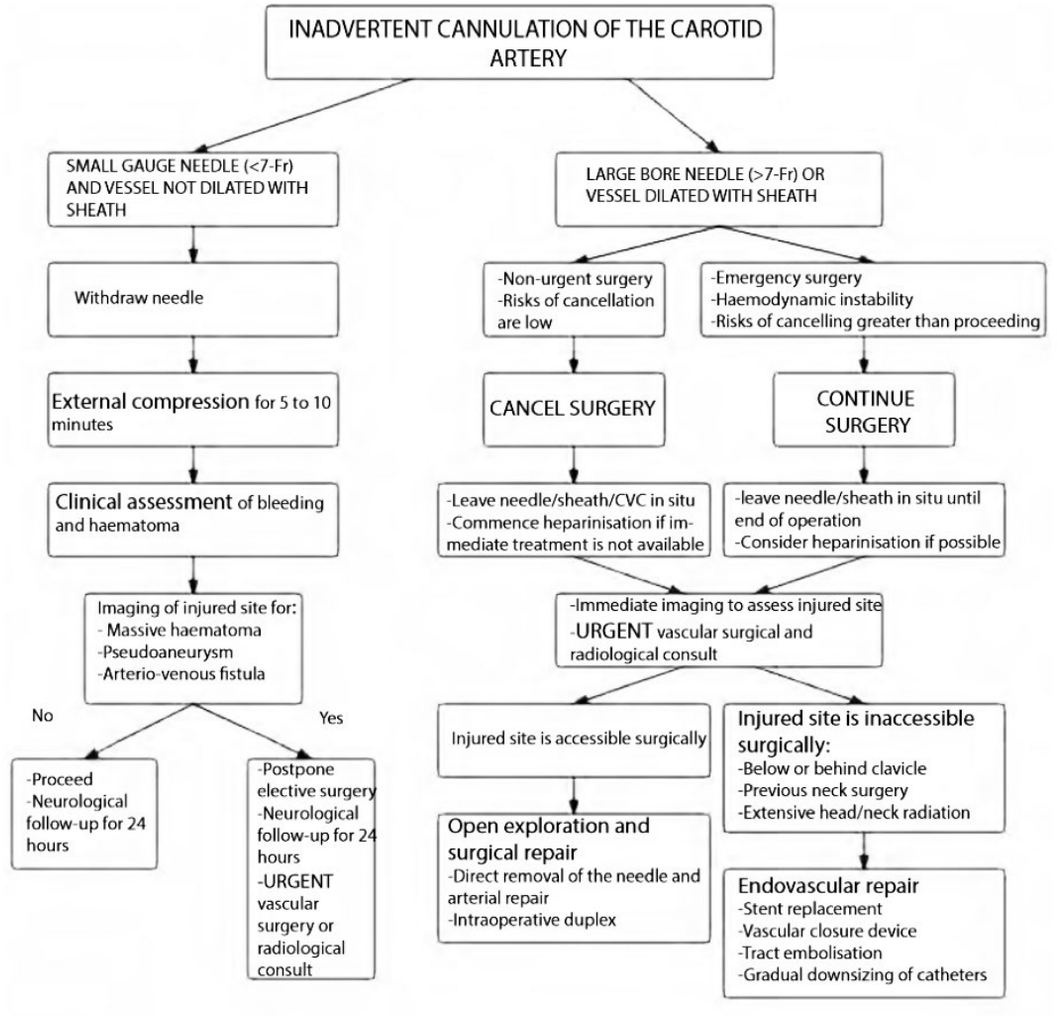
Management will depend on patient, anaesthetic and surgical factors, including insertion site, catheter size, clinical setting, presence of arterial disease or thrombus, anticoagulation status and patient stability. Immediate removal of an accidental arterial catheter can result in uncontrolled haemorrhage, pseudoaneurysm and arteriovenous fistula formation, particularly in the anticoagulated patient[21]. The "pull and pressure" approach, using direct pressure or a vascular closure device, may be reasonable in the event of femoral artery cannulation, as would occur following deliberate arterial cannulation for coronary angiography or similar interventional procedures. This approach is problematic for the carotid and subclavian arteries, where effective compression cannot be achieved safely. Studies demonstrate that leaving an arterial catheter in place, with prompt repair, carries less mortality and morbidity than catheter removal with pressure[8,40]. The trauma classification of the zones of the neck, by Monson et al[41], is utilised to guide surgical management (see Figure 4). This divides the neck into three anatomical regions: zone I extends from the base of the neck to 1cm above the clavicle, zone II is the segment from 1cm above the clavicle to the angle of the mandible, and zone III extends from the angle of the mandible to the base of the skull. Injuries in zone I require a sternotomy or endovascular approach for repair, whereas those in zone II may be repaired with direct pressure, open cutdown, or endovascular techniques.

Figure 4. Monson's classification of the neck. Zone I extends from the base of the neck to 1cm above the clavicle, zone II is the segment from 1cm above the clavicle to the angle of the mandible, and zone III extends from the angle of the mandible to the base of the skull.
Illustration by J Bath.



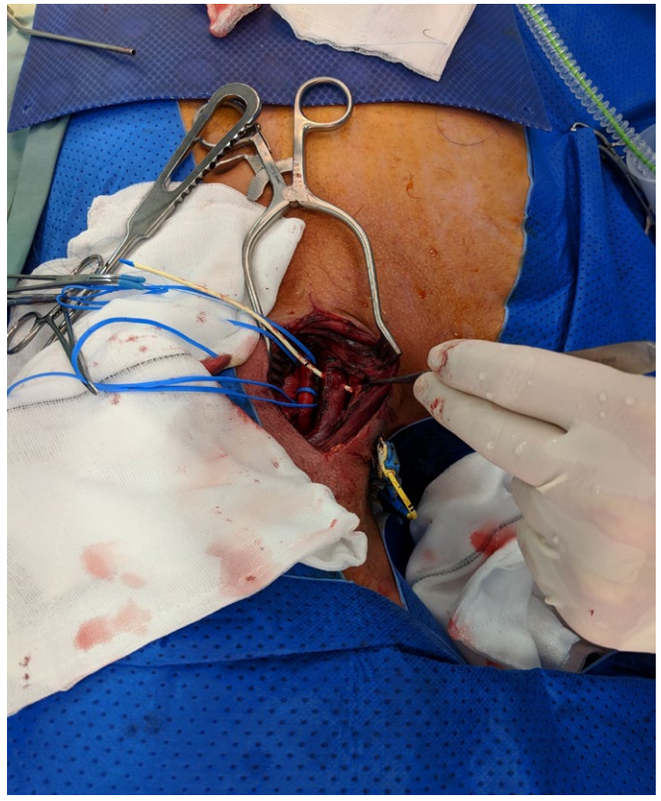
Guilbert et al[8] performed a literature review of 30 published cases of subclavian or carotid injury, and noted the pull and pressure technique to be associated with a high (47%) incidence of serious complications such as major stroke and death, whereas open surgical or endovascular repair was not associated with any additional morbidity or mortality. Similarly, in their own series of 13 patients with cervicothoracic arterial injury, all 5 patients managed with the pull and pressure approach had major complications, in comparison to no complications with open surgical (6 cases) or endovascular repair (2 cases). In an attempt to reduce further morbidity, Ho et al[39] have modified the algorithm proposed by Guilbert for management of inadvertent cannulation of the carotid artery, as detailed below (Figure 5).

Figure 5. Algorithm for the management of inadvertent catheterisation of the carotid artery.
Reproduced with permission from Ho et al[39].



Large arterial catheters (≥ 7F) should be left in place and their safe removal discussed urgently with a vascular surgeon. If the site is easily accessible surgically, such as the carotid artery, direct exploration, removal of the catheter and arterial repair are recommended (Figure 6). Conversely, if the site is not easily accessible surgically, such as a subclavian arterial injury, endovascular repair is recommended[42]. Management options in this scenario include stent placement, utilisation of a vascular closure device, tract embolisation or gradual downsizing of catheters. Under no circumstances should prolonged arterial cannulation be tolerated, and heparinisation should be considered in the event that immediate treatment is not possible.

Figure 6. Open repair of a through-and-through injury of the internal jugular vein into the carotid artery. Reproduced with patient consent.



MANAGING VENOUS INJURY

Given the variable severity of venous injuries, namely a small venous haematoma versus an expanding haemothorax or cardiac tamponade, management will depend on clinical assessment and appropriate imaging where required. A simple chest X-ray for all IJV CVCs is recommended to both assess CVC position, and exclude acute life-threatening injuries such as massive haemothorax. Early consultation with vascular surgery to guide management is advised.

Appendix 1. Central line insertion checklist

Pre-procedure	Hand hygiene ☐ Operator and assistant cleanse hands	☐
	Skin prep performed ☐ Chlorprep© (alcoholic chlorhexidine) 10.5mL adaptor used and prep allowed to dry	☐
	Aseptic technique ☐ Operator to perform surgical scrub ☐ Operator wearing hat, mask, sterile gown, sterile gloves ☐ Sterile drape covering patient's body ☐ Sterile cover for ultrasound probe	☐
During procedure	Ultrasound guidance for internal jugular vein insertions	☐
	Confirmation of venous placement of access needle or access cannula using a minimum of 2 methods ☐ Ultrasound confirmation of wire placement ☐ Column manometry ☐ Pressure transduction ☐ Blood gas	☐
	Guidewire removed	☐
	Vessel dilation ☐ Free movement of guidewire within dilator during advancement	☐
	Catheter secured and dressed with appropriate dressing ☐ All lumens of catheter aspirated and flushed ☐ Flat stopcock catheter caps placed on all lumens ☐ Catheter sutured in place ☐ Transparent bio-occlusive dressing applied with sterile technique	☐
Post procedure	Three step confirmation of catheter placement ☐ Ensure all lumens of CVC aspirate and flush freely ☐ Transduce brown (distal) lumen to ensure venous pressure ☐ Chest X-ray or fluoroscopy	☐
	Infusions connected to appropriate lumens ☐ Brown (distal) - CVP monitoring, bolus drugs ☐ Blue - vasopressors + inotropes ☐ White - vasodilators ☐ Grey (largest diameter) - fluids, miscellaneous drugs	☐
	CVC sticker placed in patient progress notes	☐

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Keep calm and know sepsis

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Dr Linden Martyr is an Anaesthetic Registrar who has been exposed to sepsis predominately in the emergency theatre and during his time in the ICU. Researching this topic has been a great opportunity to contribute to ANZCA's quality educational publications. He hopes that this work will be useful for anaesthetists in their role as perioperative specialists.

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EPIDEMIOLOGY

Sepsis presents a major global health challenge. An extrapolation of data from first-world countries estimates the global incidence of sepsis at 31.5 million cases, with 5.3 million deaths annually[1]. The World Health Organization (WHO) World Health Assembly adopted the "Improving the prevention, diagnosis, and management of sepsis" resolution in 2017, reflecting the increased awareness of sepsis and its global health burden[2].

However, the true incidence, mortality and morbidity of sepsis remains difficult to quantify. The variable definitions for sepsis, the lack of a "gold standard" diagnostic test, and growing emphasis on the prompt recognition and management of the condition, have led to marked heterogeneity in these rates and their trends over time[3,4].

In a study of more than 1 million patients in 171 intensive care units in Australia and New Zealand, the proportion of admissions to ICU for severe sepsis increased from 7.2% in 2000 to 11.1% in 2012. The absolute mortality of severe sepsis decreased linearly from 35% to 18.4% over the same period, an annual rate of absolute decrease of 1.3%[5].

The most common sources of infection leading to sepsis are the lung (65%), followed by the abdomen and bloodstream. The genitourinary tract, skin, and vascular access devices account for 5-15% each[6-8].

DEFINITIONS AND RECOGNITION OF SEPSIS

The term sepsis is derived from the ancient Greek word for "rotting flesh" and has been a recognised clinical syndrome since the time of Hippocrates[9]. In contemporary medicine, the meaning of the syndrome has been obscured by varied definitions for "sepsis", "septicaemia", "septic syndrome", and "septic shock".

In 1991, the American College of Chest Physicians and Society of Critical Care Medicine defined sepsis in a more "precise manner", with the introduction of the "Systemic Inflammatory Response Syndrome" (SIRS) criteria. These criteria reflected the understanding of sepsis as an exaggerated inflammatory host response. SIRS could exist in the absence of infection, for example in pancreatitis or following multi-trauma[10]. SIRS in the presence of infection was defined as sepsis, and sepsis in the presence of organ dysfunction was defined as "severe sepsis". "Septic shock" was defined as sepsis leading to hypotension despite adequate fluid resuscitation[10].

However, subsequent evaluation of the SIRS criteria found that it lacked both sensitivity and specificity for the detection of sepsis. A large observational study of Australian and New Zealand intensive care units found that 12% of septic patients did not have two or more SIRS criteria[11]. Further, the lack of specificity of SIRS was demonstrated by a finding that almost half of all hospital inpatients met SIRS criteria at some point during their hospital admission[12]. Although the limitations of the SIRS criteria were acknowledged when the definitions were revisited in 2001, an alternative was not put forward[13].

Sepsis was re-defined by the Third International Consensus Taskforce (Sepsis 3), in order to represent new understanding of its pathophysiology. It is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

The clinical diagnosis of sepsis now reflects an emphasis on organ failures and de-emphasises the need for SIRS criteria. To aid clinical characterisation, a change in SOFA score of 2 or greater was stipulated (where a previously healthy individual would have had a SOFA score of zero – see Table 1) to evaluate patients likely to have sepsis in ICU[14].

Table 1. Sequential (Sepsis-Related) Organ Failure Assessment Score[14].

	Score				
System	**0**	**1**	**2**	**3**	**4**
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $x10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (µmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (µmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

For patients outside ICU, a simpler system that does not require laboratory investigations was introduced to risk stratify patients suspected to have sepsis. Quick SOFA (qSOFA) looks for any 2 of systolic blood pressure less than 100mmHg, altered mentation (GCS<15) or respiratory rate 22/min or greater to prompt clinicians to investigate for organ dysfunction or escalate treatment for infection.

Septic shock, which has a mortality of 40%, is now defined as sepsis causing persistent hypotension (requiring vasopressors to maintain MAP >65mmHg) AND having a serum lactate level >2mmoL/L despite adequate volume resuscitation[14].

Notwithstanding the new definitions for sepsis some ambiguity remains. Despite the definition of sepsis being predicated on infection as a trigger, the taskforce specifically did not examine definitions or types of infection[14]. For example, some would consider malaria to be a cause of sepsis, while others would not[4]. Furthermore, the lack of ability to monitor lactate may also hinder diagnosis of septic shock in low resourced environments[16].

With the increasing use of electronic medical records, the traditional methods of history, examination and investigations have been supplemented by automated algorithms to aid screening for patients with sepsis. Though several tools have been developed much work is needed to improve them for clinical use. For example, a continuously running algorithm known as St John's Sepsis Agent (developed by Cerner, the electronic medical records corporation) when compared to a twice daily nurse administered Sepsis Screening Score detected significantly fewer septic patients[15].

PATHOPHYSIOLOGY

The inflammatory response

The model underpinning sepsis pathophysiology has historically been that of an unchecked pro-inflammatory state[17]. However, the failure of anti-inflammatory therapies for the treatment of sepsis has questioned this theory[18]. It is now understood that sepsis represents a concurrent interplay of both pro-inflammatory and anti-

inflammatory states[19]. The magnitude of the initial inflammatory response (which generally tends to predominate early in sepsis) is also influenced by factors such as bacterial load, virulence, host genetics, and co-morbidities, such that the anti-inflammatory state may predominate in the elderly[20].

The host response to infection is triggered by the recognition of microbial infection or tissue damage by pattern recognition receptors (PRRs) on antigen presenting cells (APCs). Microbial infection is detected by the presence of pathogen associated molecular patterns (PAMPs), and tissue damage is represented by the release of intracellular proteins and mediators from dying cells, termed "alarmins", or damage associated molecular patterns (DAMPs)[21,22].

The most notable PRRs in sepsis are Toll-like receptors (TLRs), which recognise a range of bacterial cell-wall lipoproteins and lipopolysaccharides, as well as fungal-wall elements and bacterial and viral nucleic acids[23]. Once bound, TLRs induce the release of several pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukins (IL-1β, IL-2, IL-6, IL-8) and interferon-γ. This may lead to a dysregulated cytokine response ("cytokine storm") resulting in excessive, damaging levels of inflammation. The majority of the early deaths in sepsis are as a result of this response[19,23,24].

Co-stimulatory molecules (CSMs) are proteins expressed on the cell surface of APCs and are key factors in the modulation of T-cell activity. The most prominent CSMs are CD80 and CD86 and bind to the CD28 or CTLA-4 receptors on T-cells. Binding of the CD28 receptor leads to T-cell activation and proliferation[23]. The significance of this receptor site was demonstrated in a clinical trial, in which healthy humans infused with a CD28 monoclonal agonist antibody developed a severe inflammatory response and clinical symptoms typical of sepsis[25].

Separate anti-inflammatory mechanisms occur concurrently with the above, leading to a degree of immunosuppression which is often recognised later in the course of sepsis[19,23]. Immunosuppression is caused by two mechanisms. Firstly, apoptosis of lymphocytes and dendritic cells lead to a direct limitation of the adaptive and innate immune systems[19,20,26]. Secondly, the uptake of apoptotic cells by phagocytes induces T-cell anergy, and diverts the CD4 T-cell response from pro-inflammatory (T_h1), to anti-inflammatory (T_h2)[17,19,20,24]. This results in a phase of "immune paralysis" in which the host is susceptible to viral re-activation, or secondary nosocomial organisms which may not have been pathogenic in an immunocompetent host (for example, Enterococcus spp., Acinetobacter spp., or candida spp.)[24,27].

Coagulopathy

The coagulopathy of acute sepsis is driven by an upregulation of procoagulant mechanisms, and down regulation of anticoagulant mechanisms[28]. Firstly, the pro-inflammatory phase of early sepsis leads to the expression of tissue factor on circulating mono-nuclear cells, leading to systemic activation of coagulation[29]. The activation of the coagulation system serves to activate platelets. Platelets may also be activated in the presence of bacteria, either directly due to the effects of bacterial endotoxins, or indirectly by binding to plasma proteins to form complexes that become ligands for platelet receptors[30].

Anticoagulant mechanisms are down-regulated by the consumption and degradation of tissue factor pathway inhibitor (TFPI), a reduction in the activation of protein C, and both the increased consumption, and down-regulated synthesis of antithrombin[28].

This pro-coagulant state may lead to massive thrombin formation and fibrin deposition in the microvascular bed. This is thought to be a key factor in the development of multi-organ dysfunction syndrome (MODS) in sepsis[31]. Consumption of platelets and clotting factors may also lead to disseminated intravascular coagulation (DIC), characterised by micro thrombosis and haemorrhage[28].

Endothelial injury

The release of inflammatory mediators in sepsis results in oxidative stress and shedding of the endothelial glycocalyx (EG), a structure consisting of proteoglycans, glycoproteins and soluble proteins on the endothelial surface[32]. Alterations in the composition of the EG following an infectious insult is one of the earliest features of sepsis[33]. EG shedding may be of prognostic significance, with evidence that blood levels of glycocalyx components are higher in non-survivors than survivors of septic shock[34].

The EG plays a key role in the regulation of haemostasis and vascular permeability, as well as the vasomotor response to fluid shear stress through the stimulation of endothelial nitric oxide synthase (eNOS). EG damage leads to increased vascular permeability, capillary leakage, and tissue oedema[32,35,36]. When this process affects the permeability of the capillaries of the lung, it leads to the accumulation of protein-rich fluid in the interstitial spaces, arterial hypoxemia and reduced pulmonary compliance consistent with acute respiratory distress syndrome (ARDS)[37].

Microcirculatory dysfunction

The microcirculation refers to vessels of less than 100µm in diameter. Microcirculatory dysfunction results from the heterogeneous dysregulated expression of inducible nitric oxide synthase (iNOS) in different vascular beds, resulting in hypoperfusion of those areas which are iNOS deficient[36].

These alterations in microvascular blood flow are a proposed mechanism for the development of sepsis-associated acute kidney injury (SA-AKI)[38]. While SA-AKI was traditionally conceptualised as an ischaemic insult, secondary to reduced systemic vascular resistance and organ hypoperfusion[39], this notion has been challenged by growing evidence that AKI can develop in the context of preserved or increased renal blood flow[40].

Furthermore, excessive NO production by iNOS is responsible for a loss in adrenergic sensitivity and vascular tone in the arteriolar and venous beds, and in addition to relative vasopressin deficiency is believed to be the cause of the vasoplegic shock characteristic of sepsis[36,41].

DETECTION OF PATHOGENS CAUSING INFECTION

Culture-based techniques are the gold standard for detecting infectious agents as they are cheap and widely available. However, they are slow and take 24-48 hours to yield results. They are prone to false positives due to contamination and are not sensitive after antimicrobial drugs have been administered. Serological tests have been used for infections like hepatitis, dengue and HIV but are also limited by false positives as well as false negatives if done too early.

Pathogen detection can also be performed using direct histology and gram stains as well as by using molecular methods which in turn may be based on nucleic acids technology or detection of pathogen related antigens. Nucleic acid technology refers primarily to the use of Polymerase Chain Reaction (PCR) assays that can be performed on body secretions, blood or tissues to detect pathogens more rapidly than culture-based techniques. PCR uses oligonucleotide primers to amplify a specific pathogen gene that is then detected using electrophoresis with the aid of a dye or ultraviolet light. PCR assays have been developed for specific pathogens, or to detect a broad range of bacteria and fungi. For example, PCR assays have been reported to have a sensitivity of 72% and specificity of 91% to detect candidaemia. Non nucleic acid-based methods rely on detecting pathogen related antigens using labelled antibodies in techniques like Enzyme Linked Immunosorbent Assay (ELISA). Galactomannan assays for example were 71% sensitive and 89% specific for proven cases of invasive aspergillosis[42].

BIOMARKERS OF SEVERITY OF SEPSIS

Biomarkers such as white cell count (WCC), lactate, C-reactive protein (CRP) and procalcitonin (PCT) are tests that have been used to assess the severity of sepsis rather than to diagnose sepsis. The WCC lacks specificity and sensitivity as a standalone test. Other WCC measures such as the monocyte distribution width (MDW) have been validated as markers of severity rather than as a diagnostic test[43].

Lactate elevation is a marker of tissue hypoperfusion and elevated serial measurements (which can now be done transdermally) have been associated with mortality in patients with sepsis but has not been specific nor sensitive for diagnosis of sepsis[44].

CRP is an acute phase protein produced by the liver in response to rising IL-6 levels and acts as a pattern recognising protein for the innate immune system, aiding in complement binding and phagocytosis of pathogens and inactivation of toxins. CRP has a half-life of 19 hours and its levels begin to rise 4 to 6 hours following an inflammatory stimulus doubling and peaking around 24-72 hours after the inflammatory stimulus[45]. Though this is sensitive, it is not specific for infections as several non-infectious inflammatory states can also cause it to rise. It may thus be more useful to track the course of infection or inflammation and its response to therapy over time[46].

PCT is the most studied sepsis biomarker and the only one that has been implemented in sepsis guidelines. It is the prohormone for calcitonin and is released into the blood in inflammatory states particularly due to bacterial infection. However, it too cannot be used as a single diagnostic test for sepsis as elevations can occur after trauma or major surgery. PCT becomes detectable after 3-4 hours and peaks between 6-14 hours after a proinflammatory stimulus and has a long half-life of 25-30 hours[47]. Furthermore, while it may be markedly elevated in bacterial and parasitic infections compared to viral infections, it is not recommended for distinguishing between bacterial and candida sepsis due to limited supporting evidence[48]. In a pooled analysis of several studies, it was found to have a sensitivity of 77% and a specificity of 79% to distinguish sepsis from a non-infectious inflammatory response[49]. The biggest potential for PCT is in reducing duration of antibiotics for presumed bacterial infection especially in the settings of primary care[50], emergency departments[51] and in ICU[52].

However, caution should be exercised in using PCT to intensify antibiotics in ICU patients as the Procalcitonin And Survival Study (PASS) suggested no benefit and possibly increased morbidity[53].

"OMICS"-BASED PERSONALISED APPROACH TO SEPSIS

The complete sequencing of the human genome in 2003 enabled detection and creation of large datasets of multiple biomarkers (for example, DNA, RNA, proteins and metabolites) which can be correlated with states of health and illness using advanced computational and statistical tools to create signature biomarker profiles for diseases from populations of interest. This biomarker big data-based approach to studying biological systems has been termed "omics" wherein genomics refers to study of DNA, transcriptomics to study of RNA, proteomics is of proteins and metabolomics is of metabolites. As sepsis is a syndrome of multiple pathophysiological processes, interest has evolved to using multi-analyte panels of such biomarkers to detect infectious agents, distinguish sepsis from SIRS and better characterise and manage the host response in sepsis[54]. For example, Davenport et al discovered two sepsis response profiles (known as SRS1 and SRS2) after gene expression analysis on 265 ICU patients with community acquired pneumonia. They noted that 41% of patients with the SRS1 response also had an immunosuppressive phenotype with higher mortality[55]. This kind of profiling may herald more personalised treatment of sepsis, in contrast to the current standard "one size fits all" approach.

MANAGEMENT OF SEPSIS

As sepsis is defined by organ failures due to a dysregulated host response to infection, source control and anti-infective therapy must be combined with strategies to support failing organs and manage the dysregulated host response. The evidence for the strategies to manage sepsis will be covered in this section and recommendations will be listed along with references to the Surviving Sepsis Campaign (SSC)[56,57].

Source control

- Source control as early as clinically appropriate is likely associated with reduced mortality.

Source control where possible is essential but has been poorly studied. In 2016 Martinez and her colleagues published a prospective observational study on the outcomes of patients who were amenable to source control versus those who were not. Despite patients in the source control group being older, sicker by organ failure indices and having less compliance with the SSC bundles, they had lower ICU and hospital mortality[58]. Another prospective study in 44 German ICUs of 1011 patients with severe sepsis or septic shock showed that source control beyond 6 hours of organ failure was associated with higher 28-day mortality (40.7%) than earlier source control (26.7%)[59].

Treating the infection

Anti-infective therapies

- Effective empirical antimicrobials should be instituted as soon as possible and likely reduce mortality and progression of sepsis.
- Blood cultures should be collected prior to antibiotics, but antibiotics should not be delayed in order to obtain blood cultures.

Antibiotics are the sole method of effectively treating the cause of sepsis in patients who do not have a surgical source. The SSC recommends antibiotic therapy within 1 hour of recognition of sepsis or septic shock[60]. An observational study on patients with septic shock showed a significant increase in mortality of 12% for every hour effective antibiotics were delayed from onset of septic shock. This was regardless of whether the pathogens were bacteria or fungi, acquired from the community or nosocomial[61]. Several subsequent analyses have suggested similar findings[62-65]. In contrast to these studies, a systematic review involving 16,178 patients pooled from 11 studies found no mortality benefit from administering antibiotics within 3 hours of ED triage or within 1 hour of recognising shock[66]. Despite these mixed results, prompt administration of antibiotics remains central to management of sepsis as evaluation in a prospective randomised controlled study will not be ethically feasible. To optimally manage sepsis, blood cultures should be sent before antibiotics to maximise the detection of pathogens and their sensitivities[67], but antibiotics should not be delayed to obtain cultures[68].

Supportive therapies

Fluids

- Starch based fluids are associated with renal impairment.
- Using albumin may result in less administered volume, but this has not translated into difference in patient outcomes.

- Both crystalloid and albumin are safe resuscitation fluids, with a possible mortality benefit towards albumin in severe sepsis.

Though there are a large number of fluids to choose from to resuscitate septic patients, the results of clinical trials provide the best evidence to guide management.

A subgroup analysis of a prospective, blinded and randomised trial (SAFE study) found that administration of albumin compared to saline did not impair renal or other organ function and may be associated with a decreased risk of death in patients with severe sepsis[69]. The renal effects of hydroxyethyl starch (HES) were studied in a randomised trial by Myburgh et al in patients admitted into the ICU. Although this paper did not only include patients with sepsis, there was increased serum creatinine, reduced urine output and increased need for renal replacement therapy in the HES group[70]. In 2014 Caironi et al conducted a randomised trial on the use of albumin 20% and crystalloid versus crystalloid alone with albumin targets of 30mg/dl in severe sepsis. The albumin group received less fluid overall with cumulative fluid balance closer to neutral despite having higher mean arterial pressures, lower heart rates and lower scores for the cardiovascular section of the SOFA score (meaning less vasopressors). Mortality at 28 and 90 days were not significantly different[71].

Vasopressors

- Noradrenaline has the most robust research behind it as a first-line agent.
- Dopamine is associated with increased arrythmias.
- Adrenaline is as effective and safe as noradrenaline but can increase lactate, heart rate and affect glycaemic control.
- Vasopressin and adrenaline are safe second line agents.

The predominant vasopressors included in current RCTs regarding sepsis management are noradrenaline, dopamine, adrenaline and vasopressin[72-75]. The largest trial was by De Backer et al and compared dopamine to noradrenaline and found no significant differences in mortality. However, the dopamine group had significantly more arrythmias[72]. This mirrors the results of a smaller RCT by Patel et al[73]. An RCT by Myburgh et al compared noradrenaline and adrenaline in critically ill patients. In the sepsis subgroup, there were no difference in time to achieve MAP goals or vasopressor free days. However, the adrenaline group had higher rates of tachycardia, lactatemia and a transient in insulin requirement[74]. A trial by Annane et al showed no difference between adrenaline vs noradrenaline and dobutamine in efficacy and safety in septic shock[75].

Second line agents

In the VASST trial, patients with septic shock on noradrenaline received a second line agent; which was either vasopressin or additional noradrenaline. There was no difference in mortality, rates of myocardial infarction, cardiac arrest, life-threat arrythmias, mesenteric ischaemia, cerebrovascular accidents, digital ischaemia or hyponatraemia[76]. A post hoc analysis found lower rates of progression to renal failure and less RRT in patient treated with vasopressin as a second line vasopressor versus noradrenaline[77]. More recently in the VANISH trial, the effects of vasopressin versus norepinephrine on incidence and severity of acute kidney injury in septic shock was investigated. There was no observed difference in rates of renal failure, requirement for RRT or mortality in all subgroups[78].

Inotropes

- Dobutamine has the most clinical data suggesting safety for use in sepsis.

Myocardial dysfunction is a common complication of sepsis and may be associated with increased mortality[79]. There is a lack of high-powered RCTs that compare the effects of different inotropes in sepsis[80,81].

From the small RCTs exploring the use of Dopexamine there is no strong evidence of any benefit compared with adrenaline or dopamine[82,83]. From the larger RCTs, there does not seem to be an increased incidence of serious adverse events with adrenaline compared with noradrenaline alone or noradrenaline and dobutamine[74,75].

The role of the inodilators levosimendan and milrinone in sepsis remains unclear. Small trials by Morelli et al and Memis et al suggest increased tissue perfusion with levosimendan over dobutamine[84-86]. The LeoPARDS trial, the largest RCT on levosimendan in sepsis studied 519 patients with septic shock who were randomised to receive levosimendan or placebo with standard vasopressors to maintain MAP of 65-70mmHg. The patients in both groups received other inotropes as necessary. There were no significant differences in organ dysfunction or mortality[87].

Transfusion

- A transfusion target of 70g/L is not inferior in septic shock patients.

In 2014 the TRISS study researchers compared conservative and liberal haemoglobin targets of 70g/L and 90g/L respectively in patients with septic shock. There was no difference in mortality or other measured outcomes in patients up to 90 days, including pre-defined subgroups of cardiac disease, older age and patients with more or less severe physiological derangement. As expected, the conservative group received far less transfusions[88].

Early goal directed therapy

- It is clear that patients with sepsis and septic shock may require organ support, but early aggressive and invasive haemodynamic management does not alter mortality or morbidity.

The term early goal-directed therapy (EGDT) is used for the institution of immediate monitoring of haemodynamics and surrogates of perfusion as well aggressive management of these variables (including many of the interventions described above) in patients with sepsis or septic shock. The Rivers trial in 2001 showed a mortality benefit in patients randomised to receive EGDT vs standard therapy in a single centre. The protocol included endpoints of CVP, MAP and SvO_2 to guide therapies over a 6-hour period in the emergency department prior to admission for inpatient team management. CVP of 8-12mmHg was achieved with crystalloid boluses followed by MAP of 65-90mmHg with vasoconstrictors or vasodilators. SvO_2 >70% was targeted with RBC transfusions to achieve a haematocrit >0.3 followed by dobutamine if needed. If it could not be achieved with these interventions, sedation and mechanical ventilation were instituted.

Subsequently, the PROCESS, PROMISE and ARISE trials which were multicentre RCTs conducted in the United States, United Kingdom and Australia and New Zealand respectively did not reproduce this mortality benefit[89-91]. Ultimately, there were significantly increased costs associated with EGDT without any significant benefit.

Steroids

- Hydrocortisone reduces vasopressor duration and may reduce time in ICU in patients with septic shock.
- Hydrocortisone and fludrocortisone may reduce mortality, shorten the length of organ failure and the duration of mechanical ventilation.

The rationale for steroids is based on the relative adrenal insufficiency or glucocorticoid resistance that exists in sepsis, and the improvement in vasopressor response with steroids in patients with septic shock[92]. The 2002 Annane trial on the effects of hydrocortisone with fludrocortisone in septic shock found that there was a significant survival benefit at 28 days in the treatment group, but no difference at 1 year. Patients with documented adrenal insufficiency had a significantly shorter duration of vasopressor requirement with treatment. No differences in adverse events were observed[92]. Sprung et al in an RCT on the use of corticosteroids in septic shock subsequently found there was no difference in mortality at 28 days. Shock reversed more rapidly in patients receiving steroids regardless of response to the short synacthen test[93].

The recent ADRENAL trial used a hydrocortisone infusion and did not integrate the synacthen test into its protocol. It confirmed no mortality benefit, but also found faster resolution of shock. The hydrocortisone group received significantly fewer red cell infusions. There were no other differences in outcomes. However, the treatment group did have higher rates of adverse events, 1.1% versus 0.3% made up of: hyperglycaemia; hypernatraemia; hyperchloraemia; hypertension; bleeding; encephalopathy; leucocytosis; myopathy; septic arthritis; ischaemic bowel; circulatory shock; and thrombocytopaenia[94]. In the same year, Annane et al published an RCT of hydrocortisone plus fludrocortisone in septic shock. Patients in the treatment group had significantly lower 90-day mortality and were more often discharged from ICU and hospital alive. They had shorter durations of mechanical ventilation, vasopressor therapy and achieved SOFA scores <6 more rapidly. This translated to more vasopressor free and organ failure free days at 28 days. In terms of adverse events the treatment group did not have higher rates of superinfection or gastrointestinal bleeding but did have more hyperglycaemia[95].

Immunotherapy

- Sepsis is a complex interplay between both pro-inflammatory and anti-inflammatory aspects of the immune response.
- Patients frequently become immunosuppressed with widespread apoptosis and/or reduced effectiveness of white blood cells. The resulting “Immunoparalysis”, may contribute to adverse outcomes through increased susceptibility to oppurtunistic infections.
- Inflammatory mediators like IL-7, IL-15, IFN-gamma positively augment the immune system improving white cell counts and/or effectiveness.
- Currently there are no conclusive human trials on immunomodulatory drugs in sepsis.

The expressed phenotype of sepsis is varied and can be hyper-immune or immunosuppressed[56,57]. Novel treatments aiming to reduce inflammation in sepsis have been largely unsuccessful[96-100]. There are a number of endogenous molecules that may have potential benefit; IL-7, IL-15, IFN-gamma, Fms-like Tyrosine

kinase-3 ligand and Chimeric Antigen Receptor. Despite having different mechanisms and different effects on different immune cell populations, they tend to have the overall effect of bolstering the immune response. Immunostimulatory monoclonal antibodies that target PD-1 such as nivolumab and pembrolizumab are an area of interest, but there are no large RCTs of these drugs in sepsis. Of all the potential immunotherapies mentioned, only IL-7 has had been tested in human sepsis. In a small RCT there was an improvement in CD4 and CD8 cell populations in the IL-7 treatment group[101]. These therapies are still a way off clinical use and given the varied response of patients to sepsis, immunotherapies need to be tailored to the specific patient.

Anticoagulation in sepsis

- Anticoagulation in sepsis is safe, but there is no convincing evidence of mortality benefit.

Disordered coagulation is common in sepsis with occult disseminated intravascular coagulation (DIC) occurring in up to 30-50% of patients. Anticoagulation has been considered as a therapeutic to not only reduce disordered coagulation, but to reduce the inflammatory signals that result from the coagulation cascade. Additionally, patients with sepsis often have risk factors for venous thromboembolic disease[102,103]. In a study on the use of prophylactic low molecular weight heparin (LMWH) or unfractioned heparin (UH) vs placebo in patients with sepsis who were receiving activated protein C, there was no significant difference in adverse bleeding events between heparin and placebo. This would indicate that heparin is safe in sepsis, despite the fact that activated protein C in no longer licensed for use in sepsis[103]. The HETRASE study on the use of 12,000 units/day of UH versus placebo in sepsis found no significant difference in bleeding events between the groups. However, there were also no significant differences in outcomes including hospital stay, mortality or organ dysfunction[102].

Other potential therapeutic targets include thrombomodulin and antithrombin. A small multicentre RCT on the use of antithrombin replacement in sepsis with DIC showed a significant improvement in resolution of DIC without difference in SOFA scores or mortality[104].

In a study of 741 patients with sepsis and DIC randomised to receive either thrombomodulin or placebo, there were no significant differences in mortality or resolution of DIC. However, the suggestion of efficacy has resulted in further development of this agent for future trials[105]

CONCLUSION

Sepsis is a global health challenge resulting in significant morbidity and mortality in both developed and developing countries. Current definitions focus on the dysregulated immune response and associated organ failure. Management includes early diagnosis, source control when possible, early targeted antimicrobial therapy and supportive measures. Personalised and targeted approaches to management may soon become possible due to the availability of whole genome sequencing.

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Midodrine and its potential role in postoperative hypotension

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INTRODUCTION

The impact of perioperative haemodynamics on the postoperative outcomes of patients undergoing non-cardiac surgery, both in the acute and long-term context, is the subject of considerable discussion in the current literature[1,2]. Perioperative hypotension is not only common[3], but is widely reported to be associated with both significant morbidity and mortality[4–8]. Intraoperative hypotension is usually rapidly detected and treated by the anaesthetist. However, recent studies have identified that the persistence of hypotension into the postoperative period is more common than previously appreciated, yet frequently missed during routine ward care[3,7,9]. While a causal relationship between postoperative hypotension and adverse outcomes is yet to be clearly defined, it is likely to be at least partially contributory. Postoperative hypotension may therefore represent an important *modifiable risk factor*. Hence, its prevention, or early detection and treatment, has the potential to improve patient outcomes.

The early identification and correction of the causes of postoperative hypotension, such as hypovolaemia or excessive sedation, are clearly indicated. However, there are limited strategies by which we may seek to prevent the occurrence of postoperative hypotension, or to treat it once it has developed. Midodrine, an oral a_1-adrenoceptor agonist, has been demonstrated to be well tolerated and clinically effective as a treatment for chronic symptomatic orthostatic hypotension[10-14]. Due to its ability to increase both venous return and systemic vascular resistance (SVR), it may offer a new pharmacological solution to the problem posed by postoperative hypotension. Premedication with midodrine to prevent perioperative hypotension has not been previously reported, but could offer the potential additional benefit of mitigating the development and severity of intraoperative hypotension. However, due to its ability to mask intraoperative haemorrhage and other pathophysiological processes, stringent use is necessary. This article will explore the potential role of midodrine exclusively in the postoperative period.

POSTOPERATIVE HYPOTENSION: A POTENTIAL TARGET FOR MIDODRINE

Pathophysiology of perioperative hypotension

Perioperative hypotension is often multifactorial and incorporates anaesthetic, surgical and patient risk factors:

Anaesthetic factors. Anaesthetic agents and techniques can produce hypotension through a broad range of mechanisms. Sympathetic depression, vasodilatation, impaired baroreceptor reflexes and bradyarrhythmias may all account for its occurrence[15]. Orthostatic hypotension and autonomic dysfunction are additionally observed, particularly in the early postoperative period[16,17]. Excessive postoperative sedation, either due to opioid excess, or the activity of residual anaesthetic agents, may also contribute. Persistent sympatholysis from neuraxial techniques may compound this hypotension or cause it de novo. Despite adequate resuscitation, patients may still require short term haemodynamic support until these effects have fully resolved. These anaesthesia factors can interact with surgical factors, such as hypovolaemia, and patient factors, such as myocardial disease, to cause prolonged postoperative hypotension.

Surgical factors. The surgical stress response during and after major surgery is associated with a systemic inflammatory response syndrome (SIRS)-like reduction in SVR, associated with pro-inflammatory cascade systems, and may be compounded by reduced intravascular volume from prolonged fasting times, bleeding and third space fluid losses[18].

Patient factors. Patients with conditions such as diabetic autonomic neuropathy, impaired systolic or diastolic cardiac function and valvular disease may be especially prone to postoperative hypotension, due to inadequate

augmentation of cardiac output to match the increased physiological demands of the perioperative period. Concomitant administration of antihypertensive medication, such as angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers and ß-blockers, may also contribute to the development of perioperative hypotension, which may be persistent and poorly responsive to conventional therapies[8,19,20].

Why is the detection and correction of postoperative hypotension important?

Multiple studies have demonstrated an association between hypotension during non-cardiac surgery and increased mortality[7,21], acute kidney injury[22,23], myocardial injury[24-26], stroke[27] and postoperative delirium[6]. However, it is unknown what constitutes an appropriate and safe blood pressure target range for the intra- and postoperative periods[28]. It is also uncertain how much causality can be attributed to hypotension[29]. Hypotension is the most common trigger for repeated vital-sign assessment on medical and surgical wards[30]. It is also one of the most common reasons for transfer from the ward to the intensive care environment[31,32]. However, while postoperative hypotension is common, it is frequently missed[3].

Most life-threatening ward complications, particularly following surgery, are preceded by abnormalities in vital signs that can occur quite some time prior to the event, and remain persistently untreated[33]. Delayed detection of haemodynamic perturbations can preclude timely escalation and appropriate intervention[34,35]. Prevention of "failure to rescue", defined as patient death after one or more potentially treatable complications, has emerged in the literature as an important outcome for quality improvement and safety[36]. This incorporates both early recognition of complications, such as clinically significant hypotension or myocardial ischaemia, and rapid escalation of treatment, which have the combined ability to improve patient outcome[37].

The definition selected for hypotension threshold alters both the reported incidence of hypotension[38], and its associated complications[39]. Employing percentage change from a patient's preoperative baseline, such as 20% or 30%, carries equivalance with absolute thresholds, which are independent of preoperative values[22], in terms of reported incidence. These are the two most commonly used approaches in the current literature. Several studies have identified that the duration of intraoperative hypotension is an independent risk factor associated with increased mortality, cardiac morbidity and renal injury[40]. During the intraoperative period, an association with organ injury has been demonstrated to occur once a patient's mean arterial pressure (MAP) decreases to less than 80 mmHg for more than 10 minutes[41]. As the MAP threshold used to define hypotension is progressively lowered, the duration spent below that threshold associated with end-organ injury appears to shorten, such that any episode of MAP less than 55 mmHg appears to be deleterious, irrespective of duration[41].

Intraoperative blood pressure is frequently monitored and appropriate interventions rapidly instituted when it decreases below arbitrary values, depending upon the individual anaesthetist and institution. This is in stark contrast to the postoperative setting. In Turan's study, up to one quarter of patients developed postoperative hypotension, defined by authors as a MAP less than 70 mmHg for at least 30 continuous minutes, and 18% of patients developed severe hypotension, defined as a MAP less than 65 mmHg for greater than 15 continuous minutes[3]. Concerningly, only half of the episodes of severe hypotension were captured by routine non-invasive measurement, typically at a frequency of 4-8 hourly[3], indicating a "failure to detect" clinically important hypotension during ward-based care[9]. In a sub-study of the POISE-2 trial, systolic blood pressure (SBP) of less than 90 mmHg in the first four postoperative days was strongly associated with myocardial infarction[7], in addition to a 30-day composite of mortality and myocardial infarction[7]. A clear association has also recently been identified between postoperative hypotension and troponin elevation, a marker of myocardial injury[5]. This emerging data emphasises that postoperative hypotension may be as deleterious to patients as intraoperative hypotension, with the added risk of being both missed and untreated.

Current strategies for managing postoperative hypotension on the ward are generally limited to fluid administration, irrespective of aetiology. A recent trial demonstrated that maintenance of higher SBP, by continuing intraoperative vasopressor infusions in the postoperative period for four hours following surgery, could produce a 25% reduction of the risk of postoperative organ dysfunction[42]. However, such an approach is resource intensive and not always practical. Perioperative administration of oral midodrine has the potential to offer a novel treatment option for ward patients where low SVR is the primary cause. Midodrine may also reduce the incidence of prolonged delays in the Postoperative Anaesthesia Care Unit (PACU), in situations where mild-moderate hypotension precludes transfer to the ward, and a High Dependency Unit (HDU) or Intensive Care Unit (ICU) bed is not available.

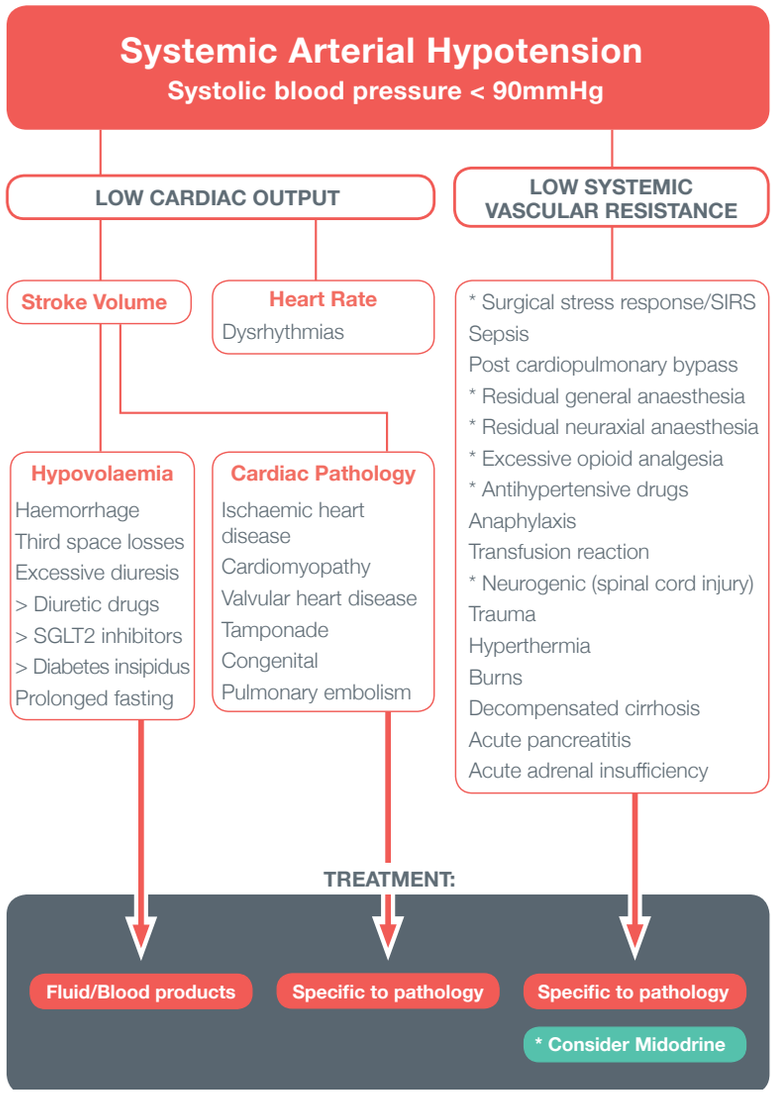
A suggested approach to the use of oral midodrine to treat postoperative hypotension

Oral midodrine can be used to treat hypotension in the postoperative period. This requires appropriate patient selection based on patient, surgical and anaesthesia risk factors, highlighted above. As a minimum, patients must have an intact swallow with no gastrointestinal obstruction. As with any abnormal vital sign, assessment of hypotension requires a systematic approach to investigate potential causes, and guide the most suitable treatment plan. Important and common causes of hypotension, such as acute haemorrhage and

myocardial dysfunction, require early identification and treatment or exclusion. Additional causes of hypotension categorised by pathophysiology are listed in Figure 1. Specific treatments for each cause are beyond the scope of this review. If it is determined that the primary cause of hypotension is reduced SVR, and the degree of hypotension is mild-moderate, midodrine should be considered to mitigate hypotension, and potentially improve longer term outcomes.

Predetermined and documented SBP targets will help guide titration or cessation of treatment. Due to the ability of midodrine to mask hypotension caused by mechanisms other than low SVR, the need for repeated dosing will necessarily require serial patient assessment, to continue to exclude other pathophysiological causes. As previously discussed, a limitation to the current ward environment is that patient observations are measured and recorded less frequently compared to the HDU or ICU, where "failure to detect" hypotension can occur. Conversely, the side effects of midodrine, such as supine hypertension, require careful monitoring until a consistent safety profile is established. In our institution, initiation of midodrine is accompanied by senior clinician ward medical review by the SAFE team (see "A resilience engineering approach to out-of-hours healthcare: The SAFE initiative" by Tim Bowles in this edition of *Australasian Anaesthesia*). For higher complexity patients, seeking early critical care support, and surgical opinion, where the potential for bleeding exists, will help to provide additional safety for patient care.

Figure 1. A suggested pathway for the treatment of postoperative hypotension categorised by pathophysiology.

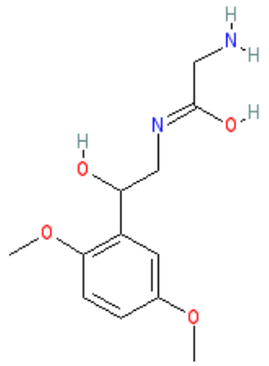


PHARMACOLOGY OF MIDODRINE

Properties: Odourless, white, crystalline powder which is water soluble.

Structure: An ethanolamine derivative.

Molecular formula: $C_{12}H_{18}N_2O_4$



Preparation: Available in 2.5mg, 5mg and 10mg tablets.

Mechanism of action: An oral prodrug, midodrine's active metabolite, desglymidodrine, is a selective a_1-adrenoreceptor agonist, leading to smooth muscle contraction of both arteriolar and venous vasculature, and an elevation of blood pressure in a dose-dependent manner.

Pharmacokinetics

Absorption: Following oral administration, midodrine is rapidly and almost completely absorbed, with a mean absolute bioavailability (as desglymidodrine) of 93%. Absorption of midodrine is unaffected by fasting status. Peak plasma concentration of midodrine is achieved at 30 minutes, with peak effect of its active metabolite at 60-90 minutes. Relevant duration of action is 4-5 hours. In healthy patients, an oral dose of 10mg typically increases the SBP 10-30 mmHg at 1 hour, with the effect maintained for a further 3-4 hours.

Distribution: Volume of distribution is 4L/kg, with minimal plasma protein binding. pKa is 7.8, with a pH of 3.5-5.5. Midodrine has a negative octanol/water partition coefficient, in keeping with its hydrophilic profile. Both midodrine and desglymidodrine poorly diffuse across the blood-brain barrier, thus exerting no central nervous system side effects.

Metabolism: Midodrine undergoes extensive metabolism via enzyme hydrolysis (deglycination) to form the major metabolite, desglymidodrine, responsible for its therapeutic effects. Only 2-4% is excreted unchanged.

Elimination: Desglymidodrine is renally cleared at 385ml/min, 80% by active secretion. Elimination half-life is 3-4 hours, increasing up to 10 hours in end-stage renal failure (ESRF), which may require an extended dosing interval[43]. Desglymidodrine is dialysable.

Toxicity: Oral LD_{50} in animals is 30-50mg/kg in rats, 675mg/kg in mice and 125-160mg/kg in dogs.

Pharmacodynamics

Route of administration: Oral

Dose: 5-15mg, every four hours for up to 24 hours.

Dose titration may be required to achieve the desired clinical effect, with dose response studies supporting a higher efficacy at 10mg dosage compared to 5mg dosage in patients with neurogenic orthostatic hypotension. Maximum doses of 30mg/day have been safely used[44]. In previous clinical trials performed in the ICU[45,46], a higher maximum dosage of 20-30mg, eight-hourly, was found to be safe. Logic and safety supports an initial dose of 10mg to achieve clinical effect, four-hourly as tolerated, with a maximum dosage of 60mg in 24 hours.

Midodrine increases SVR, with a corresponding increase in SBP and MAP, for a given cardiac output. There is a negligible effect on cardiac ß-adrenergic receptors. Midodrine improves symptoms associated with orthostatic hypotension and has been demonstrated to increase cerebral blood flow[47].

Side effects: These generally relate to the sympathomimetic profile of midodrine.

Common: Piloerection, pruritis, paraesthesia, sensation of coldness, urinary retention, sensation of urinary urgency and frequency. Managed with dose reduction[48].

Less common but potentially severe: Supine hypertension, which may be associated with reflex bradycardia.

Supine hypertension is arbitrarily defined by the Eighth Joint National Committee (JNC8) in neurogenic orthostatic hypotension patients as a SBP greater than or equal to 150 mmHg or a diastolic blood pressure (DBP) greater than or equal to 90 mmHg while in the supine position. In the community, supine hypertension is more likely to occur in patients with pre-treatment systolic hypertension[10]. Given that our primary aim of perioperative administration is the treatment of systolic hypotension, we expect that supine hypertension would occur less commonly. If supine hypertension does occur, the reverse Trendelenburg position has been shown to be effective[49]. It is recommended not to take midodrine within 5 hours of bedtime in outpatients with orthostatic hypotension[50]. However, where hypotension is a potential complication in the postoperative period, overnight treatment with midodrine may be warranted.

Table 1. Contraindications to midodrine administration.

Absolute contraindications:	Relative contraindications/caveats:
Active bleeding and hypovolaemia	Congestive cardiac failure
Known hypersensitivity to midodrine	Urinary retention
Supine hypertension	Acute kidney injury – consider increasing dosing interval
	Impaired gastrointestinal absorption
	Narrow angle glaucoma
	Severe obliterative vascular disease
	Cerebrovascular occlusion/vessel spasm
	Proliferative diabetic retinopathy
	Phaechromocytoma
	Thyrotoxicosis

Drug interactions: Midodrine may augment the effect of other sympathomimetic or vasoconstrictor drugs, such as metaraminol and ephedrine. The effects of midodrine may be antagonised by α-adrenergic blocking drugs including prazosin and phentolamine. Alternatively, these agents may have a role in rescue therapy. Concomitant use of ß-adrenoreceptor blocking agents or digoxin require close monitoring, due to the potential development of bradycardia.

PUBLISHED EVIDENCE REGARDING MIDODRINE USAGE

Official indications

Midodrine's ability to overcome orthostatic hypotension was first identified over three decades ago[51]. It received conditional Food and Drug Administration (FDA) approval in 1996 for orthostatic hypotension in the US. In the UK, midodrine was the first medication licensed for the treatment of orthostatic hypotension, and was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in 2015 for the treatment of severe orthostatic hypotension due to autonomic dysfunction in adults, where other treatment was inadequate. In 2017, the Australian Therapeutic Goods Act (TGA) authorised midodrine administration for the treatment of severe orthostatic hypotension[52]. Suggested contraindications to the use of midodrine in the postoperative setting are listed in Table 1.

Use for other indications are currently off-label and exploratory.

Midodrine in the non-perioperative setting

Midodrine and orthostatic hypotension

An early systematic review and meta-analysis analysed seven trials to assess the efficacy and safety of midodrine in orthostatic hypotension. Heterogeneity and differences in primary measurement outcomes were noted, such as SBP and MAP. While there was a significant increase in standing SBP compared to controls with midodrine, the authors recommended large observational studies to inform further practice[53].

Outpatient settings, inpatient wards, and spaceflight

Midodrine usage is increasing, with benefit observed in a broad range of non-perioperative settings, including intradialytic hypotension in patients with End Stage Renal Failure (ESRF)[54-56], post space-flight orthostatic intolerance[57,58], symptomatic improvement in stress urinary incontinence[59], treatment of refractory chylothorax[60], cirrhosis with refractory ascites[61] and orthostatic hypotension secondary to spinal cord injury[62]. Alternatively, case reports exist of insidious development of urologic adverse effects in patients with spinal cord injury[63], and vascular ischaemia in a patient with ESRF[64].

Intensive Care Unit

The vasoplegic profile of sepsis may be a specific target for midodrine[65]. Two retrospective cohort studies[45,66] in the ICU identified a potential role for midodrine in the early weaning of intravenous vasopressor support and a reduction of length of ICU stay, up to 2 days[45]. In a prospective study of 20 adult surgical ICU patients, fewer patients required intravenous vasopressors at 24 hours after initiation of midodrine[46]. For those still requiring intravenous vasopressors, the infusion rate decreased from -0.62mcg/min/hr to -2.2mcg/min/hour following midodrine administration. Midodrine may therefore offer a potential therapeutic alternative in an increasingly resource-limited ICU environment, including where medication shortages occur[67]. Two prospective, randomised control trials; the Midodrine as adjunctive support for treatment of refractory hypotension in the intensive care unit: A multicentre, randomised, placebo controlled trial (MIDAS)[68], and the Midodrine as an Adjunctive VasoprEssor for Refractory Hypotension in Intensive Care (MAVERIC) Study (ACTRN12618001158257) trials are ongoing to identify a true benefit of midodrine administration. We anticipate these results will inform ongoing practice in this cohort of patients.

Evidence for the potential role of midodrine in the perioperative setting

Limited yet promising data exists for midodrine in the perioperative setting. In patients at risk of developing postoperative hypotension, and/or orthostatic hypotension, midodrine has the potential advantages of being a well-tolerated, peripherally acting oral sympathomimetic agent that could be used within the limitations of a ward environment. The perioperative effects of midodrine can be subdivided into anaesthesia type, general versus neuraxial, and effect on blood pressure: Hypotension, earlier defined as SBP less than 90 mmHg, versus orthostatic hypotension, defined below.

Midodrine and postoperative orthostatic hypotension

Orthostatic hypotension (OH), defined as a reduction of SBP of 20 mmHg or DBP of 10 mmHg or more, after 3 minutes of standing[69], occurs commonly after surgery[70,71], with an increased incidence in older females[16.] Cerebral hypoperfusion during postoperative mobilisation[71] in patients with OH contributes to delayed recovery, increased length of stay[72], and the potential for syncope and falls[73]. Midodrine has been trialled in the perioperative period and found to be effective at improving both OH and orthostatic symptoms in kidney and pancreas recipients[74]. In elective joint replacement, 5mg midodrine administration on a single postoperative occasion did not improve OH postoperatively[75]. However, this may have been a subtherapeutic dose. A linear dose-response relationship exists between SBP and neurogenic OH[44], with 10mg dosage found to be clinically effective in chronic OH[44,76].

Midodrine, general anaesthesia and perioperative hypotension

Postoperative hypotension secondary to reduced SVR is common. Midodrine has been successfully used to treat hypotension following spinal surgery[77], and carotid artery stenting[78]. The latter patients were managed on a telemetry ward, rather than the ICU for intravenous vasopressors. This supports a new postoperative pathway for appropriately selected patients, and may aid in the reduction of cost and resources. Recent studies have assessed whether preoperative midodrine requirement predicts post-transplant morbidity and mortality outcomes, with mixed results[79-81]. In patients receiving orthotopic liver transplantation, intraoperative systemic hypotension has been previously identified to be independent risk factor for adverse outcomes[82]. A large retrospective study found that in patients requiring midodrine prior to transplantation, there was no difference in intraoperative hypotension between the two groups[81]. This was despite the midodrine group having higher ASA scores, Model for End-Stage Liver Disease (MELD) scores, preoperative hypotension and an increased need for continuous renal replacement therapy. Hansen et al concluded that preoperative midodrine requirement could not predict increased risk of intraoperative hypotension, their primary outcome[81]. However, we suggest that midodrine may offer a protective benefit for selected patients in the perioperative period. Preoperative midodrine in this study was associated with a higher risk cohort, yet there was no increase in intraoperative hypotension, vasopressor or blood transfusion requirement. Additionally, there was no difference in patient or graft survival at one year follow up. This provides a promising signal for further studies utilising perioperative midodrine.

Midodrine, neuraxial anaesthesia and hypotension

Midodrine has demonstrated benefit in treating both orthostatic hypotension[83] and protracted neurogenic shock[84] following spinal cord injury (SCI). In high SCI patients, midodrine's benefit extends to improved cerebral flow velocity[85], mitigation of impaired neurovascular coupling, and even improved cognitive function[86]. Neuraxial anaesthesia mimics the physiological effects observed in SCI, including loss of descending inhibition, impaired afferent[87] and efferent sympathetic nervous activity, and subsequent loss of both reflex vasoconstriction and venoconstriction, dependent on the level of blockade[88-90]. Hence, midodrine use may reverse persistent postoperative hypotension in patients following neuraxial anaesthesia, particularly when higher level blocks are achieved, intentionally or inadvertently, and when hypotension is observed in the postoperative period.

REFLECTIONS AND FUTURE DIRECTIONS

Midodrine has been demonstrated to be well tolerated in the community in patients with orthostatic hypotension and autonomic insufficiency. Early evidence supports midodrine being beneficial in a broad range of clinical settings, including in patients with significant comorbidities. Contemporary literature strongly supports the paradigm that perioperative hypotension is not benign and should be actively sought and treated. This is due to its association with cardiac morbidity, stroke, acute renal injury and death. Patients at increased risk of postoperative hypotension, such as those with increased frailty, pre-existing cardiac disease or those undergoing major surgery, are dually a population most vulnerable to harm if postoperative hypotension develops. Midodrine may therefore offer a mechanistically sound, clinically effective, and safe potential treatment option for the prevention and rescue treatment of postoperative hypotension, a modifiable risk factor, where reduction of SVR is the primary cause. Additional potential benefits of midodrine in the perioperative period include, but are not limited to, earlier discharge from the PACU to the ward, facilitation of early postoperative patient mobilisation, fewer Medical Emergency Team (MET) calls/Code Blues/unplanned ICU admissions, and avoidance of unnecessary fluid administration or procedures, such as central venous cannulation.

Prospective observational data and clinical experience are promising, however, further studies are required to specifically address the efficacy of midodrine in the perioperative period. In particular, prospective randomised studies need to define the effect of midodrine on orthostatic hypotension as compared to general hypotension in the perioperative period, and the need for dose adjustment in specific patient or surgical populations, such as those with intrinsic autonomic disease. Studies examining the use of midodrine in patients receiving neuraxial anaesthesia, as compared to general anaesthesia, or a combination technique, would be of further benefit. Well-designed pragmatic trials and the collection of long term follow-up data will enable clarification as to whether midodrine has the potential to alter significant complication outcomes, and become a useful adjunct to safe clinical practice.

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Coagulation/ Blood

It's about bloody time! The massive transfusion protocol in trauma

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INTRODUCTION

Massive traumatic haemorrhage is like war. As Ulysses S Grant once said "The art of war is simple enough. Find out where your enemy is. Get at him as soon as you can. Strike him as hard as you can, and keep moving on."

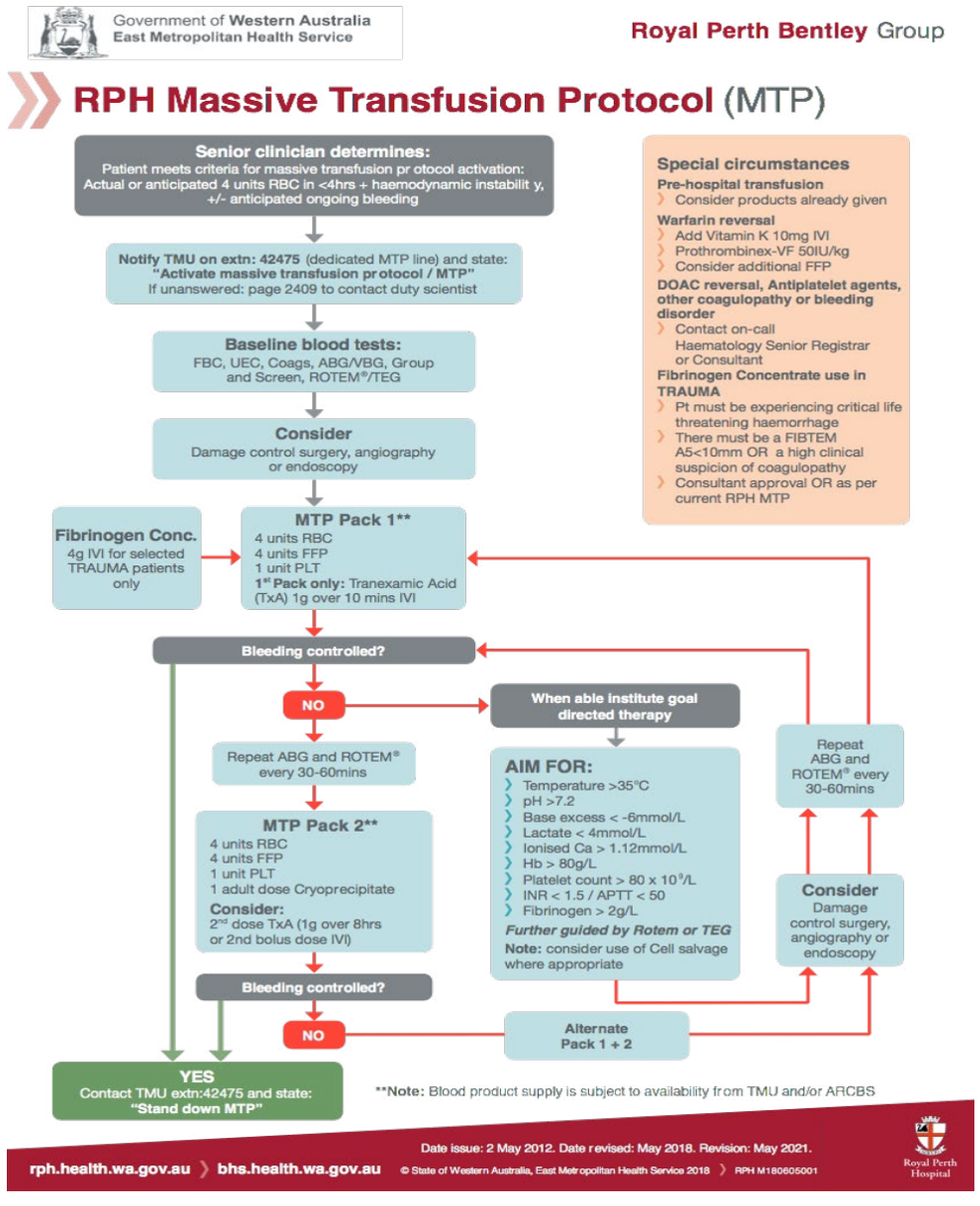
Trauma is the leading cause of death in the 18-39 years of age group. Haemorrhage remains the most common cause of death within the first hour of arrival to a trauma unit. Over 50% of trauma deaths at 24 hours are attributable to major haemorrhage and are thus considered preventable. More than 25% of trauma patients present to the emergency department (ED) with variable degrees of coagulopathy[1], and aggressive early management of trauma induced coagulopathy (TIC) and the prevention of resuscitation induced coagulopathy are points for management focus. The introduction of Massive Transfusion Protocols (MTP) has seen an improvement in trauma outcomes and a reduction in both the number of blood products used and associated complications[2]. Utilising a MTP, also known as Damage Control Haematology (DCH), is essential to target rapid haemostatic resuscitation and minimise wastage and delays. The majority of trauma patients do not, however, require a massive transfusion (MT). A MT is defined as 5 or more units of packed red blood cells in <4 hours, or >10 units in 24 hours; with only 3-5% of civilian trauma patients receiving a massive transfusion (MT). Patients who do require a MT have a significantly increased morbidity and mortality. Predicting the need for massive transfusion is complex and multi-factorial.

THE ROLE OF MASSIVE TRANSFUSION PROTOCOLS

The concept of a MTP is not new. It was initially designed to treat both established and potential coagulopathies associated with massive haemorrhage. In the trauma setting, it was adopted to focus clinicians addressing the uncertainties common in the care of patients with severe injuries[3]. The MTP is a cognitive aid to focus the clinical team on the timing of initiation for blood product transfusion and the optimal ratio of product administration, with the aim of maintaining organ perfusion and oxygen carrying capacity[4]. Over the years, it has evolved to include haemostatic adjuncts for the haemodynamically unstable bleeding patient, in an effort to combat metabolic and haemostatic failure[3]. It emphasises the concept of a multi-disciplinary team approach to DCH, providing prompts for empiric transfusion ratios, prompts for necessary investigations (for example, viscoelastic assays/conventional coagulation tests/arterial blood gases) and physiological targets (for example, temperature/ pH /Ca^{2+}/coagulation indices). Major transfusion protocols have been shown to reduce early mortality, reduce the incidence of multi-organ failure and have made a positive impact on reducing blood product use and wastage[5].

Figure 1 is the Massive Transfusion Protocol employed at the Level 1 WA State Trauma Hospital. The fundamentals are based on international guidelines whilst local nuances facilitate implementation.

Figure 1. An example of a Massive Transfusion Protocol. Reproduced with permission from Royal Perth Hospital.



As with all MTPs, it requires a delicate and co-ordinated multi-disciplinary approach to deliver a highly protocolised algorithm. From a laboratory perspective, it requires a non-specified period of high intensity workload; processing, validating and cross matching of products to deliver large amounts of blood and blood products in a time-pressed manner while ensuring the highest standards are maintained to ensure patient safety.

It has been proposed that a MTP protocol should not only cover areas of initiation, termination, resuscitative products and targets, and haemostatic adjuncts, but also product procurement; availability, delivery and transfusion. In addition, protocol performance indicators should be recorded and periodic auditing performed[6]. These indicators could include the following:

- Details of initiation criteria on a case-by-case basis.
- Percentage of positive initiations.
- Time from initiation to infusion of first packed red blood cell.
- Time from initiation to infusion of first plasma.
- Use of investigations.
- Prescribed blood product and haemostatic adjunct compliance.
- Wastage and product traceability.
- Informing blood transfusion unit of intent to terminate.
- Documentation.
- Complications including over transfusion.

ACTIVATION OF MTP: HOW ROBUST ARE OUR TRIGGERS?

Activation and initiation of the MTP is the responsibility of a senior clinician (for example, trauma, ED or anaesthesia services). It can be done prehospital or upon arrival of the patient into ED. Currently, there is no international consensus on which activating criteria or scoring system to use in order to predict the need for a massive transfusion, Damage Control Resuscitation, or the presence of TIC. Table 1 shows 14 available scoring systems and their attributes. These scoring systems have varying degrees of complexity and sub-optimal sensitivity and specificity. Many require the availability of results (for example, Hb/Lac/BE/INR/FAST scans), all of which may impact the time to initiation of a MTP and administration of blood products[7].

Table 1. Scoring systems for initiation of an MTP.

Name of algorithm	Parameters used	Predicting MT	Validation	Ease of use
Assessment of Blood Consumption Score (ABC)	1. Penetrating Injury 2. HR ≥120 3. BP <90mmHg 4. FAST +	Score >2 Sensitivity 75-90% Specificity 66-88%	Revalidated 2010 in multicentre w >1600 trauma patients	Non-weighted Parameters Score 0-4 Experienced ultrasonographer MDCAL application available to do calculation
Emergency Room Transfusion Score	1. BP < or >90mmHg 2. FAST + 3. Clinical open pelvic # 4. Age 20-60 or >60 5. Significant trauma 6. Admission from scene	Score >3 Sensitivity 98.1% Specificity 13.8%	German level 1 trauma centre >1100 severely injured trauma patients	Weighted Score 0-9.5 Easy to use Identifies pts in need for immediate transfusion No MDCAL application available to do calculation

Name of algorithm	Parameters used	Predicting MT	Validation	Ease of use
Prince of Wales Hospital/Rainer Score	1. HR ≥120bpm 2. SBP ≤90mmHg 3. GCS ≤8 4. Displaced pelvic # 5. CT or FAST + 6. Base deficit >5mmol/L 7. Hb ≤7g/dL Hb 7.1 -10 g/dL	Score >6 Sensitivity 31.5% Specificity 99.7%	PWH trauma registry >1800 trauma patients	Weighted Score 0 -10 No MDCAL application available to do calculation
Trauma Associated Severe Haemorrhage Score (TASH)	1. SBP 2. HR 3. Hb 4. Intra-abdominal Fluid 5. Complex long bone or pelvic # 6. Base deficit 7. Gender	Score ≥16 Probability >50%	German Trauma Registry Revalidated >4500 trauma patients	Weighted Score 0-28 Requires imaging MDCAL application available to do calculation
Traumatic Bleeding Severity Score	1. Age 2. SBP 3. FAST + 4. Severity of Pelvic # 5. Lactate level	Score >15 Sensitivity 97.4% Specificity 96.2%	113 severely injured trauma patients	Weighted Score 0 -57 Simple to calculate with iOS application
Code Red	1. Suspicion or evidence of haemorrhage 2. SBP <90mmHg 3. Failure to respond to fluid bolus	Score 3 Sensitivity of >89%	Emergency Medicine & Pre-hospital Care, London's Air Ambulance, The Royal London Hospital	Non weighted Score 0-3 Pre-hospital physician request policy
Shock Index	1. HR/SBP	Score ≥0.9 RR = 1.61 for MT with 95% CI:1.13-2.31	>8000 patients not yet been prospectively investigated	Easy to calculate
Larson Score	1. SBP 2. HR 3. Hb 4. Base Deficit	Score >2 Incidence of MT 54% Sensitivity 69%	Retrospective analysis of military	Non weighted Score 0-4 Requires blood results
Schreiber Score	1. Hb ≤11g/dL 2. INR >1.5 3. Penetrating mechanism	Sensitivity 85.8% Specificity 61.7%	558 military	All independent predictors of MT in military personnel

Name of algorithm	Parameters used	Predicting MT	Validation	Ease of use
Coagulopathy of Severe Trauma Score COAST	1. Entrapment 2. Body Temp 3. SBP 4. Abdo or pelvic injury 5. Chest decompression	Score ≥3 Sensitivity 60% Specificity 96.4%	Level 1 trauma unit Prospective validation study of >1200 trauma patients	Weighted Score 0-7 Pre-hospital variables to predict ATC
Massive Transfusion Score	1. INR >1.5 2. SBP <90mmHg 3. Hb<11g/dL 4. BD ≥6mmol/L 5. Fast + 6. HR ≥120bpm 7. Penetrating injury	NPV 95%	Using cohort population from the PROMMT study	Non weighted Score 0-7
Trauma Induced Coagulopathy Clinical Score TICCS	8. Orientation 9. BP 10. Extent of body injury	Score >10 Sensitivity 100% Specificity 95.9%	Single centre prospective to assess for patients requiring DCR 82 patients	Weighted Score 0-18 Recordable by paramedics

As evident from Table 1, no one scoring system is ideal. There is a need for large multi-centre retrospective validation studies to establish an easy to use, fast and predictable scoring system. The American Society of Anesthesiologists and the American College of Surgeons advocate using The Assessment of Blood Consumption (ABC) and Trauma-Associated Severe Haemorrhage (TASH) scoring systems. Both have a high sensitivity and lower specificity[9]. Most centres are dependent on senior clinician gestalt despite research showing that even in the most experienced hands in 10 Level 1 trauma units in USA, positive predictive value and negative predictive value were 34.9% and 86.2% respectively.[8]

A result of the recent MTP audit conducted at Royal Perth Hospital (RPH) showed that of the 135 activations which occurred over a 6-month period 64.9% of these occurred prior to the arrival of the patient to the Emergency Department on the basis of the information received from referring personnel. Results from the activation data indicated that 80% of patients had 1 or more physiologic derangements as the reason for triggering the MTP; 7.4% patients were in cardiopulmonary arrest; 3% were already intubated upon arrival and; 6.6% of the activations were based on "clinician gestalt" due to a suspected significant injury.

Some institutions use a combination of non-weighted criteria including senior clinician gestalt, mechanism of injury, suspected injuries and patient haemodynamics. Table 2 is an example of the activating criteria currently used at the Level 1 WA State Trauma Hospital.

Table 2. The activating criteria at RPH includes one or more of these features.

1. Senior clinician judgement (gestalt)
2. Prehospital/hospital HR >120bpm
3. Prehospital/hospital SBP <90mmHg
4. Prehospital/hospital GCS ≤8
5. Penetrating injury
6. Unstable pelvic or femoral fracture
7. Positive fast scan upon arrival into ED

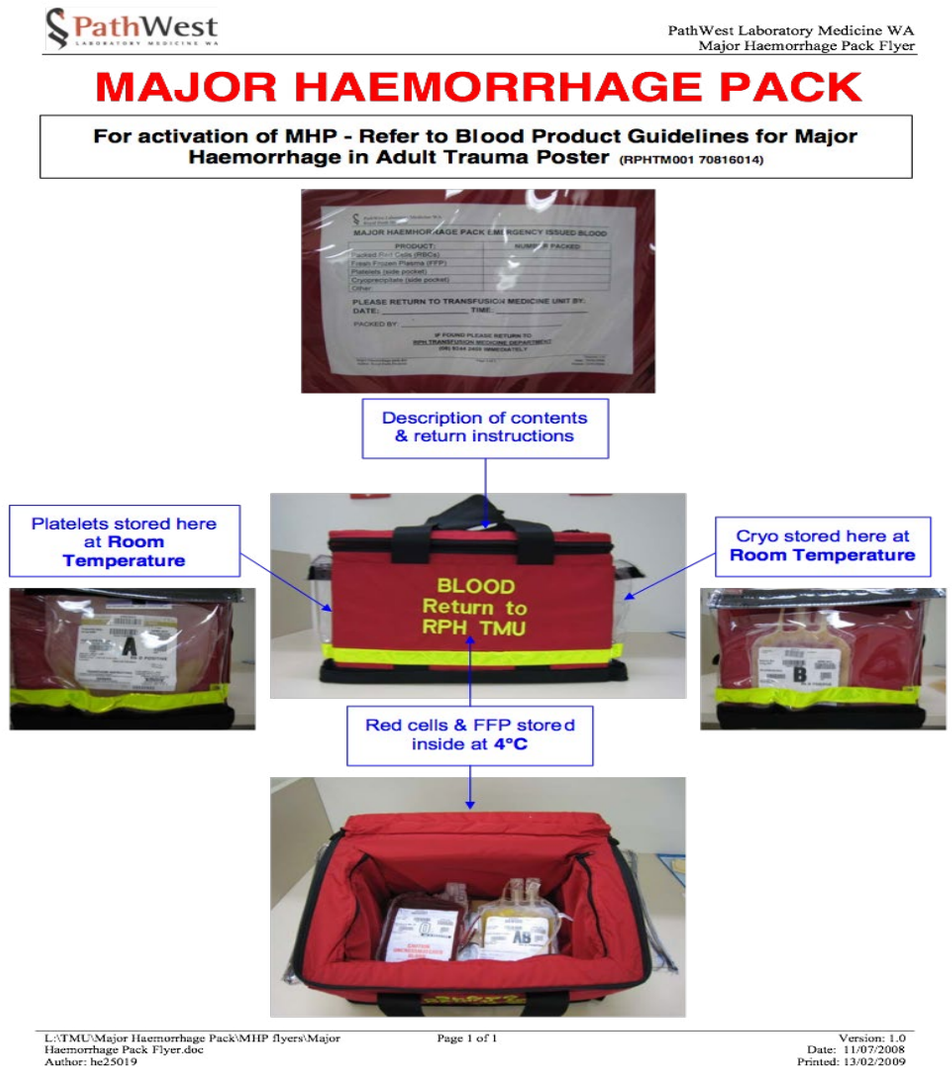
Once the decision to activate is made, a clear pathway needs to be in place. As an example, once the decision to activate has been made at RPH, the Transfusion Medicine Unit (TMU) is contacted via a dedicated phone and the technician is advised to "Activate the MTP". Once the MTP has been activated, a designated assistant is sent to deliver the completed slip to the overseeing technician in TMU and collect the first Massive Haemorrhage Pack (MHP). The current activation slip used at our institution can be seen in Figure 2.

Figure 2. An example of a Major Haemorrhage Pack request slip.

Major haemorrhage pack request slip	
Pre-arrival request – call TMU on 42475 to request *Note: Pt. ID NOT required, phone through full ID (once registered) & pack number as per Pre-arrival process*	Post-arrival request – call TMU on 42475 to request *Affix ID Label Here* *(ONLY if patient is registered)* *i.e. name + URMN + DOB)*
Senior doctor requesting	Name:
Nurse requesting	Snr Dr's Name:
Transfusion prior to arrival	YES NO Unknown
Patient gender	Male Female
Incidents details:	
Clinical activation criteria (tick all applicable boxes)	
☐ Clinician judgement	☐ Penetrating injury
☐ Pre-hospital/Hospital HR >120bpm	☐ Unstable pelvic or femoral #
☐ Pre-hospital/Hospital SBP < 90mmHg	☐ Fast scan positve
☐ GCS score < 8	
Complete above with available information – Give to PCA to collect pack from TMU.	

The first-issued MHP in Royal Perth Hospital has 1g of tranexamic acid (TxA) in addition to the standard blood products (pRBC/FFP/ platelets). Four grams of Fibrinogen Concentrate is now available on senior clinician request. The second MHP contains 1 adult dose of Cryoprecipitate in addition to standard blood products. Below are examples of a MHP used at RPH.

Figure 3. An example of a major haemorrhage pack. Reproduced with permission of PathWest Laboratory Medicine WA.



TERMINATION OF MTP

Of equal import is the action of actively terminating the MTP. Actively communicating with Transfusion Medicine Unit to "Stand down MTP" adopts a closed loop communication, ensuring effective teamwork. Timely deactivation promotes patient safety by avoiding unnecessary transfusion. It reduces blood product and economic wastage, facilitating recycling of unused blood products and redistributing personnel to other tasks. There is no consensus on criteria to prompt termination. However, some or all of the features in Table 3 provide a basis to consider standing down[9].

Table 3. Factors for consideration in terminating a MTP.

1. Anatomic control of bleeding
2. Physiologic improvements of haemodynamics (although still in acute phase of resuscitation) ▪ pH>7.2 ▪ SBP 80-90mmHg ▪ Temp >36°C
3. Further resuscitation is considered futile
4. General agreement within the team
5. Targets reached (as per RPH Algorithm): ▪ Hb>80g/L ▪ Plt>80x10^9 ▪ INR<1.5 ▪ aPTT<50sec ▪ Fibrinogen>2.0mmol/L

TIME TO DISPATCH

For maximum effectiveness, fixed ratio blood products should be available without delay. International consensus on this key performance indicator is less than 10 minutes from request to delivery of the first MHP. The audit conducted at RPH identified the time to dispatch (that is, time from activation of MTP to the first MHP delivery into ED) ranged from 0 minutes to a maximum of 35 minutes. Most (88%) major transfusion packs were dispatched in under 10 minutes, with the average time to dispatch being 7 minutes.

In some institutions, the TMU will on a daily basis pre-allocate blood and blood products to the trauma service, which may be available in a fridge in the emergency department. The hope is that with blood being immediately available, it might result in fewer premature activations of MTP for patients who do not require it, with an ultimate decrease in the burden of blood product wastage.

PRODUCTS USED

Many institutions utilise a hybrid approach to MT. Initial therapy is an empiric balanced transfusion in a 1:1:1 ratio of Plasma:Platelets:RBC using universally compatible red blood cells O Rh – or O Rh + and thawed AB plasma. Both pRBC and plasma should be administered via a fluid warmer. Once characterisation of the coagulopathy has been identified via viscoelastic assays and conventional coagulation tests, conversion to goal directed therapy is appropriate. Similarly, conversion to cross-matched products should occur within an hour of activation.

The targets for haemoglobin and platelets are greater than 80g/L and 80 x10^9 respectively. An INR <1.5 and activated partial prothrombin time <50sec is targeted. Qualitative and quantitative platelet abnormalities play a major role in TIC. While CCTs quantify the platelet count, their function is examined by VHAs with an EXTEM A10 <40mm and FIBTEM A10 <10mm suggesting poor platelet contribution to clot formation and integrity, and the potential need for transfusion[10].

Half of all trauma deaths are due to bleeding, with the majority of these occurring in the first 6 hours. Trauma-Induced Coagulopathy (TIC) is a haemostatic abnormality, occurring within minutes of the inciting injury. The presence and severity of TIC correlates with the severity of the trauma and is compounded by traumatic brain injury associated coagulopathy, evolving acidosis and hypothermia. This is the lethal triad or bloody vicious cycle.

The pathophysiology of TIC is complex and still under investigation. It is a unique entity which evolves as a direct consequence of trauma and hypoperfusion, existing in >25% of trauma patients presenting to ED with or without prior fluid resuscitation. Cohen et al, as a result of the PROMMTT study, concluded that Activated Protein C played a pivotal role in generating the coagulopathy[11]. Chang et al published a review article in *Blood Journal* in 2016 detailing the purported roles of Activated protein C (with the subsequent depletion of factors I, II, V, VII,VIII,IX,X) the endothelial glycocalyx dysfunction, platelet "dysfunction vs exhaustion" and fibrinogen abnormalites[12]. Over the last number of years, research has focused on the use of early and aggressive blood product and clotting factor administration. The PROMMT and PROPPR trials have sought to identify the optimal balanced ratio of blood products. The PROPPR study published in 2015 by Holocomb et al, remains

the most robust trial to date and forms the basis of empiric ratio driven guidelines. It showed that among patients with severe trauma and major bleeding, early administration of plasma, platelets, and red blood cells in a 1:1:1 ratio compared to 1:1:2 ratio did not result in significant differences in all-cause mortality at 24 hours or 30 days. However, more patients in the 1:1:1 group achieved earlier haemostasis, lower transfusion rates and fewer deaths due to exsanguination by 24 hours[13]. The corollary of higher fixed ratio empiric MTP is the increased risk of prolonged multi-organ failure/ PRMODS and nosocomial infection presumably due to the augmentation of the immunosuppressive response after trauma[14].Fibrinogen is a key clotting protein. It is essential for clot strength, clot stabilisation, platelet aggregation and haemostasis. It has a large molecular weight and long half-life of 3-5 days and contributes to a greater extent to clot strength in injured vs non-injured controls, when measured at initial presentation and at 72 hours[12]. It is the first clotting factor to reach critically low or sub-therapeutic levels in bleeding trauma patients due to a predominant hyperfibrinolysis phenotype specific to trauma[1,15]. This phenotype plays a central role in the endogenous coagulopathy and its presence confers an early mortality disadvantage[16]. A retrospective study correlating the fibrinogen level with mortality in critically injured patients revealed that fibrinogen levels less than 1.8g/L were significantly associated with higher in-hospital mortality rates[15,16].

The target level for fibrinogen is >2g/L. Viscoelastic assays will aid in identifying abnormalities in fibrinogen. For example, when using ROTEM the goal is Fibtem A5 ≥ 10mm and Extem A5 >35mm / CT<80sec. Fibtem A5 <7mm correlates with fibrinogen of <1.5g/L. The targets when using TEG include K time <4 minutes and α angle >60°.

Delivery of replacement fibrinogen can be in the form of 10 units of cryoprecipitate. As per the protocol at RPH, this is in the second MHP. Concentrations of fibrinogen are variable, with approximately 1.6g/L of fibrinogen in FFP and 1.3g/150ml in cryoprecipitate. Chowdury et al, observed the need for 30mL/kg of FFP to produce a significant increase in fibrinogen[17]. Cryoprecipitate is a donor pooled product requiring group specific compatibility, without being pathogen inactivated. Once thawed it has a 6-hour window of use. Although plasma is a source of fibrinogen, this is variable and potentially would require >30mL/kg of plasma to increase the fibrinogen level by 1.0g/L, thus increasing the risk of volume overload, TRALI and MOF. Fibrinogen concentrate is available in Australia under the tradename RiaSTAP. RiaSTAP is a pasteurised lyophilised pooled donor product and has been pathogen inactivated. It delivers 1.0g/50mL of fibrinogen. This will also obviate the time to thaw, cross matching, potential pathogen related reactions and should deliver a more consistent dose. Current guidelines for managing bleeding in trauma patients with fibrinogen levels of 1.5 to 2.0 g/L recommend an initial fibrinogen concentrate dose of 3 to 4 g, with further dosing guided by laboratory testing[18]. The FEISTY pilot study showed that Fibrinogen Concentrate was faster to administer. The FEISTY 2 study which is underway will hopefully elucidate further on early use of fibrinogen in traumatic haemorrhage[19].

Although 3-factor Prothrombin Complex Concentrate is available in Australia, it is not routinely used unless a patient on vitamin-K antagonist anti-coagulation therapy presents with a traumatic brain injury. Large multi-centre trials for the efficacy, safety and cost effectiveness of 3 & 4 factor PCC is currently lacking with only level 3 evidence at best available to support the safety of both products with 4F-PCC being most effective[20]. There is recent supporting evidence, albeit level 4, in favour of 4 factor-PCC plus FFP versus FFP alone in reversing acute traumatic coagulopathy with significant reduction in correction of INR, blood and blood products used and mortality without any difference in thromboembolic events[21].

PHARMACOLOGICAL ADJUNCTS: TRANEXAMIC ACID

Tranexamic Acid (TxA) is a lysine analogue, used in major haemorrhage when there is evidence of excessive clot breakdown in the presence of hyperfibrinolysis. There is robust evidence, such as in the Crash 2 and military MATTERS studies, both of which showed overall survival without an increase in vaso-occlusive events in those that received 15-20mg/kg of TxA within 3 hours of an inciting injury[22,23]. The results of CRASH 3, a multi-centre international randomised pragmatic trial are due in April 2020. This trial will look at the effect of early administration of tranexamic acid on mortality and disability in patients with traumatic brain injury. Secondary outcomes will review risk of vascular occlusive events and seizures[24].

INVESTIGATIONS

Baseline bloods are taken on arrival. These include FBC/Group & Screen/ABG/CCTs and VHAs. These form the basis for assessing for TIC, prognostication and response to therapy. International guidelines recommend serial testing every 30-60 minutes.

CCTs such as INR/aPTT/fibrinogen levels, measure single parameters in isolation. They provide no information on clot mechanics, platelets or fibrinogen activity and when used on their own have a low predictive value for bleeding or transfusion requirements. In addition, the time taken to obtain a result may be prohibitive.

Pre-hospital point-of-care INR testing may avoid this once it is validated in the trauma setting against conventional laboratory plasma-based INR[25]. CCTs can however identify a cohort of coagulopathic patients not immediately identifiable with viscoelastic assays alone[26]. Patients presenting with abnormal CCT alone or in combination with abnormal VHA were more profoundly coagulopathic with a higher morbidity and mortality. As our understanding of the pathophysiology around TIC improves, the combination of CCTs and VHAs might shed light on the different forms of coagulopathy that trauma induces[26]. Thus, CCTs still have a role in the management of massive transfusions.

VHAs are used in characterising clot dynamics in whole blood; from initiation through propagation, to stabilisation and breakdown. This point of care test allows for goal directed resuscitation. It provides real time measurements of the clot kinetics and quantifies deficiencies in clotting factors, platelets and fibrinogen. VHAs can identify the transition to a hypercoagulable state. In 2017 Prat et al, showed an increased use of platelets and fibrinogen in the early resuscitative phases while Mohammed et al in 2017, and Tapia et al in 2013, observed a reduction in trauma mortality, length of stay in hospital and ICU, and overall blood transfusion costs[27-29]. To date, however, there is no international consensus on VHA defined coagulopathy and there has been a paucity of validated VHA-guided transfusion algorithms. In May 2018, the Trans-Agency Consortium for Trauma-Induced Coagulopathy (TACTIC) group published the results of their prospective observational multicentre study, to develop pragmatic data driven algorithms for the management of trauma induced coagulopathy utilising VHAs. They constructed algorithms for ROTEM, TEG and CCTs to be used in addition to ratio driven transfusion and tranexamic acid. It remains to see how these will affect our blood component management, once adopted into clinical practice[29].

CONCLUSION

Accurate documentation and product traceability both facilitate the audit process and thus quality improvement. Interestingly, there is a paucity of audits in this field. Royal Perth Hospital has recently completed an in-house audit while The Alfred in Melbourne are currently reviewing their Massive Transfusion Protocol in the context of their trauma reception process. The data emerging from RPH is reassuring, however it does highlight areas of improvement in activation criteria, active termination and product traceability.

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Differentiation of preoperative anaemia

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INTRODUCTION

Anaemia is a common finding in patients undergoing major surgery, and is independently associated with infectious and thrombotic complications, blood transfusion and mortality. Its aetiology is complex, as pathologies may co-exist and laboratory findings overlap, which may afford diagnostic uncertainty. Furthermore, effective treatment modalities exist which rely upon accurate diagnosis and prompt treatment preoperatively to optimise the patients red cell mass in preparation for haemorrhage.

This article outlines the common aetiologies of anaemia encountered by the perioperative physician, and details the diagnostic modalities available to identify these causes and direct therapeutic management. Additionally, it provides an algorithm for assessment and management which can be easily incorporated into perioperative care pathways.

PREVALENCE AND SIGNIFICANCE

Anaemia is defined by the World Health Organization as a haemoglobin of less than 120 g/L in women and 130 g/L in men. Under this definition, 2.2 billion people suffered from anaemia worldwide in 2010[1]. Anaemia is widely prevalent in the surgical population, with one third of patients undergoing major elective non-cardiac surgery found to be anaemic pre-operatively[2]. Moreover, greater than half of the non-anaemic patients were iron deficient[2]. Australian data has indicated that 34% of patients are anaemic prior to admission to hospital, and 35% of those who were not anaemic preadmission developed the condition during their hospital stay[3]. This represents a significant proportion of at-risk patients with potential for optimisation before surgical intervention.

Adverse outcomes associated with anaemia have been widely acknowledged[3-6]. In the surgical population, preoperative anaemia is associated with increased morbidity and mortality and results in an increased exposure to blood transfusion[5,6]. The degree of anaemia is also important, with moderate to severe anaemia resulting in poorer outcomes compared to mild anaemia[4]. In obstetrics, a threshold of 110 g/L is used to define pre-operative anaemia, although there is currently debate in the literature about the appropriateness of this lower cut-off as comorbid conditions such as iron deficiency (ID) are major contributors[7]. Similarly, the harms of blood transfusion have been examined extensively. Receiving a blood transfusion is a risk factor for mortality, wound infection, sepsis and pneumonia in the surgical population[2,8,9]. Even single unit transfusion has been shown to increase the risk of major adverse cardiac events[10].

Preoperative correction of iron deficiency anaemia (IDA) with iron replacement can be achieved before elective surgery and reduces transfusion requirements[11-13]. The use of an erythropoietin-stimulating agent coupled with iron therapy has been shown to improve haemoglobin levels in cardiac surgery patients, and reduced transfusion rates among patients undergoing orthopaedic surgery[14]. However, there is no level I evidence to suggest that correcting anaemia improves outcomes and reduces post-operative complications.

PHYSIOLOGY OF ERYTHROPOIESIS

Erythropoiesis begins in the bone marrow from haematopoietic stem cells and ends with the production of erythrocytes, the primary oxygen carrier of the body. Stimulated by various DNA transcription factors, these stem cells differentiate down the erythroid cell line into burst-forming unit-erythroid cells. As they mature, they develop into colony-forming unit-erythroid cells which develop around a central macrophage[15]. The first phase of differentiation is dependent on erythropoietin, a hormone secreted by the renal cortex in response to tissue hypoxia, which directs differentiation and prevents apoptosis. An erythropoietin-independent phase then follows, which focuses on the production of haemoglobin molecules. Nucleated erythroblasts are produced, which express the transferrin receptor on the cell membrane to promote iron uptake and facilitate haemoglobin synthesis. As these cells develop, soluble transferrin is shed and the nucleus is extruded to form reticulocytes. Reticulocytes enter the circulation, losing mitochondria and mRNA in the process, before assuming the biconcave disc morphology of the erythrocyte; this shape is crucial for red cell passage through capillary beds and thus oxygen delivery to the mitochondria. Erythrocytes remain in the circulation for approximately 120 days, before being sequestered by the reticuloendothelial system and recycled[16].

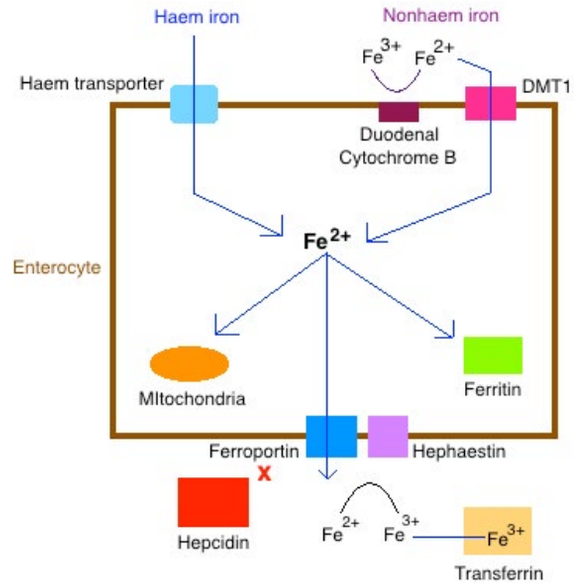
Iron is the central ionic element of the haem molecule. Sixty per cent of total body iron is stored in haemoglobin; 10% is found in myoglobin, enzymes and cytochromes; and the remainder is stored in liver, bone marrow and macrophages. Iron is essential not only in erythrocytes as an oxygen transporter, but also for DNA synthesis, mitochondrial respiration and cellular immunity[17].

Iron is absorbed from the proximal small bowel in two ionic configurations. Haem iron in the ferrous form (Fe2+) is found in animal food sources and is readily absorbed through the gut mucosa via the haem transport enzyme ferroportin, accounting for over 40% of total absorbed iron. Non-haem iron is less readily absorbable as ferric iron (Fe3+) and must be converted into its ferrous state by the duodenal cytochrome B enzyme of the gut mucosa before being actively transported intracellularly. This form of iron is present in non-meat sources such as legumes, grains, nuts and vegetables. Absorption of non-haem iron is increased in the presence of haem iron and ascorbic acid (Vitamin C). Vitamin C prevents the formation of insoluble iron compounds and reduces ferric to ferrous iron[18]. Many iron supplements are compounded with Vitamin C to take advantage of this phenomenon. Absorption requires an acidic milieu in the stomach, and compounds such as tannins (found in tea), phytates (cereals and legumes) and calcium all inhibit this process.

Typical dietary intake totals 1-2 mg per day, however 20 to 30 mg daily is required for red cell production and cellular function. Therefore, recycling of iron stores from senescent erythrocytes and exchange of iron-containing enzymes plays a large part in iron homeostasis[17]. This process occurs primarily in the spleen, where haem oxygenases within macrophages degrade haem compounds to release iron. Iron can be stored in macrophages by binding to ferritin, an intracellular iron storage protein that is also expressed in enterocytes and hepatocytes. Alternatively, iron is exported out of the macrophage into the circulation by the protein ferroportin, converted into its ferric form, and carried in the circulation bound to transferrin. Transferrin is the primary iron transport molecule and levels are increased in iron deficiency to increase iron availability in the tissues[16,19].

The discovery of hepcidin in 2001 was revolutionary in the understanding of the regulatory pathways that control iron availability. This hormone, produced primarily by hepatocytes, controls the surface expression of the iron-exporting protein ferroportin on enterocytes and macrophages. Hepcidin expression is upregulated in the presence of high iron concentrations, which in turn blocks the absorption of iron from the gut and the release of iron from macrophages, in order to reduce plasma iron concentrations. Crucially, inflammation will also increase hepcidin expression; this is one mechanism by which anaemia of chronic disease results in functional iron deficiency. Conversely, low hepcidin expression causes a rise in plasma iron concentrations, which can occur in absolute iron deficiency, erythropoiesis or hypoxia[16].

Figure 1. Diagrammatic representation of intestinal iron absorption.



Haem iron is readily absorbed from the lumen of the intestine through the divalent metal transporter (DMT1), whereas nonhaem iron is converted to its ferrous state by the enzyme duodenal cytochrome B, before being transported intracellularly. Ferrous iron is either stored intracellularly as ferritin, utilised for mitochondrial function, or exported into the circulation by ferroportin. The action of ferroportin is inhibited by hepcidin. Ferrous iron is converted to ferric iron by the enzyme hephaestin and carried in the circulation by transferrin.

Erythropoietin, a glycoprotein produced by the kidneys in response to tissue hypoxia, is the stimulatory hormone for erythropoiesis. Its two fundamental roles are to maintain red cell mass (and haemoglobin concentration), and hasten red blood cell (RBC) recovery after haemorrhage. Erythropoietin deficiency as a result of renal parenchymal damage is the main mechanism underlying anaemia in chronic kidney disease. Its primary effect is on red cell precursors in the bone marrow, providing cytoprotection from apoptosis and interacting with growth factors (interleukin-3, interleukin-6, glucocorticoids and stem cell factor) to promote erythropoiesis. Treatment with recombinant human erythropoietin is commonplace in chronic kidney disease, and less commonly in the management of anaemia in myelodysplastic syndrome.

AETIOLOGY

IDA and anaemia of chronic disease (ACD) are the two most common diagnoses of anaemia in the surgical population, and the majority of research has focused on the management of these conditions. However, it is important to recognise other forms of anaemia which may coexist or present as a primary aetiology.

Iron deficiency anaemia

ID is the most prevalent nutritional deficiency worldwide. IDA occurs when iron loss or requirement exceeds intake and absorption. For this reason it is common in infants, pre-menopausal women and pregnancy. Several pathological conditions may contribute to its development. Gastrointestinal blood loss is the leading cause of ID in developed countries, with colorectal and gastric cancer the predominant causes, followed by peptic ulcer disease, inflammatory bowel disease and medications such as non-steroidal anti-inflammatory drugs[17]. Malabsorption syndromes such as coeliac disease, *Helicobacter pylori* colonisation, post-gastrectomy or bowel resection reduce mucosal handling of iron and subsequent release into plasma for transportation to bone marrow. Interaction with proton-pump inhibitors (which raise gastric pH and inhibit the reduction of ferric iron) or food elements (which chelate iron in the lumen) can also occur[17,20,21]. Finally, rare genetic disorders including iron-refractory IDA, where “loss of function” mutations result in inappropriately high hepcidin levels and can prevent adequate iron absorption.

It is important to note that ID can occur in the absence of anaemia; a recent systematic review highlights its importance as a disease entity[22]. Symptoms of fatigue and reduced exercise tolerance are commonplace and

improve with oral or intravenous iron replacement[23]. Chronic conditions such as inflammatory bowel disease, cancer, and chronic kidney disease are associated with ID, while ID in the setting of heart failure results in decreased quality of life and worsened exercise tolerance[24]. A single-centre study in cardiac surgery suggests an association between non-anaemic iron deficiency and longer hospital stay and poorer outcomes[25].

Anaemia of chronic disease

ACD is primarily caused by inflammation. Examples include acute infection from bacterial, viral or fungal pathogens; chronic systemic inflammatory conditions such as autoimmune diseases; or low-grade inflammation as seen in chronic renal failure, heart failure or cancer. There are several purported mechanisms:

1. *Iron*. Inflammation reduces iron availability, a protective mechanism whereby iron is sequestered and stored in macrophages to limit its availability to microbial pathogens, which require iron for proliferation. Hepcidin expression is increased in the presence of inflammation and cancer by cytokines such as interleukin-6, which increases its hepatic synthesis. This in turn prevents the release of iron from the reticuloendothelial system, resulting in inefficient mobilisation of iron stores. This "functional iron deficiency" reflects a state of reduced tissue availability of iron, despite apparently normal total body iron stores.
2. *Response to erythropoietin*. A reduction in marrow response to erythropoietin is not exclusive to patients with renal impairment, however the pathophysiology of its involvement in ACD is unclear. Erythrocyte development is dependent on erythropoietin in the initial phase; it is possible that erythropoietin production is insufficient to allow erythropoiesis (relative erythropoietin deficiency), or that the erythropoietic response is somehow blunted.
3. *Therapeutic agents.* Patients with cancer commonly develop ACD, which has many of the elements of inflammatory anaemia, while being potentiated by cytotoxic therapies. Many chemotherapies impair the bone marrow response to erythropoiesis. Approximately 65% of patients with lung and gynaecological cancer treated with platinum-based drugs develop anaemia, which reduces survival and worsens quality of life in patients with cancer[26]. Erythropoiesis-stimulating agents such as erythropoietin and darbapoetin have been shown to improve haemoglobin concentration and reduce transfusion[27]. These agents are currently licensed for use in patients with anaemia receiving chemotherapy for non-myeloid cancers[27,28].

Anaemia of pregnancy

Anaemia is highly prevalent in pregnancy, where it is associated with a number of adverse outcomes including low birth weight and prematurity[29]. The aetiology is multifactorial: a rise in plasma to red cell ratio causes a dilutional anaemia with a fall in Hb concentration starting in the second trimester, while ID is near ubiquitous in pregnancy. Many women enter pregnancy with pre-existing ID (owing to menstrual iron loss), where the elevated iron requirements of the pregnancy and fetus overwhelm gastrointestinal absorption of iron. Thus, iron limited erythropoiesis may contribute relatively more to the physiological anaemia of pregnancy and is attenuated by iron supplementation[30].

Macrocytic anaemia

Macrocytic anaemias are less frequently encountered, and can be subdivided into megaloblastic or non-megaloblastic depending on the appearance of the nucleated red cell precursor on blood film or bone marrow aspirate. The most common cause of megaloblastic anaemia is Vitamin B12 deficiency, due to nutritional deficiency (for example, alcoholism), malabsorption (post-gastrectomy, ileocaecal inflammatory bowel disease, gastritis) or autoimmune impairment of intrinsic factor secretion (pernicious anaemia). Vitamin B12 deficiency can also occur in the absence of macrocytosis, if other forms of anaemia are present (such as ID)[31]. Folate deficiency is commonplace in coeliac disease and alcoholism, or may be induced by drugs such as methotrexate or hydroxyurea. Dietary folate deficiencies are rare in the developed world due to fortification of cereals and grains. Vitamin B12 is essential to converting folate from its inactive form (5-methyltetrahydrofolate) to its active form (tetrahydrofolate), which is the cofactor responsible for the production of several coenzymes in erythropoiesis. Non-megaloblastic macrocytic anaemias have a wider differential, which includes myelodysplastic syndromes, hypothyroidism, alcoholism, and drugs such as antiretrovirals and anticonvulsants[32].

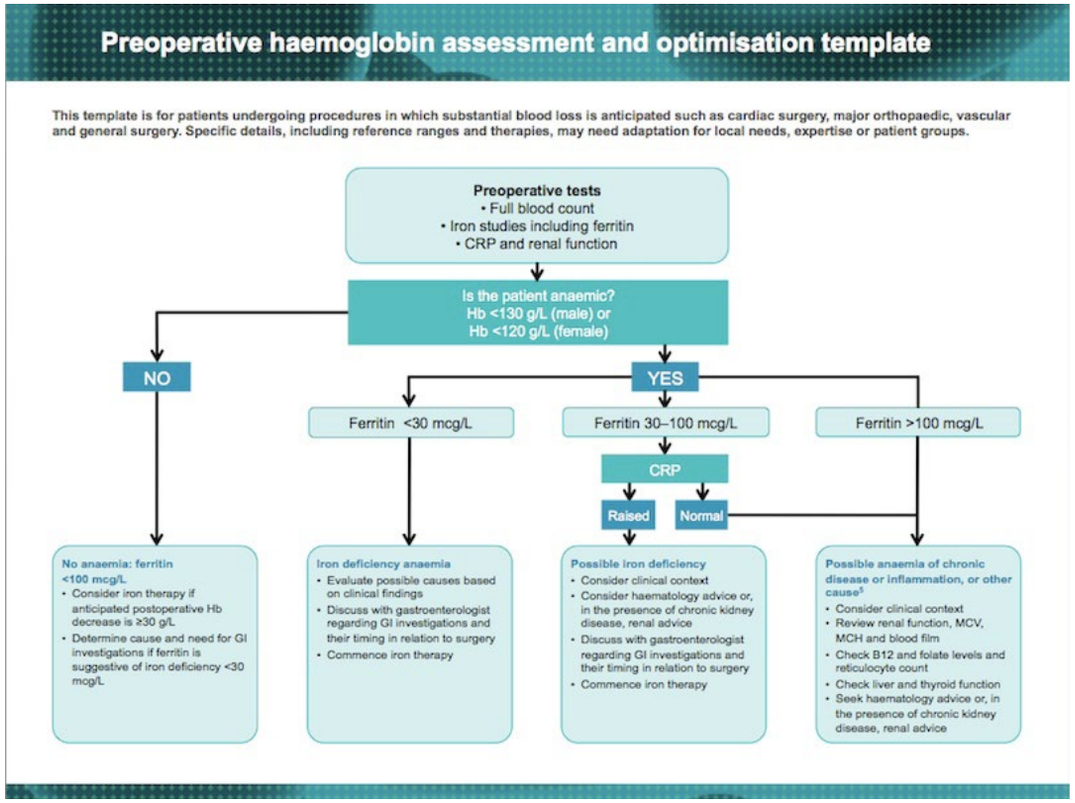
Hereditary red cell disorders

Haemoglobinopathies are a common cause of anaemia worldwide, with thalassaemias and sickle cell anaemia most commonly encountered due to mutations of the alpha or beta globin chains. The clinical phenotype can vary significantly and it is important to identify if this may be a cause of anaemia, keeping in mind that concomitant causes of anaemia can exist. In thalassemia trait or minor, there may be no or mild anaemia associated with a microcytosis. Thalassemia major syndrome may result in significant microcytic anaemia and require regular transfusions[33]. Red cell membrane disorders such as hereditary spherocytosis occur due to abnormalities in erythrocyte membrane proteins resulting in spherical red cells. These fragile cells are more susceptible to extravascular haemolysis in the spleen, resulting in anaemia[34]. The most common red cell enzyme disorder is glucose-6-phosphate deficiency, where defects in the hexose-monophosphate pathway predispose to oxidative haemolysis and anaemia[35].

DIAGNOSIS

Differentiation of anaemia may be difficult, as subtypes frequently co-exist and laboratory parameters often fail to neatly follow textbook descriptions. A suggested algorithm for perioperative practice is presented here.

Figure 2. Flow diagram for differentiating pre-operative anaemia in Fiona Stanley Hospital.



This diagram is based on the National Blood Authority Australia Perioperative Patient Blood Management Guidelines on Pre-operative Haemoglobin Assessment and Optimisation[36] which has been adapted for use in our local institution (with permission from Fiona Stanley Hospital WA).

Classification of anaemia

There are multiple classification systems available, but the most commonly used system divides anaemia into three categories based on morphology from a full blood count; microcytic, normocytic and macrocytic. Mean cell volume is estimated using automated cell counters.

1. Iron deficiency anaemia is classically microcytic, with a mean corpuscular volume (MCV) of under 80 fL, and hypochromic, with a mean cell haemoglobin (MCH) of less than 27 pg/cell, although this picture can also be seen in thalassaemia, sideroblastic anaemia and ACD.
2. Normocytic anaemia is commonly seen in ACD but may also be suggestive of renal failure, haemolysis or a mixed microcytic macrocytic picture.
3. Macrocytic anaemia with MCV greater than 100 fL may be megaloblastic or non-megaloblastic.

MCV and MCH are useful for diagnosis of anaemia and for monitoring trends over time, but are not helpful in the acute setting to monitor response to treatment.

Assessing iron stores

As IDA is the most common aetiology — and also the most amenable to therapeutic intervention –iron studies should be the initial investigation of choice in the perioperative setting.

Ferritin is the key iron storage protein and the most specific laboratory test to correlate with total body iron stores[17]. Low plasma concentrations (less than 30 μg/L) in the presence of anaemia denotes IDA and no further testing is required. Ferritin less than 30μg/L in the absence of anaemia signifies absolute ID. International perioperative guidelines reference a plasma ferritin concentration less than 100 μg/L as diagnostic of inadequate iron stores for major surgery[37], however this definition is not commonly used outside the Patient Blood Management literature. In the setting of chronic renal failure on haemodialysis, a level above 200 μg/L may be considered an acceptable therapeutic target for iron supplementation[38]. As ferritin is an acute phase reactant, concentrations greater than 30 μg/L will be seen in the setting of inflammation; therefore a high ferritin does not preclude systemic ID.

Transferrin saturation is a measure of the iron availability for erythropoiesis. It may be used with other variables such as ferritin or reticulocyte haemoglobin concentration in the diagnosis of ID, particularly when ferritin is spuriously elevated by inflammation. A cut off of 20% with a ferritin of less than 100 μg/L could be consistent with absolute ID in this setting[37]. Alternatively, low transferrin saturation in the presence of inflammation, where ferritin levels will be elevated above 100 μg/L, may suggest functional ID where total body irons stores are normal but erythropoiesis is restricted by the unavailability of iron in the marrow. When used in isolation, transferrin saturation is a poor predictor of response to intravenous iron.

The soluble transferrin receptor is a useful marker in differentiating the presence or absence of ID in the setting of inflammation, cancer or in ACD. It is derived from the breakdown of membrane transferrin receptors and is highly expressed in ID, haemorrhage and disorders of expanded erythroid marrow[17,39]. Inflammation will have little effect on soluble transferrin receptor levels; thus high levels are useful for identifying the presence of ID in the context of ACD. It is the defining feature of functional iron deficiency. The drawback to this test is that it is relatively expensive, not widely available, and is not superior to serum ferritin in determining ID in the average patient[20].

Reticulocyte parameters

The reticulocyte count is a measure of the bone marrow response to anaemia and is useful for monitoring response to treatment. Reticulocytes are precursor cells to erythrocytes released from bone marrow erythroblasts. A low reticulocyte count reflects inadequate bone marrow erythropoietic activity. A high reticulocyte count is an indicator of red cell degradation or loss (with haemolysis or haemorrhage as common examples), while also signifying adequate response to haematinic treatment.

Reticulocyte haemoglobin content is a measure of adequacy of iron incorporation into the reticulocyte. It correlates with the MCH of the reticulocyte population, with values > 29 pg signifying adequate iron stores. Low values indicate reduced haemoglobin content in reticulocytes and ID. This is true even in the presence of a normal ferritin and transferrin[38]. It can also be used to predict an adequate response to intravenous iron, as levels rise acutely in the first 72 hours post intravenous iron infusion[40].

Other parameters

Red cell distribution width (RCDW) describes the variability of size of erythrocytes in the population, defined by the coefficient of variation of the MCV. RCDW is frequently increased in IDA, folate and vitamin B12 deficiencies. It is helpful in determining chronicity of the anaemia, and may reflect recent haematinic replacement with bone marrow response.

The ferritin index is an infrequently used parameter to predict a response to intravenous iron replacement. This number is derived from the ratio of soluble transferrin receptor level to the log of ferritin and may improve the specificity of the soluble transferrin receptor test.

Several other biomarkers have more limited clinical value and are not routinely ordered in the clinical investigation of anaemia. One example is serum hepcidin levels, which are elevated in the setting of inflammation; its utility as a diagnostic tool remains unclear and is limited by availability of the hepcidin assay which is expensive, time consuming and thus remains limited to research[38]. Similarly, serum erythropoietin levels are not measured routinely in clinical practice. Patients with chronic renal failure are known to have diminished levels and require supplementation, however response to treatment is better guided by other markers (such as haemoglobin concentration) over time.

Haematinics

Vitamin B12 deficiency is diagnosed on both history and laboratory tests, as there is no gold-standard test for its diagnosis. Most assays measure total serum cobalamin, though some laboratories measure holotranscobalamin, the proportion of conjugated vitamin B12, which may improve sensitivity. Definitive cut-off values for deficiency will vary between laboratories given the variability of different testing methodologies. Serum folate levels are generally taken along with serum cobalamin, however folate deficiency is uncommon in countries with fortified wheat products[41].

Blood film and bone marrow biopsy

Examination of the blood film can give many clues as to the likely aetiology of anaemia. While detailed knowledge of red cell morphological changes is more the remit of a haematological pathologist, they are frequently noted in full blood count reports and are thus useful background knowledge for the perioperative physician. While useful for differentiating anaemia prior to surgery, a peripheral smear will identify more sinister causes of anaemia, such as marrow infiltration and proliferative disorders, which might impact on the primary surgical procedure. Important morphological changes include:

- Size
  - Macro-, normo- or microcytosis
  - RCDW, where a highly variable erythrocyte size is suggestive of IDA
- Poikilocytosis (shape abnormalities)
  - Red cell fragmentation, suggesting destruction within the vascular space, for example, thrombotic thrombocytopaenic purpura or disseminated intravascular coagulation
  - Sickle cells
  - Target cells, seen in liver disease or thalassaemia
  - Spiculated RBC, seen in uraemia or liver disease
  - Spherocytes, indicating autoimmune haemolytic anaemia or hereditary spherocytosis
- RBC inclusions
  - The mature erythrocyte has extruded its nucleus and contains few cytoplasmic organelles
  - Nucleated RBC (normoblasts) are an abnormal finding outside of neonates and pregnancy, and are associated with haemolysis, marrow stress and infiltration
  - RBC parasites such as malaria
- Non-red cell elements – changes in other cell lines in addition to anaemia should arouse suspicion
  - Elevated and or abnormal lymphocytes may be associated with lymphoproliferative disorders
  - Co-existing neutropenia and thrombocytopenia may occur for a number or reasons including infection, medication effects and marrow disorders

A bone marrow biopsy may be a useful diagnostic modality for chronic anaemia if a bone marrow disorder is suspected. Where there is uncertainty regarding a diagnosis of iron deficiency, the presence or absence of iron on Prussian Blue stain is the gold standard for diagnosis. Due to its obvious limitations such as availability and cost, it is not routinely performed as part of a perioperative anaemia work up.

CONCLUSION

Preoperative anaemia detected on routine laboratory testing, or as part of a Patient Blood Management screening program, may present the perioperative physician with diagnostic uncertainty. It also provides an opportunity for modulation of surgical risk, as timely optimisation of the patient's own red cell mass with the use of haematinics, and in some cases erythropoiesis-stimulating agents, coupled with pragmatic scheduling of the primary surgical procedure may reduce the morbidity associated with anaemia and blood transfusion. The anaesthetist as a perioperative physician is well placed to provide this intervention when armed with simple algorithms (such as that offered by the National Blood Authority of Australia), timely preoperative assessment, involvement of primary care physicians and access to specialist haematology services. Assessment of this modifiable risk factor should form a key component of modern anaesthesia practice.

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Regional

An update on the management of patients with rib fractures

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INTRODUCTION

Rib fractures are a painful injury associated with high patient morbidity and mortality. Approximately 10% of chest trauma patients have one or more fractured ribs, blunt trauma being the most frequent mechanism[1]. Patients with five fractured ribs have a mortality of 10%, increasing to 34% for eight ribs or more. Respiratory complications of rib fractures include atelectasis, pneumonia, pleural effusion, acute respiratory distress syndrome, aspiration and pulmonary emboli. Patients with rib fractures use significant hospital resources, often requiring intensive care unit (ICU) admission and mechanical ventilation for respiratory complications.

Evidence for risk factors of morbidity and mortality in patients with blunt chest trauma is conflicting, but significant risks may include: the severity of the injury, for example, number of fractured ribs, bilateral fractures, flail segment, pulmonary contusion; patient factors, for example, age, comorbid disease and frailty; clinical indicators of respiratory function, for example, SpO_2 and $PaCO_2$ on admission. Identification of patients at risk of complications allows for early interventions aimed at decreasing respiratory complications, for example catheter-based analgesia, physiotherapy and rib fixation. We endorse the development and introduction of institutional multidisciplinary rib fracture pathways to promote standardisation of care.

PATHOPHYSIOLOGY

Respiratory failure after blunt thoracic trauma may be multifactorial.

Pain: The inability to splint fractured ribs during respiration and the subsequent pain may cause a reduction in tidal volume, atelectasis and hypoventilation. The avoidance of deep breathing and coughing can lead to retained secretions and infection.

Lung contusion: A lung contusion and subsequent oedema can also affect lung aeration, decreasing compliance and increasing shunt. These pathophysiological changes following injury typically do not peak until more than 48 hours post injury.

Flail segment: Flail segment is generally defined as the fracture of three or more adjacent ribs in at least two places. A broader definition also includes three or more bilateral consecutive rib fractures, and three or more rib fractures with an associated sternal fracture, as both of these patterns of injury result in mechanical disadvantage[2].

A flail segment alters the efficiency of respiratory mechanics and ventilation, with negative intrapleural pressure causing inward or paradoxical chest wall movement during inspiration. Failure of lung aeration underlying and adjacent to the flail increases shunt, while the loss of lung available for gas exchange results in an increased respiratory rate to maintain minute ventilation.

PATTERNS OF INJURY

Upper zone ribs 1-4: Typically require high velocity trauma. Adjacent structures that may be damaged include subclavian vessels, brachial plexus, as well as fractures to the scapula and sternum[4]. The risk of vascular injury rises with increasing injury severity (that is, injury to other parts of the body)[4], probably a reflection of overall trauma force.

Middle zone ribs 5-9: Adjacent structures at risk are the lung and pleura resulting in pulmonary contusions and haemopneumothorax.

Lower zone ribs 10-12: Adjacent structures include the liver, spleen, kidneys and diaphragm. Approximately 50% of patients with multiple lower rib fractures also have a solid organ injury[3].

PREDICTING MORBIDITY AND MORTALITY

Several risk factors that predict morbidity and mortality in patients with rib fractures have been identified from observational studies. These risk factors are useful in early identification of asymptomatic patients, allowing intervention aiming to decrease the risk of developing respiratory complications.

Injury severity

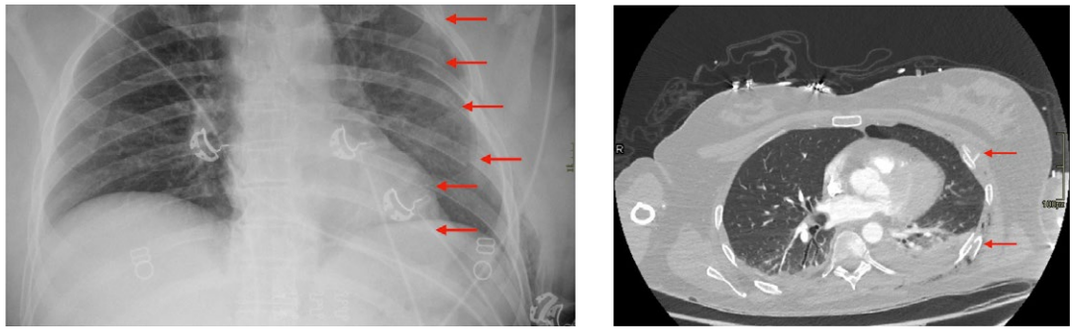
Number of ribs fractured: Increasing number of ribs fractured is consistently associated with poorer patient outcome[1,5-7]. It is unclear if this is an independent predictor of morbidity and mortality, or a marker of overall trauma severity[1,8]. A meta-analysis indicated an odds ratio (OR) for mortality in patients with three or more rib fractures of 2.02, compared to those with less than three[6].

Location and pattern of rib fractures: Bilateral rib fractures increase mortality significantly, with patients suffering greater than three fractured ribs bilaterally having a mortality of 41%, OR 3.43[5].

Flail segment is also a risk factor. Patients with a flail segment have a high rate of mortality at 16-17%[9,10], with a higher rate of mechanical ventilation, respiratory complications, and longer hospital stay compared to a matched cohort without a flail segment[11].

Pulmonary contusion: Radiographically determined injury to lung parenchyma has a strong association with adverse outcome. Patients with severe pulmonary contusions (>20% contusion on CT, see Figure 1) are more likely to be admitted to the ICU (OR 2.74), and develop morbidity such as empyema (OR 4.8)[12]. Further, a unilateral lung contusion confers mortality of 25%, OR 1.82, with bilateral lung contusions and haemopneumothorax conferring mortality of 53%, OR 5.1[5]. Chest x-ray changes are often not present until 24 hours after the injury, implying that imaging on admission may underestimate the severity of injury.

Figure 1. CXR and CT of a patient with a left flail segment and pulmonary contusion (published with patient permission). The red arrows indicate rib fractures.



Patient factors

Age: Increasing age has consistently been associated with poor outcomes following rib fractures[13]. Although age cut-offs for poor outcome are described in observational studies and often used in institutional clinical care pathways, the risk of poor outcome is likely to increase continuously with age. Thresholds that have been described vary from age >45 to age > 65[6,14,15,99]. A meta-analysis found patients older than 65 have an OR of 1.98 for mortality compared to those younger than 65[6].

Comorbid disease: Comorbid disease is also associated with increased mortality in patients with rib fractures[6], likely due to a decreased physiological reserve. Comorbidities that have been identified include respiratory

disease[16], congestive cardiac failure[17,18] and diabetes[16,18]. Unfortunately, criteria for diagnosis of each of these comorbidities was not reported.

Frailty: There is increasing awareness that frailty may predispose to poor perioperative and trauma outcomes[19-21]. Frailty is defined as the decrease in physiologic reserve as well as multisystem impairments which are separate from the normal process of aging. These changes lead to increased vulnerability and place the patient at greater risk of morbidity and mortality. Frailty is associated with complications from blunt thoracic trauma with an OR 30.66 (2.35-36.79)[22] using the modified Frailty Index. Multiple tools are available to assess frailty, although there is no consensus about which tool is best.

Clinical indicators

Physiological derangements on admission: Low oxygen saturation has been correlated to respiratory morbidity[18] in patients with rib fractures, however the study did not include a threshold for low SpO_2 or indicate an effect size. Further, $PaCO_2$ greater than 45 mmHg within 60 minutes of arrival in the emergency department also predicts respiratory complications with an OR 7.63 (2.31-25.18)[22].

Table 1. Risk factors for morbidity in patients with rib fractures.

	Risk factor
Injury	≥ 3 ribs fractured[3]
	Bilateral rib fractures[5]
	Flail segment[9,10]
	Pulmonary Contusion[22]
Patient factors	Age ≥ 65[6,99]
	Frailty[22]
	Congestive cardiac failure[17]
	Respiratory disease[16]
	Diabetes[18]
Clinical presentation	$PaCO_2$ > 45 mmHg[22]
	Low SpO_2[18]

DISABILITY AFTER RIB FRACTURES

Observational studies show disability from rib fractures is a problem that persists for patients long after their acute hospital admission. A case series of patients with isolated rib fractures (mean of 2.7 ribs fractured) showed mean total days lost from work or usual activity was 51 +/- 39, increasing further in patients with associated extrathoracic injuries[23]. Another cohort showed patients with multiple rib fractures had significantly lower quality of life two years post injury, with 29% of patients working prior to the injury not returning to any work[24]. Rib fixation does not appear to improve pain or quality of life at two years in patients with a flail segment [24]. Understanding the significant disability associated with rib fractures allows early planning for rehabilitation, occupational therapy, and social work that may assist patients after their acute admission.

PAIN AND ANALGESIA

Rib fractures are a painful injury due to the unavoidable movement of fractures when breathing. Patients with rib fractures value good analgesia, and it may confer a morbidity and mortality benefit, although data is conflicting and is discussed below.

Many regional techniques have the potential to provide analgesia in chest trauma. Analgesia is typically required for three to seven days, meaning techniques allowing catheter placement are ideal and are the focus of discussion here. Options include thoracic epidural analgesia, paravertebral block, and newer myofascial blocks including the erector spinae and serratus anterior block.

It is worth noting that even if regional analgesia functions well, systemic analgesia may still be required. Regional analgesia only covers nociception from thoracic spinal nerves. It will not cover phrenic nerve (C3/4/5) innervation of the diaphragm, for example, diaphragmatic irritation from blood or a chest tube, nor vagus nerve innervation of the visceral pleura and mediastinum, for example, mediastinal injury. Thoracic trauma is also frequently associated with other injuries that will not be managed by a single regional technique, for example fractures of the clavicle, scapula and upper or lower limbs.

SYSTEMIC ANALGESIA

Opioids continue to be the mainstay of systemic analgesia in most centres. Their side effects can be a significant problem for patients, and in the perioperative setting are associated with increased postoperative length of stay and 30-day readmission[26-28]. Opioid sparing medications should be prescribed[29] with or without regional analgesia. This is particularly important for patients at risk of opioid related side effects, for example, obstructive sleep apnoea[30,31], severe lung disease, or for whom their efficacy may be limited, for example, opioid tolerance. A Cochrane review concluded that opioids delivered by a patient-controlled analgesia system provided slightly better pain control and increased patient satisfaction compared to conventional parenteral opioids[32].

Paracetamol: Paracetamol is an effective analgesic for acute post-surgical pain[33] which reduces opioid consumption[34], reduces nausea and vomiting[35], and has few adverse effects.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): A small observational study in patients with traumatic rib fractures showed the use of a NSAID improved pain scores and lowered opioid requirements with a trend to lower hospital length of stay[36]. Another observational study showed the use of a NSAID decreased the incidence of pneumonia (OR 0.14 95% CI 0.04 - 0.46), and decreased the duration of intensive care unit stay[37]. Neither study showed an increase in adverse outcome during the relatively short duration of use.

Ketamine: A randomised controlled trial of patients younger than 65 showed ketamine lowered opiate consumption in patients with rib fractures with more significant overall trauma burden (Injury Severity Score >15)[38]. This finding agrees with other observational studies in the setting of rib fractures[39], and a Cochrane Review which found ketamine probably reduced postoperative analgesic consumption, pain intensity, nausea and vomiting[40].

Gabapentinoids: There is limited data on the use of gabapentinoids in patients with traumatic rib fractures. Although acute post-surgical pain studies show gabapentinoids reduced opioid consumption and increased somnolence[41,42], a small randomised study of patients with rib fractures showed no benefit to the addition of gabapentin to other opioid sparing medications[43]. Somnolence is concerning in patients with rib fractures as it may increase respiratory complications.

Tramadol: Tramadol is an effective analgesic for post-surgical pain, but may not provide sufficient analgesia for moderate to severe pain at typical doses of 50 to 100mg as required[44]. Pharmacogenomic variation in metabolism of this pro-drug can also limit its use due to inadequate metabolism resulting in poor analgesia, or ultra-rapid metabolism resulting in tramadol-related opioid analgesic effects such as addiction, nausea and respiratory depression[45]. There are no studies in patients with rib fractures specifically comparing tramadol to systemic opiates.

Tapentadol: Immediate release tapentadol appears to offer similar analgesia to immediate release opioids for acute post-surgical pain[46,47], although there are no specific studies investigating the efficacy of tapentadol in patients with rib fractures. Its use is appealing due to the lower incidence of nausea, vomiting and constipation compared to oxycodone, although it causes similar somnolence[48].

Lignocaine patch: Topical lignocaine patches have been used in some institutional rib fracture pathways. A randomised trial showed lignocaine patches offer no improvement in pain control, opioid consumption, pulmonary complications or length of stay[49]. This finding is supported by a review which concludes there is currently no evidence to support the use of topical lignocaine patches in patients with traumatic rib fractures[50].

REGIONAL ANALGESIA

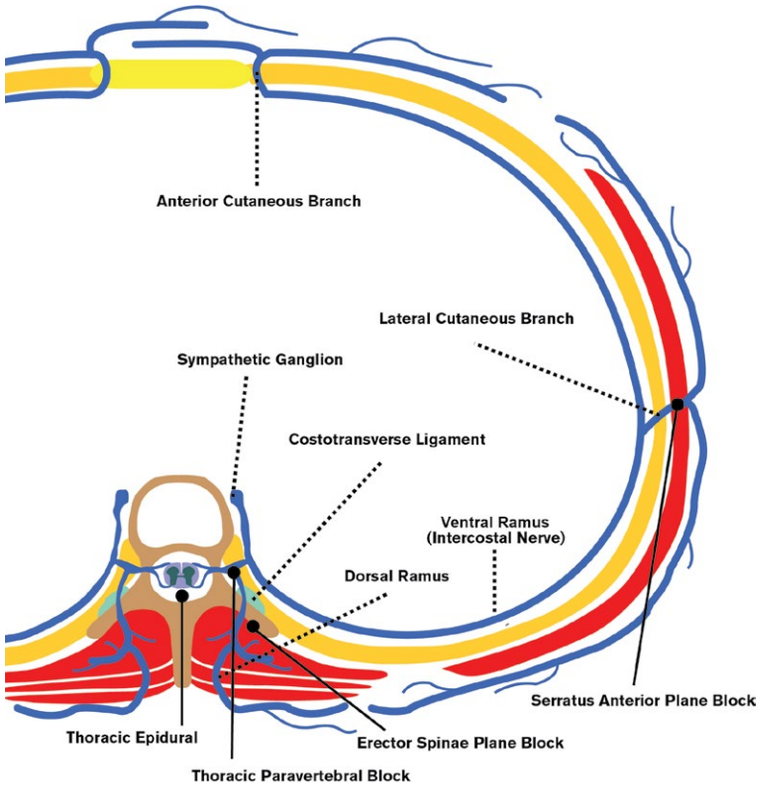
Catheter-based regional analgesia has consistently shown improved pain scores in patients with rib fractures compared to systemic analgesia[51]. Of these techniques, epidural analgesia is the most studied, and patients with greater injury severity seem to benefit most[52]. Epidural analgesia has also been associated with reduced mortality in rib fracture patients[53] and reduced cost of inpatient care[54].

The quality of evidence for catheter-based analgesic techniques in decreasing morbidity and mortality is low, with many observational and small, single centre studies. Several studies have indicated patients receiving catheter based thoracic analgesia for rib fractures have a lower incidence of pneumonia, shorter duration of mechanical ventilation[55], decreased ICU length of stay[56,57], decreased delirium[58], and decreased mortality[59]. Other meta-analyses have shown no difference[51,60]. Recent editorials have called into question the rapid uptake of the newer myofascial regional techniques with a low evidence base, while acknowledging that due to their ease of insertion and low risk profile they are here to stay[60].

The Eastern Association for the Surgery of Trauma and the Trauma Anesthesiology Society have published a document on the analgesic management of blunt chest trauma[29]. It provides evidence-based recommendations to aid decision making in patients with rib fractures. It places a high value on patient preference for analgesia, and conditionally recommends thoracic epidural analgesia over non-regional modalities of pain control whilst making clear that this recommendation is based on very low-quality evidence.

The efficacy of catheter-based regional analgesia for multiple rib fractures is likely to be affected by the delivery of local anaesthetic. Local anaesthetic spread in a myofascial plane is influenced by the volume of the bolus injected[62]. It seems reasonable that analgesia for multiple rib fractures is improved with boluses of local anaesthetic compared to a continuous infusion, for example, a programmed or patient-controlled boluses. Anecdotally, analgesia is improved with the use of programmed intermittent ± patient demand boluses and many institutions have adopted this[63], although there is an absence of peer reviewed literature to support this. Coverage of a large number of rib fractures may potentially be achieved by larger volume boluses of local anaesthetic, or the insertion of two unilateral catheters. Higher local anaesthetic concentrations for a given volume may also provide superior analgesia[64]. The safe daily dose for patients receiving local anaesthetic for a number of days is unclear.

Figure 2. Anatomical location of regional blockade. Illustration by Dr Ben Darby.



Thoracic epidural

Thoracic epidural analgesia is historically considered the gold standard for rib fractures unresponsive to systemic analgesia. Thoracic epidural analgesia blocks the spinal nerves by depositing local anaesthetic within

the epidural space, preventing nociceptive pain signals from the intercostal nerves. Classically, insertion should be at the midpoint of any rib fractures to block transmission from intercostal nerves above and below this point.

Paravertebral block

Paravertebral block for thoracotomy has shown equivalent analgesia to thoracic epidural analgesia, with a better side-effect profile[65]. Local anaesthetic is deposited deep to the transverse process of the vertebrae in the paravertebral space, blocking nociception from thoracic spinal nerves close to their path through the intervertebral foramen. The paravertebral space also communicates with the intercostal and epidural spaces, and local anaesthetic deposition produces unilateral motor, sensory and sympathetic blockade. A single 15 ml injection has been shown to produce unilateral somatic block over a mean of 5 dermatomes, though spread may be unpredictable with a range 1-9[66]. The spread is typically both cephalad and caudad to the site of injection.

A recent meta-analysis of patients with rib fractures receiving catheter-based analgesia indicated paravertebral blocks had similar pain scores and length of ICU or hospital stay compared to epidural analgesia[51]. The complication rate of ultrasound guided paravertebral catheter placement for rib fractures is low, with a retrospective observational study showing 2% of catheters removed for ineffective analgesia, and less than 1% of patients having minor side effects[67].

Erector spinae plane block

This novel interfascial plane block was first utilised for analgesia from chronic neuropathic chest wall pain[68] and has since been successfully used for chest trauma analgesia[63]. A retrospective observational study of 79 patients with rib fractures who received an erector spinae plane block showed improved spirometry in the first 24 hours after receiving a block, along with reduced pain scores[69].

The technique involves depositing local anaesthetic deep to the erector spinae muscle and above the transverse process with catheter placement possible into this potential space. The local anaesthetic is then in proximity to the costotransverse foramina and blocks nociceptive transmission at the dorsal and ventral rami at their thoracic spinal nerve origins in the paravertebral space, resulting in a hemithorax block. The cephalad and caudad spread of local anaesthetic is facilitated by the thoracolumbar fascia giving sensory changes and analgesia over the hemithorax[70]. Cadaveric studies suggest 3 to 4 spinal nerves are blocked in the mid-thoracic region with a 20 mL injection[71], and two catheters may be required if greater spread is required.

Serratus anterior plane block

This relatively new regional analgesic technique[72] involves the deposition of local anaesthetic and catheter insertion either superficial or deep to the serratus anterior muscle. The potential space surrounding the serratus anterior muscle originates from the anterior surface of ribs one to eight. Performed laterally close to the mid-axillary line, local anaesthetic deposition blocks nociception from the lateral cutaneous nerves as they travel through the serratus muscle. The dorsal ramus innervating the posterior thorax, and the anterior cutaneous nerve innervating the anterior thorax will not be covered. Analgesia can potentially be provided over seven levels from T2 to T9, with a 40 mL injection of local anaesthetic covering six dermatomes versus four with a 20 mL injection[62]. The superficial approach (local anaesthetic deposited in the myofascial plane between serratus anterior and latissimus dorsi muscles) provides a greater duration of analgesia with a theoretically reduced risk profile[72].

Table 2. Comparison of catheter based regional analgesic techniques.

	Advantages	Disadvantages
Thoracic epidural block	Historical gold standard Bilateral coverage with single catheter Block can extend multiple spinal segments	Increased hypotension Increased urinary retention Contraindicated if anticoagulated, for example, medication, coagulopathy of trauma Contraindicated in the presence of significant spinal fractures Small risk of severe neurological complications

	Advantages	Disadvantages
Thoracic paravertebral block	Equivalent analgesia to thoracic epidural Unilateral coverage	Risk of damage to nearby structures for example pneumothorax Risk of epidural spread of local anaesthetic Contraindicated if anticoagulated due to risk of haemorrhage
Erector spinae plane block	Technically simple block Unilateral block Probably safe if anticoagulated Provides unilateral hemithorax block	Recently described with little literature regarding patient outcomes Variable local anaesthetic spread
Serratus anterior plane block	Technically simple block Unilateral block Can be inserted supine Probably safe if anticoagulated	Block only covers lateral rib fractures

Anticoagulation and catheter-based regional analgesia

The American Society of Regional Anaesthesia recommends that the management of plexus blocks be based on site compressibility, vascularity, and potential consequences of bleeding[73]. Both the erector spinae and serratus anterior plane blocks are relatively superficial and compressible, are myofascial plane blocks away from a neurovascular bundle, are in locations that do not easily allow occult bleeding, for example, in to the thorax or retroperitoneum, and bleeding is unlikely to cause significant neurological damage, for example, within the spinal canal. A small case series of the use of erector spinae blocks in anticoagulated patients post thoracotomy for left ventricular assist device implantation did not show bleeding complications[74].

OTHER SUPPORTIVE THERAPY

Physical therapy

There are numerous methods of chest physiotherapy aiming to decrease lung atelectasis and clear pulmonary secretions. These techniques include positive expiratory pressure (PEP), postural drainage with percussion, active cycle of breathing techniques, autogenic drainage, oscillatory positive expiratory devices, thoracic oscillating devices (for example, Vest), and BiPaP (a PEP system delivering both positive inspiratory and expiratory pressure). Although little evidence supports these techniques in postoperative recovery[75], long term outcomes for patients with cystic fibrosis[76], or patients with pneumonia[77], they are appealing due to the lack of harm. There is an absence of literature on physiotherapy in patients with rib fractures, and compliance may be difficult for patients if analgesia is not optimal.

High Flow Nasal Cannulae

High Flow Nasal Cannulae (HFNC) deliver warmed, humidified gas to a patient, and allow the modification of the percentage of inspired oxygen and gas flow rate. HFNC with flows over 30L/min deliver approximately 1 mmHg of Positive End Expiratory Pressure (PEEP) for every additional 10L/min with the mouth closed[78]. It is better tolerated and non-inferior to non-invasive ventilation (NIV) in most studies[79]. An observational study indicated HFNC may be beneficial for patients with rib fractures in decreasing the need for mechanical ventilation, ICU length of stay and hospital length of stay[80].

There is a theoretical concern that positive airway pressure may increase the size of a pneumothorax, or prolong the duration of a persistent air leak. These fears may be unfounded, with a meta-analysis concluding that neither non-invasive positive pressure ventilation (NPPV) or continuous positive pressure ventilation (CPAP) were associated with significant morbidity or mortality in patients with rib fractures[81]. Both these techniques deliver higher airway pressures than HFNC.

RIB FIXATION

Surgical rib fixation to stabilise the chest wall, improve pulmonary mechanics and possibly reduce pain is increasing. Three randomised controlled trials have been published[82-84], showing improved patient outcomes and health economic benefits. Two of these studies included only patients with a flail segment who were

mechanically ventilated[82,85]. Meta-analyses of these and other observational studies show rib fixation for patients with a flail segment reduced mortality, duration of mechanical ventilation, ICU and hospital length of stay and morbidity including pneumonia and tracheostomy[85,86].

The Eastern Association for the Surgery of Trauma published guidelines for surgical rib fixation in 2017[87] recommending rib open reduction and internal fixation compared to nonoperative management in adult patients with flail chest after blunt trauma. It also states that there is currently insufficient evidence to offer a recommendation for surgical rib fixation for non-flail rib fractures.

Although there is regional variation in practice, many trauma centres will only consider rib fixation for patients with a flail segment who are mechanically ventilated. Some authors have proposed extended indications for rib fixation, including >= 3 rib flail not requiring mechanical ventilation, >= 3 ribs with (bicortical displacement), or >=3 ribs with displacement and >50% reduction of expected forced vital capacity despite optimal pain management[88].

Patients appear to receive the greatest benefit from rib fixation within the first 24-72 hours after injury[87], suggesting operative management should occur after resuscitation and management of other serious injuries is completed.

Patients may not benefit from rib fixation if they have another indication for prolonged ventilation, for example, traumatic brain injury, cervical cord injury. Patients with moderate to severe traumatic brain injury are unlikely to derive the full benefit of rib fixation in terms of improved pulmonary mechanics allowing for earlier extubation, mobilisation and discharge, nor does the health system gain the same health-economic benefits. These patients have been excluded from prospective studies investigating rib fixation due to the confounding need for ventilation, and increased incidence of tracheostomy, pneumonia and longer length of stay.

USE OF RIB FRACTURE SCORING SYSTEMS TO GUIDE CLINICAL DECISION MAKING

There is no universally accepted scoring system to predict morbidity and mortality in patients with rib fractures. The most commonly used scoring systems are the rib fracture score[56], chest trauma score[89] and RibScore[90]. These scoring systems assign points to a number of variables (for example, patient premorbid characteristics, clinical, radiological), each variable being weighted and the cumulative score correlating with morbidity and mortality. A recent study indicates no one score is superior to another in prognostication of a patient's outcome[91]. The scoring systems do, however, heighten awareness of a patient at increased risk of morbidity[92] and may be useful as a decision making tool for care[93], for example, catheter based analgesia, physiotherapy, high-flow nasal cannulae, intensive care unit admission.

USE OF AN INSTITUTIONAL CLINICAL CARE PATHWAY FOR MULTIDISCIPLINARY MANAGEMENT OF RIB FRACTURES

Multidisciplinary standardisation of care has shown impressive improvements in patient and health economic outcomes in other areas, for example, enhanced recovery after surgery[94,95]. Multidisciplinary clinical care pathways for management of patients with rib fractures typically involve elements relating to emergency department management, triage of patients based on injury pattern, patient risk factors and clinical signs, management of both high and low risk patients, and discharge criteria. These pathways attempt to identify patients at increased risk of complications and rationalise the resources to care for them with the aim of decreasing patient morbidity, mortality, and cost of care. A number of before and after observational studies have shown improvement in outcomes following the introduction of such pathways including decreased mortality, pneumonia, ICU length of stay and hospital length of stay[96-98].

SUMMARY

Rib fractures are a painful and serious injury associated with high morbidity and mortality. Effective analgesia is valued by patients, and may improve patient outcomes. Catheter based regional analgesia offers superior pain relief to systemic analgesia alone. Recently described myofascial plane blocks potentially increase the safety of these techniques. Early rib fixation for patients with a flail segment may improve patient and health economic outcomes. We suggest the development and use of an institutional multidisciplinary rib fracture pathway to improve care for patients with blunt thoracic trauma.

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Parallel processing pathways for regional anaesthesia: An introduction to block rooms

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INTRODUCTION

Regional anaesthesia is the process of administering local anaesthetic to a specific part of the body to provide surgical anaesthesia or analgesia. It offers several advantages including superior analgesia, a reduction in general anaesthesia, less post-operative nausea and vomiting, earlier participation in physiotherapy, and increased patient satisfaction[1,2]. Many surgical "Early Recovery After Surgery" (ERAS) protocols, particularly in orthopaedic surgery, incorporate the use of regional anaesthesia due to the benefits it offers to patients[3,4]. Given the current world opioid epidemic as well as the increasing prevalence of chronic and persistent post-surgical pain, there is a greater focus on regional anaesthesia in a wide range of clinical settings[5,6]. Arrangements for the provision of regional anaesthesia vary between institutions and health systems and are influenced by caseload, volume, experience and personnel available. In Australia, blocks are most commonly performed in the operating room before or after the induction of anaesthesia, adding to the total overall time utilisation of operating theatres. With the exponential growth of ultrasound utility, surgical acceptance, and teaching of regional anaesthesia, the need to meet these demands has never been more topical.

BARRIERS TO PERFORMING REGIONAL ANAESTHESIA

Regional anaesthesia is a skill that requires both time and technical expertise[7]. Despite evidence demonstrating benefit, barriers to performing regional anaesthesia include a busy operating theatre environment, theatre time pressures, and each individual anaesthetist's current scope of practice. Time pressure relates to failure rates of regional anaesthesia due to less dedicated time for patient positioning and anatomical landmark identification[8], which can result in inconsistent delivery of care and less buy in from the theatre team, surgeons, recovery, nursing staff, and patients. Surgeons may even decline regional anaesthesia, preferring to locally infiltrate themselves. This experience can be further heightened in clinical settings where the expectation to teach and supervise anaesthetic trainees and junior doctors can result in longer block performance, extended "non-operative" time in the operating theatre, higher block failure rates and varying levels of expert supervision[9-11].

OPERATING THEATRE EFFICIENCY

Optimising cost effectiveness of health care through efficient service delivery while maintaining safe patient care is a significant challenge[12]. In the surgical setting, maximising operating theatre efficiency requires expanding the use of operating time and reducing periods of non-operative time[11]. Factors that can enhance this efficiency include streamlining processes, coordinating patient flow, timely patient preparation, capacity in recovery and on the ward, and continuous process improvement[13,14].

Strategies aimed at reducing non-operative time in operating theatres improve operating room throughput and capacity[14,15]. In regional anaesthesia, an example of a strategy to reduce non-operative time is parallel processing patients by placing the regional block prior to the patient entering the operating theatre. One of the challenges in regional anaesthesia is being able to balance the benefits of the patients receiving a block with the use of operative time required to perform and test the block[14,15]. There is a need to develop new models of care that enhance performance in this area.

THE BLOCK ROOM

A “block room” is an environment where regional anaesthesia is performed in a parallel streaming process before the operating room has turned over from the previous case. It is best considered as more of a system than a specific physical space, as it has taken many forms over the years from using space in an anaesthetic induction room or recovery, to a separate area designated for regional anaesthesia.

Discussions surrounding block rooms have been present in the literature for decades, pioneered in North America, with more recent uptake in the United Kingdom in the past 5-10 years[7,24]. There are also a few examples of block rooms in Australia and New Zealand which have been established more recently[26]. In many institutions with established block rooms, there is a dedicated space for regional anaesthesia performance. In many institutions newer to the concept of block rooms, it is a mobile unit of personnel and equipment who move between different locations to perform the block of the next scheduled patient while the principle anaesthetist for each theatre remains in the operating theatre with their current patient rather than a set location.

ADVANTAGES OF A BLOCK ROOM

The main advantage of block rooms described in the literature is an increase in theatre efficiency through reduction of non-operative time for each case. The time saving benefits have been demonstrated in parallel processing models for brachial plexus blocks[16,17], femoral nerve blocks[18,19], and spinals[19]. Recently evidence from a new block room showed a decrease in total operating room time as well as improved failure rates from 16% to 5.6% with thoracic epidural insertions[8]. By completing the intravenous line, block, allowing time for the block to be tested, and in some cases assisting to transfer the patient to theatre with monitoring already in situ, the time spent on anaesthesia set up and induction in the operating theatre is reduced. In some cases of regional anaesthesia, particularly in upper limb surgery, patients may not require a general anaesthetic for surgery. This can reduce surgical time, anaesthesia time in theatre, and time spent in recovery, all of which can also improve overall theatre efficiency[21].

As a result of improved operating theatre efficiency, there is a potential to increase the caseload for a list[22]. While there is some suggestion that the saved time is not enough to add an additional case to many lists[23], hospitals in Europe and Canada have both shown a significant increase in productivity, resulting in an actual increase in case number per day, depending on the type of cases listed[8,16,22,24,25].

Other advantages of a block room set up include improved rate of block success, as blocks are being performed in an environment with time to formally test them and rescue them if they are not working. Successful blocks translate into improved recovery profiles measured by reduced pain scores, lower opioid use, reduced post-operative nausea and vomiting, increased patient satisfaction and a reduced duration of time in recovery[26-29].

The American Society of Regional Anesthesia (ASRA) explicitly comments using class 1 evidence that interscalene blocks should not be performed in anaesthetised or heavily sedated patients due of the documented risk of spinal cord injury from case reports[30]. Additionally, ASRA states that peripheral nerve blocks should not be routinely performed under general anaesthesia or heavy sedation because this removes the ability of a patient to communicate symptoms of peripheral nerve injury[30]. The ANZCA professional document regarding major regional anaesthesia highlights the need for rigorous systems with formalised procedures and protocols to prevent a wrong-sited block and to allow appropriate patient monitoring of conscious state, respiratory rate, and blood pressure during and after the initiation of a block[31]. Regional anaesthesia in a block room is performed in awake or lightly sedated patients in keeping with current best practice guidelines which promotes a culture of safety[30,31].

With less time pressures, a block room can facilitate regional teaching for trainees and consultants interested in up-skilling. There is more time for sonoanatomy scanning, discussions about block options, and skill development. Good data sets from block rooms also provide opportunity for increased research productivity and quality improvement studies[7,16,23,32].

There are other “non-measurable” cost reductions that may also be applicable to the use of block room, although have not been formally studied such as length of hospital stay, shorter recovery from surgery, and avoidance of ICU admission. There is growing evidence that regional anaesthesia can improve surgical outcome, such as improved fistulae patency rates[33]. These figures have been used in some hospital business proposals analysing the cost benefits of a regional anaesthesia block room[34].

COMMON BARRIERS TO BLOCK ROOM IMPLEMENTATION

There are many potential barriers to implementing a block room in different institutions. Probably foremost is a lack of culture surrounding regional anaesthesia. Previous frustrations from time delays to complete a block, block failures, and poor education about regional anaesthesia leading to confusion by home teams and patients can result in a lack of belief in regional anaesthesia, which can make establishing a program incredibly challenging.

Adding another team to a patient journey has the potential to add errors or impede patient continuity and this can also lead to patient confusion about who is ultimately responsible for their care. When there is more than one patient in a block room at a time there is the potential for wrong sided or sited block, which requires steps to ensure this does not happen.

Reliably staffing a block room can also be challenging. Setting up a functional service requires enough consultants comfortable with regional anaesthesia being allocated sufficient time to provide a dedicated regional anaesthesia service. Having competent people who are willing to work in the block room is essential to ensure that blocks are successfully completed in a limited time frame. Staffing appropriately to monitor patients following block placement is also important to consider. While patients require less intensive post-operative care in recovery, they do require observation following their block until care is transferred for their procedure. Presenting a business case to obtain funding for dedicated staff members can be extremely difficult, particularly in a health climate aimed at reducing costs. Therefore, the support of hospital and departmental administration is essential for funding and designating physical space to allow a functioning block room.

CONSIDERATIONS IN ESTABLISHING A BLOCK ROOM

Implementation of a new regional anaesthesia service must be seen to improve the value of perioperative care by demonstrating quality improvement through cost reduction[20]. In the Australian healthcare system the benefit would most likely be seen in the public sector, particularly institutions performing large volumes of orthopaedic, plastic, and vascular surgery. A recent systematic review evaluating the impact of parallel processing on resources utilisation has concluded that while there is little evidence on cost benefits, resource utilisation appears to be improved in parallel processing settings with a signal to improved clinical and patient outcomes[35]. The study states that these benefits appear to only be demonstrated in large university centres so may not be widely applicable, or may not have been widely researched, as there are fewer examples of block rooms in non-tertiary centres.

When considering whether a block room would be of benefit in an institution, it’s important to consider the following factors:

- Case mix: A hospital system that operates on orthopaedic, plastic, and/or vascular surgery is more appropriate than predominantly neurosurgery hospital.
- Case volume: Parallel processes such as block rooms are more justifiable where the turnover of cases is high. In these environments, reducing non-operative time could lead to a higher case load[7,14-16,22]. Whereas it is difficult to justify a parallel stream in an environment performing mostly long complex plastics flap procedures, which may still while benefit from a block.
- Supportive stakeholders: It is crucial to involve stakeholders early when planning a large change project such as a block room and keep them involved with regular reporting of cases completed and data collected. Stakeholders to consider include administration, where business cases need to be applied, as well as staff on the floor communicating with the block room case by case including surgeons, anaesthesia colleagues, nursing staff, pain service, and patient support staff. This aligns with ANZCA Professional Document *PS53 Statement on the Handover Responsibilities of the Anaesthetist*, especially when the operating theatre anaesthetist is not the anaesthetist who administered the block[36]. It is important to note that the handover should include an appropriately monitored and escorted patient to the operating theatre from the block room with clear documentation for the receiving anaesthetist[36]. Regular meetings with these stakeholders individually and as a group will maintain awareness and buy-in.
- Workable logistics and infrastructure: Process mapping the patient journey and potential options for how and where a block room would be set up in the perioperative environment prior to preparing a business case[21]. A well-prepared plan detailing this structure costs, cost savings, and a timetable is important for gaining acceptance from administration[34].
- Recommendations and suggestions from ANZCA Professional Documents: Guidance from the ANZCA Professional Documents can help support the need for staffing and equipment in a block room as a minimum standard for patient safety. In particular, ANZCA *PS03 Guidelines for the Management of Major*

Regional Analgesia[31], *PS09 Guidelines on Sedation and/or Analgesia for Diagnostic and Interventional Medical, Dental or Surgical Procedures*[37], *PS37 Guidelines for Health Practitioners Administering Local Anaesthesia*[38] and *PS55 Recommendations on Minimum Facilities for Safe Administration of Anaesthesia in Operating Suites and Other Anaesthetising Locations*[39] outline requirements and expectations for staffing, facilities, and workstation equipment safety. They specifically note the provisions needed for monitoring and resuscitation, with an emphasis on preventing and managing potential local anaesthetic toxicity. These robust and evidence-based support documents are important reminders for maintaining patient and staff safety and can also be of benefit when developing a business case for the project development and maintenance.

- Appropriate timeline and support: Change theory and also documented block room implementations demonstrate that working within longer-term goals and long-term investment from staff is necessary to achieve sustained innovation[24] Communication with people who have worked in block rooms and speaking with specialist regional interest groups such as the ANZCA/ASA Regional SIG can assist in refining plans and predicting and troubleshooting potential issues early.
- Collect data: Prior to commencing an institutional change, it is important to gather baseline data about where blocks are currently performed, who does them, how long is it taking to complete, and how well are they working. These questions help to clarify current practice as well as need. Continued data collection and analysis will help demonstrate the benefits of the block room and subsequently contribute to a business case for the service to remain. Some used and suggested metrics are total number of blocks, efficacy, compliance with consent and safety procedures, time spend for anaesthesia, start times, number of cases in operating theatre, education based on block numbers by trainees and patient satisfaction[7].

CONCLUSION

In the coming years, healthcare will undoubtedly continue to be viewed through a results-driven and economic lens. Thus the ability to increase productivity in an already maximised system could be seen as a breath of fresh air. A parallel processing concept for regional anaesthesia could work well in certain institutions in Australia and New Zealand, similar to the already well-established pathways in North America and the United Kingdom. The above strategies can assist planning and establishing a block room, and will assist in providing clinical, teaching, research, and quality improvement opportunities in regional anaesthesia.

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Ultrasound-guided erector spinae plane block

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INTRODUCTION

The erector spinae plane block (ESPB) is a novel ultrasound-guided regional technique first described by Forero et al[1] in mid-2016. It rarely has contra indications, the most common being patient refusal. ESPB can be safely performed in patients on anticoagulation and/or dual anti platelet therapy. Technically, it is an easy block to perform and is extremely versatile clinically. It is also easy to teach, with the learning curve usually fast.

ESPB clearly has its place in the arsenal of a well-rounded anaesthetist who may use it as part of a multimodal approach for treatment of acute and chronic pain. It is also an important component of the opioid sparing strategy. Ultimately, as it provides good levels of patient satisfaction in pain relief, the need for opioid use decreases.

At the Royal Adelaide Hospital, South Australia, ESPB has fast become the standard of care for patients with fractured ribs. These patients usually have a myriad of comorbidities. In the vast majority of cases where ESPB is provided, patients use less opioids, are capable of doing earlier chest physiotherapy and have an overall good recovery. Nowadays, a single shot of femoral nerve block for pain relief in patients with neck of femur fractures is common practice in emergency departments all over Australia. Given the benefits of ESPB with little risk, we foresee a single shot, or catheter-based, ESPB could become common practice. This is especially foreseeable for patients with rib fractures at the time of hospital admission as ESPB offers prompt pain relief to allow for focused early chest physiotherapy, a vital component for good recovery. The goal of using ESPB is to break the vicious pathophysiological cycle of atelectasis, accumulation of secretions, and pneumonia that usually follows fractured ribs.

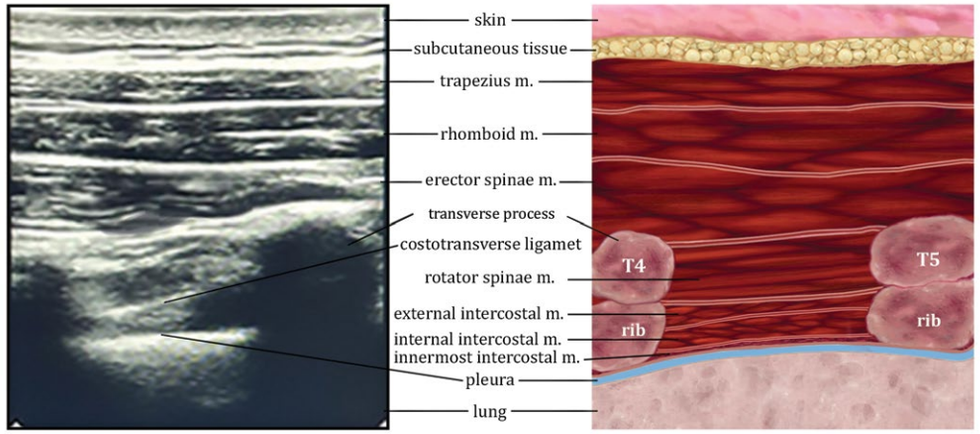
ESPB can also be used in many in different types of surgery. It can provide somatic and visceral analgesia and, in some cases, even anaesthesia. It has been used to cover thoraco-abdominal, spinal, and upper and lower limb surgeries.

The literature shows clear evidence that regional anaesthesia is very beneficial to our patients. We challenge you to read this article and ask: should we be doing more regional anaesthesia for our patients?

INSERTION TECHNIQUE

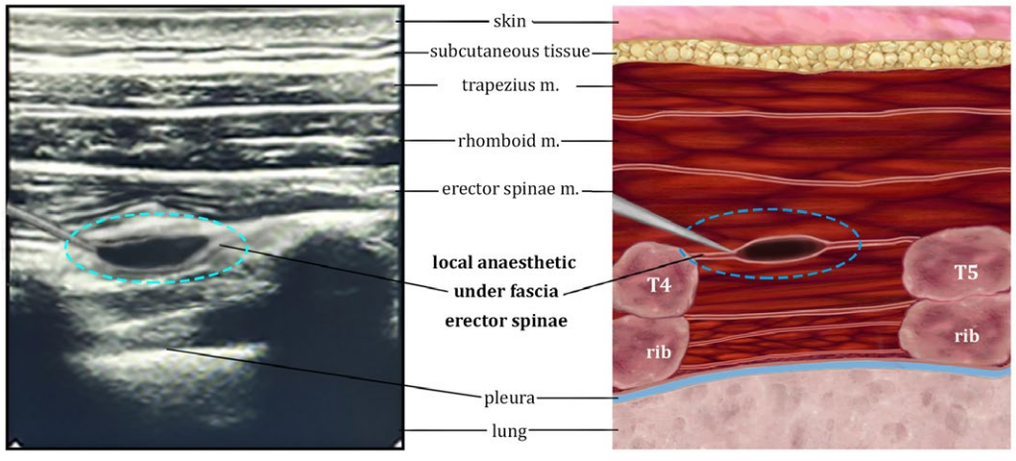
Forero's original description of the ESPB insertion technique[1] remains the standard practiced in many subsequent studies, with a variation being the target level of the transverse process. An ultrasound probe is placed longitudinally in the parasagittal plane, 3 cm from the midline on the posterior chest. The lateral aspect of the transverse process is identified by its flat appearance as compared to the rib, which has a rounder appearance and often appears more superficial as the probe moves laterally. The costotransverse ligaments can be seen deep to, and between, each of the transverse processes and superficial to the pleura (see Figure 1). The target level can be determined by scanning up and/or down from a known level and marked on the skin for reference. The chosen target should represent roughly the midpoint of the dermatomal levels requiring blockade.

Figure 1. Sonoanatomy for ESPB.



Classically, the needle insertion is described as a cephalad-caudad approach, although a caudad-cephalad approach is just as appropriate. Indeed, if a catheter is to be placed it may be sensible to use a caudad-cephalad approach to allow the catheter tip to sit superior to the target transverse process as injectate will typically spread more caudally due to gravity. An in-plane technique is typically used to allow monitoring of needle trajectory, and is certainly ideal if placing a catheter so that the catheter will thread in a cephalo-caudad fashion instead of in a medial or lateral direction. After contact with the transverse process injection of a small volume of injectate will visibly lift the erector spinae muscle off the transverse process creating an anechoic fluid-filled space (see Figure 2). This confirms insertion within the appropriate myofascial plane. At this point the residual injectate can be delivered or a catheter can be inserted through-needle and left in the space for continuous or intermittent use.

Figure 2. Local anaesthetic bolus below fascia of erector spinae muscle.



In most patients, a high frequency linear probe is suitable to detect the necessary sonoanatomy and guide needle insertion. However, in the experience of the authors a curvilinear probe using the penetration setting may be necessary in patients with higher BMI and deeper target structures. Although this will aid in the detection of transverse process and other associated features, the definition of the needle is lost with distance. Here, the proceduralist may need to rely on other techniques to guide the needle tip to the target, such as the needle path within the superficial tissues and intermittent hydrodissection.

While ESPB was originally developed to treat pain in the thoracic levels, effective proximal neural blockade has been reported with the use of a similar technique in both cervical and lumbar levels. Cervical ESPB has been described as an alternative to brachial plexus block for procedures including forequarter amputation[2] and shoulder disarticulation surgery[3]. In these instances, the catheter was placed either by direct insertion at the cervical level or was threaded in a cephalad direction from a thoracic insertion. A case report describing long-acting analgesia from L4 ESPB in a patient undergoing total hip arthroplasty[4] suggests this technique as an alternative to quadratus lumborum or psoas compartment blocks.

Ultrasound improves both efficacy and safety of regional anaesthesia[5] and is typically used for ESPB placement. Nevertheless, the ESPB can be performed as a landmark technique, especially when the block is clinically indicated and ultrasound is unavailable. Such was done in the case of an incarcerated inguinal hernia repair performed on a patient with critical aortic stenosis who received a block and sedation only[6]. In fact, the endpoint for a landmark ESPB is merely the first waypoint in the landmark technique for paravertebral block. The needle is inserted perpendicular to the skin, 3 cm lateral to the spinous process and the transverse process is carefully probed for (ideally with fingers acting as a depth guard) until contact with the transverse process is made.

MECHANISM OF ACTION

The exact mechanism of action of the erector spinae plane block (ESPB) remains the subject of some debate. In his landmark paper Forero[1] postulated that the extent and distribution of the observed block implicates involvement of both the ventral and dorsal rami of the thoracic spinal nerves. In accepting this proposed mechanism, Costache[7] defined the ESPB as a "paravertebral by proxy", eliciting the effect of a paravertebral block (PVB) without the needle tip entering the paravertebral space and instead relying on a proximal spread of injectate. This terminology differentiates the ESPB from other chest wall myofascial blocks, such as the serratus plane block which acts only on the lateral cutaneous branch of the ventral ramus of the spinal nerve.

Forero went on to study the effects of the block on a cadaver. To simulate a true ESPB, he injected 20 ml of methylene blue deep to the erector spinous muscle and superficial to the transverse process. Subsequent dissection of the cadaver showed heavy staining of the erector spinae and intercostal muscles with dye penetration deep to the intercostal muscles adjacent to the dorsal and ventral rami. However, direct staining of the rami was not seen. A number of other cadaveric studies have been published. In one study (Yang et al[8]), 10 cadavers were each subjected to a unilateral ESPB and a contralateral retrolaminar block (RLB) and the distribution of injectate was compared by dissection. In another study (Ivanusic et al[9]) 20 ESPBs were performed on 10 cadavers and the spread mapped by dissection.

Common to all dissections was significant staining deep to the erector spinae muscles with spread in all directions. Injectate often spread lateral to the angle of the rib at multiple levels. Cephalo-caudal spread was extensive and frequently involved the T1 vertebral level and above, with the T12 vertebral level showing staining in a smaller number of cases. Medial spread in the levels adjacent T5 – consistently the injection target for block placement – often included the costotransverse foramen. In their study, Ivanusic et al showed staining of the dorsal ramus of the spinal nerves to be inconsistent and there was no observed staining of the ventral rami. Yang et al showed staining within the paravertebral space and that spinal nerve involvement was mostly in the T4–T6 levels but as broadly as T3–T7. A further cadaveric study by Adhikary et al[10] comparing unilateral ESPB to contralateral RLB in three consecutive cadavers with injectate containing both methylene blue and radiopaque contrast, showed epidural and neural foraminal spread on MRI despite no report of dye in those sites on dissection. It is impossible to know whether this epidural spread arose from the ESPB or the RLB.

The inconsistencies raised by these studies regarding the spread of the injectate serve to undermine confidence in the proposed mechanism of action. However, these findings may be partially explained by the limitations of the cadaveric model including the absence of both intrathoracic pressure changes that may assist spread[9] and active cellular processes that may assist with transport of local anaesthetic across tissue planes. Added to this is the gravitational effects of prone positioning compared to sitting. Furthermore, post-mortem blood pooling and clotting in the adjacent vasculature may cause a "cork-in-bottle" effect that obstructs the flow of injectate into the paravertebral space[11].

Radiologic investigation in living patients is likely to better quantify the spread associated with ESPB. A group including Forero conducted an MRI on a patient following ESPB at T10 level with 30 ml injectate containing local anaesthetic and gadolinium[12]. A subsequent MRI study showed contrast deep to the erector spinae as well as within both the paravertebral and epidural spaces. Epidural spread was a notable finding as it was circumferential across multiple adjacent levels (T5–T12) and correlated clinically with reduced sharp and cold sensation T6–T12 on the left. No sensory block was discernible on the right, an outcome likely due to diminished local anaesthetic dose at the site; however, in a separate case study[13] a unilateral ESPB was found to provide bilateral sensory block on dermatome mapping performed by an assessor blinded to technique (unilateral vs bilateral injections). This suggested injectate had spread through the epidural space to affect the contralateral dorsal rami. Epidural spread facilitating the blockade of the thoracolumbar splanchnic nerves is the likely explanation for the visceral anaesthesia observed in case studies[12].

LITERATURE REVIEW

Indications

Despite the first description of this block by Forero et al[1] being indicated for the management of chronic thoracic neuropathic pain, the ease of performing this block and its favourable risk profile has resulted in a proliferation in the application of ESPB, with 85 publications by September 2018[14] including two randomised controlled trials.

Due to the variable local anaesthetic penetration to target nerve sites, it should be emphasised that the block should not be relied upon as the sole anaesthetic or analgesic technique but, rather, as part of a multimodal anaesthetic and/or analgesic regimen. This is outlined by a pooled review of the ESPB in the literature by Tsui et al in 2019[14], reporting on 242 published cases with results outlined in Table 1.

Table 1. Summary of published ESPB cases.

Category	Cases n (%)
Adult	219 (90.5%)
Paediatric	23 (9.5%)
Part of a multimodal technique	220 (91%)
Side effects reported	0 (0%)
Adverse events	1 (0.4%)

Clinical applications of ESPB described in the literature are predominantly case reports. These case reports include both acute and chronic pain management in a variety of clinical scenarios. These reports are summarised in Table 2, providing supplemental analgesia for the thorax, abdomen, spine, upper and lower limbs.

Table 2. Summary of published ESP block indications.

Region/Indication	ESPB Level	Notes
Chest		Covers posterolateral incisions/injuries better than SAP block:
Breast[15-20]	T_{4-5}	▪ RCT[21] reports superior analgesia to systemic opioid alone
Rib fractures	T_{4-5}	▪ Significant improvement to respiratory function and analgesia[22]Rescue for TEA/TPB[23-24], Alternative to TEA/TPB[25-28]
Thoracotomy/VATS	T_{5-6}	
Sternotomy	T_{5-6}	▪ Given in fully heparinised patients[29-31], Improved outcomes[32-33]
Abdomen[34-36]		Use described in both laparoscopic and open procedures:
Upper-Mid surgery	T_{6-9}	▪ Ileostomy closure37, Hepatobiliary38, Cholecystectomy39, Open epigastric hernia40, Renal41-43, Bariatrics44, Caesarean-section45
Lower surgery	T_{9-12}	▪ Inguinal hernia repair[6, 46], Open radical prostatectomy[47]
Spine		Bilateral catheters can be placed well outside surgical field
Cervical[48]		Does not appear to impair intraoperative monitoring of spinal cord function.
Thoracic[49]		
Lumbosacral[50]	T_{10-11}	Can be effective even in the presence of existing surgical hardware.
Upper Limb[51]		Analgesia may be incomplete
Shoulder	T_{2-3}	ESP block at T2-3 to treat painful conditions of shoulder girdle
Proximal upper limb		For example, Herpes zoster[52], Burns[53], Shoulder surgery[3,54], Amputation[2]
Lower Limb	L_{2-4}	For example, Hip[55], Treating CRPS[56], Hip joint and proximal femur surgery[4,57] Attachments of iliocostalis and longissimus to these TPs can make it difficult to obtain the characteristic pattern of linear fluid spread – consider targeting a low thoracic TP and thread a catheter caudally[58]. Priapism from sympathetic blockade may occur[59]

SAP=serratus anterior plane, TEA=thoracic epidural, TPB=thoracic paravertebral block, VATS=video assisted thoracoscopic surgery, TP=transverse process

COMPLICATIONS

The ESPB appears to have a large margin of safety with the theoretical advantage of a relatively superficial target for needle insertion and adequate sonographic windows to facilitate real-time needle placement. This has been reflected by the paucity of adverse events reported in literature; however, even in the absence of large-scale trials, caution should be exercised given the current evidence base is prone to reporting bias.

Local Anaesthetic Systemic Toxicity (LAST)

The most significant risk to note would be that of potential local anaesthetic systemic toxicity (LAST). In the largest published single-centre series to date[60], LAST-related findings were noted in 3 out of 182 patients (1.6%). Notably, none of these patients suffered from cardiac arrest or seizures. Following ESPB, it is proposed that local anaesthetic will dissipate into the systemic circulation due to the highly vascular muscle tissue along the interfascial plane combined with the spread of local anaesthetic into the paravertebral and intercostal tissue planes. The time from interfascial block to peak local anaesthetic plasma concentration is reported to be 30-45 minutes[61], therefore it would be recommended that patients are monitored for at least 30 minutes following an ESPB in an environment that has resources in place to manage LAST.

In the same case series, inadequate analgesia (defined as a requirement for rescue analgesia or a numerical rating score >6 in the first hour after a block) was reported in 12 (6.5%) patients. These patients had varying indications and no predictors of block failure could be determined in this case series.

Sympathetic blockade

A single case report describes priapism occurring following unilateral lumbar ESPB with the proposed mechanism being inadvertent bilateral sympathetic blockade. Anatomical studies would suggest that penetration in the epidural space is variable and that clinically significant sympathectomy with subsequent hypotension would be a rare adverse effect – there have been no reports of this occurring to date.

Pneumothorax

There has been a single case report of pneumothorax[62] following ESP block at the T4 level in an anaesthetised patient under positive pressure ventilation. There is no description of the patient's underlying lung condition and whether the reported pneumothorax, which was diagnosed by ultrasound, may have been due to another cause. Without knowing the type or length of needle, or whether real-time ultrasound was used during the procedure, it is difficult to determine possible factors that may mitigate what appears (at present) to be a rare complication of this procedure.

BENEFITS

The ESPB has been demonstrated in several small (n=30–106) randomised controlled trials (RCTs) to reduce opioid consumption as outlined in Table 3. Larger scale studies are required to evaluate the best indications for this technique and further delineate its potentially favourable risk profile.

Table 3: Reported RCTs of the ESPB.

Author	Population	N	Groups	Summary
Tulgar et al[63]	Laparoscopic Cholecystectomy	30	ESPB versus control	Bilateral ultrasound guided ESPB leads to effective analgesia and a decrease in opioid requirement in first 12 hours.
Gürkan et al[21]	Breast surgery	50	ESPB versus control	ESPB exhibits a significant analgesic effect in patients undergoing breast cancer surgery.
Oksuz et al[64]	Breast surgery	43	ESPB versus Tumescent anaesthesia	Bilateral ESPB in breast reduction surgery was more effective than tumescent anaesthesia concerning opioid consumption and pain scores.
Altiparmak et al[65]	Breast surgery	38	ESPB versus PECS	Modified PECS block reduced postoperative tramadol consumption and pain scores more effectively than ESPB after radical mastectomy.
Nagaraja et al[66]	Cardiac surgery	50	ESPB versus TEA	ESPB is a promising alternative to TEA in optimal perioperative pain management in cardiac surgery.
Krishna et al[32]	Cardiac surgery	106	ESPB versus control	ESPB provided significantly better pain relief for longer duration as compared to intravenous paracetamol and tramadol.

CONCLUSION

With the ubiquitous availability of ultrasound, technical simplicity, favourable safety profile and versatility, ESPB is a valuable addition to the repertoire of clinicians in both the acute and chronic pain setting. It is best used as part of an opioid-sparing, multimodal analgesic regimen to take advantage of its superior safety profile compared to neuraxial techniques.

Being a relatively new technique, ESPB requires further delineation by large well conducted studies comparing it to more established analgesic options to better determine its efficacy and role in clinical practice.

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Pain

The "opioid crisis"

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INTRODUCTION

For more than 6000 years, humans have relied on the pain-relieving effects of opioids; no other medication in history has remained in use for as long as opioids[1]. Very early, other effects of opioids such as sedation, anxiolysis and induction of euphoria became obvious. Therefore, the medical use of opioids has always been complicated by the dilemma that opioids are not only analgesics, but also drugs of abuse. Throughout most of history, doctors, politicians, governments and the legal system have tried to find a balance between appropriate therapeutic use and misuse/abuse, concepts of licit and illicit use and medical needs and regulatory issues. To maintain this balance between all these factors has been a continuous struggle; failure to find an appropriate balance has resulted in many problems, accentuated over the past 30 years.

What we see as a result today are on the one hand extreme discrepancies in access to opioids, their availability and usage between countries[2]. On the other hand, there is an excessive and uncritical use of large amounts of opioids outside the conventional indications of acute and cancer pain, that is, in chronic non-malignant pain such as low back pain in a limited number of developed countries such as Canada, the US and also Australia[3]. While the latter has recently been described as the "opioid epidemic" (with the US government mandating the Center for Disease Control (CDC) to deal with this epidemic), it is possibly better described as an "opioid crisis"[4]. However, there is another "opioid crisis" in many less well-developed countries. This opioid crisis is an "unrelieved pain crisis", as in about 150 countries even simple oral morphine is not available to treat postoperative, trauma and in particular cancer pain; many patients in severe pain have no access to opioids at all[2]. The discrepancies in access are so extreme, that the relatively small populations of the developed countries (Canada, the US, Australia and the European Union) consume now far more than 90% of the legal opioids prescribed worldwide, while billions of patients in most of Africa, Asia and Latin America have only minimal if any access to opioids.

HISTORICAL PERSPECTIVE

To understand how we ended in this double crisis it is worthwhile to look at the history of opioid use with a focus on the past hundred years and in more detail on the past 40 years. While there were previous attempts to control and regulate access to opioids, namely opium in the commonly referred to "opium wars", opioids were typically freely available and under no national control in the United States in the 19th century. Even heroin was sold, by the pharmaceutical company Bayer, as an over-the-counter medicine for all types of ailments in adults and even children. However, increasing concerns in particular about the exposure of younger patients to opioids led to the development of international and national drug control measures[5]. The International Opium Convention, the first international regulatory approach to opioids, was ratified by the US in 1912[6]. National legislation in the form of the famous Harrison Narcotic Tax Act followed in 1914 and both measures restricted access to opioids in the US and the rest of the world significantly from then on[7].

The initial International Opium Convention was subsequently replaced by the Single Convention on Narcotic Drugs; it regulates the production, manufacture, import, export and distribution of narcotics for medical use[8]. An organisation of the United Nations was founded to ensure adherence to this convention; the International Narcotics Control Board (INCB)[9]. Its initial task was to combat illicit drug trafficking and therefore its approach to opioids was heavily on the restrictive side. This approach encouraged government authorities in many countries, even if not explicitly banning opioids, to put up multiple legal and administrative barriers to limit the access to medical use of opioids.

It was not surprising that in a paper in 1985 a diagnosis of "opiophobia" among healthcare providers was made and described as "customary underutilisation of opioid analgesics based on irrational and undocumented fear"[10]. Major barriers to opioid use have been summarised under the headlines insufficient knowledge, inappropriate attitudes, regulatory and organisational issues and economics[1,2]. Even in developed countries like Germany, opiophobia prevented appropriate cancer pain management in many patients due to attitudes of

government bodies, physicians, nurses[11], pharmacists[12], allied health professionals and even patients[13], their relatives and the general public[14]. The legal terminology reinforced this phobia; German regulation required storage of opioids in a safe called “Giftschrank” (poison cupboard) and prescribing on “Giftrezepte” (poison prescriptions). The statement that “the only good dose of morphine is the last dose of morphine” illustrated a widespread attitude among physicians.

In this setting of widespread opiophobia, the unacceptable undertreatment of cancer pain in all countries of the world was then addressed by initiatives of the British Hospice Movement and subsequently by the World Health Organization (WHO). In particular the publication and aggressive promotion of their cancer pain guidelines, initially in 1986 and then their revision in 1996, promoted management of cancer pain by appropriate use of opioids[15,16]. Global consumption of morphine quadrupled in 10 years from 2.4 tons in 1983 to 10 tons in 1992 and then doubled again, reaching 20.3 tons in 1999[17]. Similar trends of increase in consumption have also been reported for many other opioids. Until the end of the last century, this increase was primarily driven by increased use to treat acute and in particular cancer pain with significant benefits for these patients.

THE FIRST WORLD OPIOID CRISIS

However, until the mid-1990s, most doctors would have regarded the long-term use of opioids in chronic non-malignant pain as contraindicated. This attitude changed around this time. Seminal was the publication by Ronald Melzack (one of the two authors who published the gate control theory) in *Scientific American* with the provocative title “The Tragedy of Needless Pain”[18]. In this he asked “What though should be done for people who suffer from debilitating chronic pain but who do not have fatal illness? These people have traditionally been excluded from long-term therapy with narcotics again for fear they would become addicts”. American pain physicians with longstanding interest and experience in cancer pain management followed this lead by supporting opioid use in chronic non-malignant pain, primarily based on small case series[19,20]. In parallel there was aggressive marketing of opioid formulations, in particular slow-release oxycodone, by the pharmaceutical industry; these issues are currently undergoing legal scrutiny[21]. The suggested approach was questioned by a number of pain medicine specialists, who challenged how a complex biopsychosocial phenomenon such as chronic pain could be treated by a single drug[22]. Other issues of concern were the externalisation of locus of control contradicting classical approaches to chronic pain aiming for increased self-efficacy, poor data on improvement of function and quality of life and concerns about opioid-induced hyperalgesia[23,24].

However, despite a lack of supporting evidence, prescribing behaviour changed in favour of the use of opioids in chronic non-malignant pain. Within 10 years, the use of opioids, often in very high doses, for chronic pain patients became commonplace in the United States, followed by many other developed countries, in particular Canada, Australia and the European Union. The increasing availability of large amounts of opioids resulted in a dramatic increase of prescription opioid abuse, very appropriately described in a paper in *The New England Journal of Medicine* in 2010 with the title “A Flood of Opioids, A Rising Tide of Deaths”[25]. The authors present a steep increase in the number of unintentional drug overdoses in the US beginning in the early 1990s in parallel to the promotion of opioid use for chronic non-malignant pain. Heroin was replaced by prescription opioid analgesics such as oxycodone and hydromorphone as the main drug of abuse. The most current data published by the CDC highlight the problem[26]: From 1999 to 2017, almost 218,000 people died in the United States from overdoses related to prescription opioids. Overdose deaths involving prescription opioids were five times higher in 2017 than in 1999. Furthermore, almost 2 million people in the US are abusing or are dependent on prescription opioids; daily more than 1000 patients are treated in emergency departments of the United States for misusing prescription opioids. Similar data are reported from other countries, for example, Australia; it saw dramatic increases in opioid consumption over these years with defined daily doses (DDD) increasing from 4.6 to 17.4 DDD/1000/day from 1990 to 2014[27], while the prescribing pattern changed from primarily weak and short-acting opioids to strong and long-acting ones. Substantial geographic variation in the prescription pattern of opioids was observed with rural areas having much higher use of all opioids possibly caused by prescribing by general practitioners due to limited access to pain clinics[28]. In the state of Victoria in Australia, oxycodone consumption increased from 2000 to 2009 by 800% and deaths related to oxycodone overdose increased by 2000%[29]. In Australia overall, there were 1045 opioid-induced deaths in 2016, of which three quarters were related to prescription opioids[30].

THE “OTHER” OPIOID CRISIS

While these concerning developments in the developed countries occurred, the resulting data on global opioid consumption quoted above are highly misleading[31]. Even the initial increase in worldwide morphine consumption described above in response to the WHO initiatives resulted mainly from usage in a few developed countries. In 2008, Australia, Canada, New Zealand, the United States and the member States of the European Union together accounted for more than 96 per cent of global consumption of fentanyl, 90 per cent of global consumption of morphine and 98 per cent of global consumption of oxycodone[32]. To illustrate the striking discrepancies a comparison of annual per capita consumption of opioids expressed in milligram morphine equivalent is useful; in 2014 countries like Canada (967 mg), the United States of America (700 mg) and Australia (494 mg) differed by orders of magnitude from countries like India (0.56 mg), Zambia (0.8 mg) and Nicaragua (1.1 mg). Sixty-six percent of the of the world population have virtually no access to opioids[33]. Even worse, governments which were previously successfully lobbied by WHO and palliative care initiatives to loosen control on opioids, are now feeling confirmed in their stance against opioids in view of the data coming from the developed countries.

CONCLUSIONS AND PROPOSED SOLUTIONS

In conclusion, there are actually two opioid crises – one of overuse and oversupply with detrimental consequences for chronic pain patients and society as a whole in the developed world and one of no or very limited access to opioids in the developing world leading to poor quality of postoperative, post trauma and cancer pain relief with terrible suffering, in particular in the terminal care setting (see https://www.bbc.com/news/health-42871641). Both of these issues need to be addressed in the future to avoid further harm and suffering.

The overprescribing of opioids in chronic non-malignant pain does not help chronic pain patients, but is in many cases harmful as the outcomes were much worse than expected[34]. There is now overwhelming evidence, that opioids have little or no effect on improvement of function and quality of life, the most important outcomes in these patients[35]. In addition, opioid-induced hyperalgesia (OIH) can make their pain experience worse[36], opioid-induced androgen deficiency (OPIAD) results in reduced activity, weight gain and fatigue[37], and immune suppression by opioids increases the risk of infections[38,39]. These patients also experience adverse effects of opioids such as constipation and are exposed to the risks of tolerance, addiction and overdose[40,41]. In addition, the increased availability of opioids due to this approach has resulted in diversion of prescription opioids to the black market with significant harmful effects[42]. This crisis is currently addressed from multiple angles with appropriate, but also some very inappropriate measures such as concepts of mandatory weaning of these patients discussed in the US[43]. The most important approach is most likely to improve access to multidisciplinary pain management facilities[44], as addressing chronic pain as a sociopsychobiomedical issue has the most promise to improve self-efficacy, function and quality of life of these patients[45]. Other approaches shown to be effective are discouraging further prescribing of opioids in chronic pain, following stringent guideline for implementation (and more importantly discontinuation in case of failure) of opioid treatment[3,46], careful selection of patients with identification of those at risk[47], preferential use of atypical opioids (such as buprenorphine patches and tapentadol)[48], slow dose reduction by tapering in patients with high-dose use or lack of benefit and involvement of drug addiction services in appropriate patients[3,46]. Appropriate opioid stewardship by anaesthetists (and surgeons) to reduce excessive opioid supplies at hospital discharge with the risks of continued use and diversion is another important measure[49]. In view of the large number of overdose deaths, the discussion on take-home naloxone to be used by friends and relatives of patients abusing opioids continues[50].

Addressing the lack of access to opioids in the many countries where opioids are barely available is another difficult issue. The causes are complex; as outlined above, there are many barriers to use of opioids best summarised under the headings insufficient knowledge, inappropriate attitudes, political, regulatory and organisational issues and economics[1,2]. All these issues need to be addressed while respecting the cultural and political realities of the countries affected. Attempts to do this are continuing with initiatives such as the:

- Pain & Policy Studies Group (PPSG), a global research program at the University of Wisconsin Carbone Cancer Center, which has pushed for more than 20 years improving pain relief by achieving balanced access to opioids worldwide[51].
- Global Opioid Policy Initiative (GOPI) of the European Society of Oncology (ESMO) (see https://www.esmo.org/Policy/Global-Opioid-Policy-Initiative)[52].
- Opioid Price Watch Project of the International Association for Hospice and Palliative Care (IAHPC) (see https://hospicecare.com/opioids/reports/map/).

Even the International Narcotics Control Board (INCB) recently changed the balance in its efforts from combatting illicit drug trafficking to encouraging the medical use of opioids. A paper sponsored by the INCB is now stating: “Use of opioid analgesics has increased, but remains low in Africa, Asia, Central America, the Caribbean, South America, and eastern and southeastern Europe. Identified impediments to use urgently need to be addressed by governments and international agencies”[31].

Readers are referred to a complementary article entitled “Opioid harm reduction strategies – stemming the tide” by Michael H Toon within this edition of *Australasian Anaesthesia*.

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Opioid harm reduction strategies – stemming the tide

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INTRODUCTION

A landmark 2010 paper in the *New England Journal of Medicine* heralded the current opioid crisis, describing the problem in terms of a flood, amidst a rising tide of deaths. Indeed, the current opioid epidemic has seen a wave of prescription opioids from the healthcare system precipitating a sequence of misuse, abuse, overdose and a subsequent deluge of diversion[1].

The storm signal of the opioid flood has been long-sounding from the United States with per capita consumption of prescription opioids increasing markedly, since the 1990s, and growing at an alarming rate[2,3]. In the decade following this the number of drug poisoning deaths involving a prescription opioid more than quadrupled[4]. In the US, a strong correlation exists between states with the highest opioid consumption and abuse rates to medical emergencies and drug-poisoning mortality[1,2].

The tide is rising in Australia with a surge of opioid prescriptions on the Pharmaceutical Benefits Scheme (PBS) from 2.4 million in 1992 to almost 7 million in 2007. Much of this is due to an increase in oxycodone use with 152% increase in prescriptions in the 5 years prior to 2008 with a corresponding 20% decrease in morphine over the same period[4]. Close to 3 million Australians were prescribed at least one opioid under the PBS in 2014[5]. This growth has been linked to increases in harm with accidental death from opioids reaching 788 in 2016, rising in parallel with an increase in supply and at a more rapid rate in regional areas[6,7]. Hidden consequences such as car accidents, immunosuppression, hormonal dysfunction, osteoporosis, confusion, delirium and falls add to the burden on the Australian healthcare system[5]. Misuse and diversion are also rising in Australia, with prescription opioids accounting for a higher proportion of reported injections than heroin at supervised injecting centres[2].

Historically, opioid prescription volumes began to swell in the 1990s following patient advocacy movements focusing on pain control, coupled with aggressive promotion of treatment of acute and chronic pain with opioids, buoyed largely by the pharmaceutical industry[8]. The risk of opioid-naive patients developing persistent opioid use after surgery is 6-10% for both major and minor surgery[9,10]. Nevertheless, health professionals are caught between a desire to treat pain and a fear of causing harm[2]. Focusing the goal on providing optimal analgesia, “a technique that optimizes patient comfort and facilitates recovery while minimizing adverse effects of analgesics”, provides a resolution of this conflict with acknowledgement of the therapeutic pollution caused by inappropriate use of opioids in pain management[2,8].

Reducing opioid harm from the healthcare system must target multiple causative factors including: inappropriate prescribing, inadequate counselling and monitoring in addition to access through diversion creating and further enabling misuse and abuse[1]. Interventions to mitigate the hospital systems significant contribution to the epidemic can be seen as conceptually corresponding to flood mitigation, with interventions upstream, midstream and downstream.

Upstream of the hospital system is the pharmaceutical industry that can be urged to further efforts to manufacture and package opioids in abuse deterrent formulations. Furthermore, the preadmission setting contains opportunities for screening of patients at risk of chronic post-surgical pain and opioid misuse for more targeted monitoring and intervention.

The hospital episode is midstream where prescribers can be educated to avoid inappropriate prescribing of discharge opioid prescriptions. Patients are able to be educated on the potential harms of short and long-term opioid use. Pharmacists and pain service teams, under the direction of anaesthetists, in a framework of opioid stewardship, can guide prescribers and patients[4].

Downstream, where the devastation of the flood is seen the most in the post-discharge setting, provides opportunities for effective, practical disposal solutions for unused opioids and follow-up, support and cessation strategies for patients at-risk of harm or chronic post-surgical pain syndromes in the form of transitional pain clinics.

UPSTREAM INITIATIVES

Changes in formulation to those with abuse deterrent properties may have important benefits in reducing harm[2]. Public health authorities have called for development of these analgesic formulations and the pharmaceutical industry has to some extent responded[11]. The addition of naloxone to oral opioid formulations to discourage injecting via the attenuation of euphoria and to invoke an aversive response has been developed[2]. This tamper resistant strategy may reduce the risk of diversion and injection but not necessarily abuse by another route. The introduction of an oxycodone-naloxone formulation in the US in late 2010 was followed by reductions in diversion rates and street value as well as a decrease from 36% to 13% of those reporting oxycodone extended release as their primary prescription opioid of abuse. Many of these patients however indicated that they had endeavoured to substitute with another opioid, commonly heroin[4]. Of note, extended-release hydromorphone is only available in the US as an abuse deterrent formulation with a low-level of observed abuse of this product[12].

Another regulatory option includes up-scheduling; for example, codeine in Australia which is now a prescription-only medication, or schedule 4 as per the Health (Drugs and Poisons) Regulation. There is appropriate pressure to review pack sizes of Schedule 8 (controlled drugs of addiction) opioids with the standard pack size of 20 tablets of immediate-release oxycodone for example, being called into question[5]. The standard sizes being often in excess of therapeutic requirements exposes the risk and reality that the path of least resistance, default option and implied limitation of choice leads to surplus opioids being prescribed, especially when reflected in endorsed PBS quantities, as is the case with 20 tablets of oxycodone 5 mg immediate-release.

The preadmission stage for elective surgical procedures, being a planned event at a designated time-point, provides upstream opportunities to initiate procedures to optimise pain control during the surgical journey[10]. The use of preoperative screening tools and preadmission clinics can maximise the capture and intervention success of patient strategies to influence pain management.

One potential preventable outcome contributing significantly to the problem of opioid misuse is the development of chronic post-surgical pain (CPSP), defined as pain relating to areas of the surgery persisting for a month longer than it takes for most injured tissues to fully heal. CPSP clusters with other symptoms such as mood and sleep disturbance and is associated consistently with psychological factors of anxiety, depression and pain catastrophising. Risk factors for CPSP have been consistently identified across several domains (see Table 1).

Table 1. Risk factors for the development of Chronic Post-Surgical Pain (CPSP)[10].

Domain	Risk factor
Demographic	Young adults
	Low level of education
	Seeking compensation
	Smokers
Clinical	Greater prior disability
Surgery	Longer operative time
	Increased complication rate
Pain related	Pre-existing pain
	Stronger post-operative intensity and duration
Psychological	Fear, anxiety, depression
Physical function	Worse pain interference

Identification of risk factors for CPSP and opioid misuse allows targeting of patients at risk and subsequent provision of interventions to reduce the risk of adverse outcomes. Rather than divesting patients with acute pain of analgesia, such recognition and stratifying aims to avoid long term harm by optimising analgesia using multi-modal approaches, opioid-sparing techniques and rigorous follow-up. Available screening tools include the Opioid Risk Tool (ORT), the Screener and Opioid Assessment for Patients with Pain (SOAPP) and the Brief Risk Interview. The availability of a psychologist is invaluable in the assessment process as a focused clinical interview by a psychologist has the highest sensitivity for predicting aberrant behaviour. This observation led to the development of the Brief Risk Interview, which more frequently identifies aberrant behaviour than the SOAPP and ORT which are self-report tools. Specialist expertise and time is a limitation however. The ORT

stratified greater than 90% of patients into the high-risk group that are likely to display opioid-related adverse behaviour and was an even better predictor when completed by a psychologist. The ORT is simpler and faster to administer than the SOAPP; however, the SOAPP while more involved was more reliable at predicting abnormal behaviour and risk of abuse[4].

Anxiety and depression are recurrent factors in studies looking at unintended long-term opioid use post-surgical discharge following expected short-term management of acute pain. These psychological factors, together with post-traumatic stress disorder and personality disorders are also linked to greater opioid use, opioid misuse, addiction and higher pain scores, in what has been described as a process of adverse selection[4]. These patients are at risk of developing maladaptive behaviour and are being provided with the means to inappropriately cope with stress via high-risk medications used in non-prescribed ways.

The preoperative anaesthetic assessment, with or without referral from a screening program, is an ideal time to educate patients about pain relief strategies and expectations. The benefits of multimodal analgesia should be outlined emphasising the imperative to ensure safety as well as comfort, which may necessitate considered restraint in opioid use. Optimal analgesia cannot be achieved without managing patient expectations within a subjective biopsychosocial framework. Education regarding realistic goals and pain treatment and avoidance of unintended harms can ideally occur in the preoperative environment[8].

Some institutions use and advocate for a pharmacist to enable the identification and notification of patients who would benefit from a proactive pain management plan to ensure the most appropriate treatment following surgery and to guide discharge therapy[3]. Pharmacists can use local prescription monitoring systems, counselling and drug use evaluation interview skills to gather information and convey a plan.

MIDSTREAM INITIATIVES

The commencement of opioids in the acute care setting sets a course for further opioid use with a significant number of patients swept away in a stream of ongoing opioid dependence and misuse. As a source of opioid initiation, the hospital-based surgical journey is a unique opportunity to quell the rising tide of opioid misuse.

Patients who received opioids for their primary pain therapy in the acute perioperative period commonly require increased doses to maintain the same analgesic effect. Mechanisms postulated for this include acute tolerance and opioid-induced hyperalgesia[8]. Studies have revealed however no association between quantity of opioids dispensed and measures of pain satisfaction or pain scores at 2 weeks; yet a direct correlation exists between quantity dispensed and opioid related side-effects[6]. Considering most acute pain, while almost ubiquitous after surgery, can be controlled and mostly resolves within one week, the duration of treatment should be limited to the expected duration of pain or the interval before the patient's primary care practitioner can evaluate the need for ongoing analgesia[4]. Dispensing medications in limited quantities with defined therapeutic endpoints is a practical harm reduction measure[2]. To envision this, the concept of the "reverse pain ladder" has utility for patients and prescribers illustrating reverse steps of the WHO pain ladder to emphasise and visually direct de-escalation of opioid analgesia[4].

The concept of opioid stewardship programs (OSP) is evolving and aims to borrow lessons from the success of stewardship programs for other mass medication management endeavours. Of emphasis in these programs is the need to actively engage medical staff, hospital leaders and establish systems for anaesthesia, surgery, nursing and allied health teams to work together[8,10]. One such program at Brigham Health in Boston has involved the entire organisation in implementing initiatives involving prescribing, addiction, education, information technology and creation of opioid related objective markers with an ultimate goal of measuring the reduction of fatal and non-fatal overdoses in patients receiving opioids[13]. Over a three-year period this system decreased monthly opioid prescriptions from 9000 to 6500 per month across a 1000-bed institution. Using similar principles, a quality improvement project in an Australian institution devised, implemented and evaluated 5 sequential interventions based around auditing the number of oxycodone tablets dispensed per month. These involved educational materials for patients, anaesthetic departments and junior doctors with pain medicine follow-up of complex pain patients in the first instance; followed by an analgesic discharge plan implementation by the acute pain service (APS), a letter in the junior medical officer bulletin, guideline production for hospital pharmacists and finally audit and targeted academic detailing of monthly performance to individual treating teams. This final step was associated with a rapid 40% reduction in the number of opioid tablets prescribed; however, previous interventions were also modestly successful. The average number of oxycodone tablets decreased by 32 per 100 surgical admissions following the first intervention and fertile ground was laid for each subsequent initiative[7].

Other opioid stewardship programs described in Australia have established three pillars of care consisting of inpatient review with an APS, outpatient follow-up of APS patients and the provision of quality improvement and education within the hospital. Key elements of this system are an exit strategy for opioids, patients being discharged with the exact number of tablets rather than full packs and post-discharge follow-up to ensure the strategy is actioned[5].

Education in the form of awareness of realistic patient requirements for analgesia, harms of overprescribing and availability of guidelines positively influences behaviour. Many hospitals have incorporated prescribing guidelines to influence prescribing practices at discharge, coupling opioid consumption in the 24 hours prior to discharge with the dose dispensed, with one institution decreasing the total number of tablets prescribed by 40%. The transition of many hospitals to electronic prescribing creates opportunities. One hospital adjusted the default number of tablets using an electronic system from 30 to 12 for discharge prescriptions for 10 common surgical procedures without experiencing a reciprocal increase in opioid refill prescriptions[6]. One education initiative reviewed, analysed and recommended a defined number of tablets be prescribed for specific operations, namely a partial mastectomy (5 tablets), sentinel lymph node biopsy (10), laparoscopic cholecystectomy (15), laparoscopic inguinal hernia repair (15) and open hernia repair (15). The mean number of tablets was significantly decreased in each of the 5 operations following this simple guideline implementation by a remarkably consistent amount (14-15 tablets per operation with a range of 23.7 vs 9.6 for sentinel lymph node biopsy and 35.2 vs 19.4 for laparoscopic cholecystectomy) over a total of 34 individual prescribers. This equated to a remarkable 53% reduction in the number of tablets prescribed (6170 vs 2932 actually prescribed) with only 1 of 224 patients requiring a refill prescription within 30 days of their operation. Even following this reduction only 34.3% of prescribed tablets were actually taken[14].

Minimising opioid use during the perioperative period should be an important goal of anaesthetic care given that a significant proportion of opioid-naive patients entering surgery may ultimately become chronic users[8]. Opioid use is by no means a mandatory requirement of anaesthetic care. In the United States 77% of patients undergoing hip fracture surgery and 82% after ankle fracture surgery receive opioids. This compares to none and 6% respectively in the Netherlands, with negligible variation in measures of satisfaction depending on the country[6]. Additionally, a comparison of one US hospital performing head and neck surgery versus a Hong Kong hospital found that 87% versus 1% of patients received opioid orders after surgery. Various strategies exist for tailoring the conduct of anaesthesia to achieve this end including: multimodal anaesthesia, encompassing opioid-free anaesthesia and regional anaesthesia. The synergistic effects of targeting different elements of the pain pathway reduces the side-effects of any one medication used alone and the amount of opioid needed to control pain postoperatively. A significant amount of research has established many drug classes and specific agents as having utility in a multi-modal approach to analgesia. These include: paracetamol and non-steroidal anti-inflammatory drugs, gabapentinoids (gabapentin and pregabalin), alpha-2-agonists (clonidine and dexmedetomidine), NMDA receptor antagonists (ketamine and magnesium), intravenous lignocaine and dexamethasone; all reduced opioid consumption in the perioperative period. In the case of ketamine various investigators found that opioid-dependent patients had reduced pain 6 weeks to 6 months after surgery compared with controls[8].

Opioid sparing techniques are of vital utility in certain patient groups. The use of regional anaesthesia is a fundamentally applied component of any multimodal analgesia plan allowing a patient to remain opioid free for hours to many days post-surgery depending on the type of block. These techniques are most favourable for opioid-tolerant and dependent patients who have poorly controlled postoperative pain. The performance of opioid-free anaesthetics (OFA) is also feasible and of distinct importance in patients with obstructive sleep apnoea (OSA). Mulier et al described a reduction of post-op morphine equivalents to 6 mg in the first 24 hours in the OFA group vs 21 mg in the non-opioid free group in their bariatric surgery cohort (5000 patients). This accompanied fewer complications and shorter length of stay overall and similar complication rates in those with obstructive sleep apnoea[8].

While these approaches have been shown to reduce the use of post-operative opioids evidence of an effect on CPSP remains elusive[10]. Given that opioid consumption is a strong predictor of likelihood of weaning long term and that the provision of opioids at discharge expands a vast reservoir for diversion, the use of opioid sparing techniques to prevent far reaching adverse effects is an imperative of modern anaesthetic practice[15].

There is an emerging understanding that in terms of abuse potential, not all opioids are the same, even when accounting for the absence of abuse deterrent formulations. Much of the efforts and study in opioid reduction strategies have focused on oxycodone and the reasons for this are manifest. Oxycodone use by any route has risen significantly, coronial cases in which oxycodone was detected have risen exponentially. Oxycodone and hydrocodone/paracetamol combinations are the most common drugs of choice for prescription opioid abuse in the US and oxycodone is the one unifying compound in those most commonly abused and involved in overdose in the US, Australia and Canada[4,16]. The fast onset and shorter duration of action is more likely to induce positive and negative reinforcement with problematic behaviours arising of consequence[2].

In an effort to substitute drugs with high abuse potential for those with lesser forces fostering their non-medical use attention is being drawn towards atypical opioids, drugs in which their analgesic actions rely on unique and possibly synergistic actions rather than pure opioid receptor affinity. These drugs, also termed “multigesic agents”, (buprenorphine, tramadol and tapentadol) have appealing pharmacologic profiles and evidence for mitigating abuse potential[2]. Buprenorphine is a semi-synthetic opioid in clinical use since 1979 with potent agonist activity at the MOP-receptor but antagonistic properties at the KOP-receptor. There is a greater margin of safety for buprenorphine relative to other potent opioids frequently used as observed in one study where doubling the dose of buprenorphine increased its peak analgesic activity by a factor of 3.5 while leaving the respiratory depressive effects unchanged[17]. Tramadol, licensed in the United Kingdom in 1994 was developed as a synthetic opioid but has only weak opioid receptor affinity. Much of its action is due to inhibition of the reuptake of serotonin and noradrenaline at synapses in the descending neural pathways involved in analgesia. Unlike other opioids it appears relatively free of unwanted side effects of ventilatory depression, causing only mild reductions in normoxic ventilation and no significant suppression of the hypoxic ventilator response, contrasted with 50-60% suppression produced by morphine[18].

While tramadol does feature in the causative agents for deaths from overdose, this is largely due to neurological effects and it has the lowest desirability of abuse in post-marketing surveillance of drug misuse. More than a decade of research has demonstrated that tramadol is undesirable for abuse and has a prevalence of abuse similar to non-steroidal anti-inflammatory drugs[11]. Lastly, tapentadol has a 50-fold lower affinity for the MOP-receptor than morphine and relies on its analgesic efficacy via inhibition of noradrenaline reuptake in addition to activation of opioid receptors. Randomised controlled trials for both acute and chronic pain have shown that equianalgesic doses of tapentadol and oxycodone immediate-release formulations have comparable efficacy[19]. While they are mechanistically and therapeutically distinct, tapentadol and tramadol do share a commensurate low desirability for abuse. While a relatively new analgesic molecule early findings suggest the risk of tapentadol abuse is the lowest of all the comparators studied (oxymorphone, hydromorphone, hydrocodone, morphine, fentanyl, oxycodone, tramadol and buprenorphine)[12].

DOWNSTREAM INITIATIVES

Consideration of the lifecycle of an opioid prescription reveals a large burden of diversion to dependent opioid users in addition to opioid-naive patients resulting in initiation of opioid misuse and harm. Each tablet dispensed is a drop in a vast ocean of potential opioid misuse and abuse. There is evidence of a large range of sources for diverting prescription opioids including pain patients, elderly people supplementing their income by selling opioids, friends and relatives of users and doctor shoppers with a small contribution from internet sources and theft[2,6]. Harms arising from this unsanctioned use include fatal overdose, intoxication, dependence and unsafe injection practices in addition to conversion to illicit drug use with a survey of heroin users reporting that 75% initially started with a prescription opioid[2,8]. Multiple studies have revealed a very large pool of unused opioid medications in postoperative patients with one systematic review reporting two-thirds of patients having leftover prescription opioids following surgery[3,7,20]. Reasons are not limited to over-prescription but include patients self-limiting intake due to fear of addiction and side-effects[21]. It is known that these are frequently given to friends or relatives and was shown in one study to be the most common source of prescription opioids for non-medical use in the US in 2010-2011. Similarly, in Australia around half of those who accessed morphine and oxycodone for non-medical use sourced these drugs from friends[4]. Studies reveal that in excess of 90% of patients receive no disposal instructions for leftover opioids and a similar proportion keep them, usually in an unsecure location in the home[3,4,8]. Disturbingly, the availability of these opioids contributes to the risk of unintentional poisoning in children[4]. This is despite evidence that provision of education in the form or printed materials regarding opioid disposal and take-back locations results in an increased frequency of disposal of leftover medication[6,7]. Provision of education regarding the need and means of safe disposal of opioids is therefore crucial in reducing this reservoir.

Pharmacies are the most common portal of return however they assume unwanted costs and safety liabilities in administrating and storing rigorously controlled medication, resulting in a tacit disincentive for their involvement in such schemes[20]. Other initiatives to reduce the supply of leftover medication are the introduction of secure medication disposal boxes in medical facilities and take-back events, which could even include financial incentives or reimbursement, either at a patient or a pharmacy-as-small-business level; similar to other government sponsored buyback campaigns with a view to securing public health protections[6].

Formulation and activation of an opioid exit plan is imperative for discontinuation of opioids in postoperative patients since there remains little good evidence for any benefit from long-term opioid therapy for the management of chronic pain[3,4]. Furthermore, duration of use rather than dosage of opioid is strongly associated with subsequent misuse with each additional week of opioid prescribing associated with an average increase in the rate of misuse of 34.2%. Patients who received even one post-discharge prescription are three times more likely

to be taking opioids at one year across a range of specialties[22]. Follow-up for adherence to these plans and satisfactory analgesia in addition to reminders for disposal have been ideally pharmacist-led in some centres[3].

In those that experience complex postoperative pain demands, such as those that develop CPSP and those whereby pain may not be the main driver of continued opioid use, transitional pain clinics have been advocated and established, with proven cost-effectiveness and beneficial outcomes. CPSP is an increasing public health problem due to the distress and disability it causes and past approaches to management have contributed to the current opioid crisis. Transitional pain clinics are a pragmatic approach to bridge the neighbouring shores of acute post-operative pain services on surgical wards and outpatient chronic pain clinics. As discussed, integrated services can identify patients at risk via preoperative screening and refer inpatients using established prognostic indicators. Clinic visits are then used to review treatments and liaise with primary care providers and surgical teams. Other services are available for referral including: rehabilitation, mental health professionals, addiction medicine, physiotherapy and occupational therapy. Benefits are cost savings, encompassing medical treatment costs, unplanned readmissions, reduced long-term disability and failure to return to work in addition to a source of research, audit, training and education[10]. The interplay between depression, anxiety, pain catastrophising and CPSP, and persistent opioid use opens opportunities to provide psychiatric support reducing the forces accounting for postoperative opioid use[6].

The experience of Toronto General Hospital's transitional pain service is instructive, encompassing pre-, post-operative inpatient and post-operative outpatient stages up to six months after surgery to address the specific problems of CPSP and opioid use. Utilising a team including: nurse practitioners, physicians, psychologists and allied health based on patient need, pain and function were both significantly improved in patients, with consumption reduced in opioid-naive and opioid experienced patients by 69% and 44% respectively with 46% and 26% weaned completely. As few as three professionals (anaesthetist, psychologist or other mental health professional and nurse or nurse practitioner) are required to staff a functional transitional pain service with the goals of effectively managing long-term pain, maintaining function, reducing opioid consumption and monitoring efficacy of interventions[15]. It is only recently that health systems have had transitional pain services that aim to prevent the development of CPSP and assist patients return to baseline levels of opioid medications or wean to zero. Results from these services suggest a large unmet need in most hospitals around the world[10].

CONCLUSION

The mitigation of the advancing flood of opioid misuse, abuse and harm at each stage of its course is a pressing demand in Australian healthcare systems. The use of evidence and initiative is increasingly steering targeted interventions amidst the surging stream of opioid prescribing. Only increased awareness, ongoing education and organisational adaptation will see the tide ebb.

Readers are referred to a complementary article entitled "The 'opioid crisis'" by Stephan A Schug within this edition of *Australasian Anaesthesia.*

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The changing face of complex regional pain syndrome treatment

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INTRODUCTION

Complex regional pain syndrome (CRPS) is a debilitating condition that most often occurs in a limb following injury/trauma/surgery, with a typical post-traumatic incidence of 0.5-2 per cent[1]. The current diagnostic criteria include regional pain that is disproportionate to the initial trauma, skin colour and temperature changes, oedema, vasomotor and sudomotor changes, motor dysfunction and trophic changes[2]. CRPS type I, formerly known as “reflex sympathetic dystrophy”, occurs in the absence of any obvious nerve injury, whereas CRPS type II, formerly “causalgia”, indicates a confirmed nerve lesion[3]. The acute phase of CRPS is dominated by inflammatory symptoms, such as warmth, redness, swelling and sweating, however, approximately 30 per cent of patients present with a “primary cold” phenotype, characterised by a cold, white or blueish, ischaemic limb[4]. The pain is restricted to the affected limb and accompanied by hyperalgesia. The disease can transition into a chronic phase, typical inflammatory signs fade and centrally-driven symptoms prevail, such as chronic pain that may spread up the limb, hyperalgesia, sensory deficits, motor symptoms (for example, dystonia, tremor, myoclonus), and pathological behaviours (for example, fear avoidance leading to limb disuse), which contribute to body perception disturbances[4].

CRPS is also seen in the paediatric population typically in early teenager years although cases as young as 6 years old have been described. It seems much more readily treatable with intensive physical therapy / rehabilitation therapy than the adult version of the disease for reasons unknown[5].

TRADITIONAL VIEWS

CRPS was first clearly described in 1872 by US physician Silas Weir Mitchell in his book “Injuries of nerves and their consequences”[6]. He suspected that a role for “the irritation of a nerve at the point of the wound might give rise to changes in the circulation and nutrition of the parts in its distribution, and that these alterations might be of themselves of a pain-producing nature”[7]. In 1872, he adopted the term “causalgia”, which focused on the regionally restricted features[8]. Next came the work of Paul Sudeck, who described “acute inflammatory bone atrophy”, since named “Sudeck’s atrophy”, in his paper of 1900[9]. This term later became synonymous with the term “Reflex Sympathetic Dystrophy” (RSD), following the identification of a role for the sympathetic nervous system in chronic neuropathic pain[8].

The International Association for the Study of Pain (IASP) was established in 1973, and has since held multiple consensus conferences to classify chronic pain syndromes[10]. The IASP replaced the term RSD with CRPS and established the Budapest diagnostic criteria[11]. To provide a distinction between CRPS without evidence of nerve injury (RSD) and CRPS with evidence of nerve damage (causalgia), the subtypes I and II were established. Progress has and continues to be made in refining the diagnostic criteria for CRPS[2,12-15].

TRADITIONAL THERAPIES

Over the past 30 years, therapy for this condition has often been applied ad hoc and without reference to evidence-based literature. Either traditional physiotherapy or limb desensitisation techniques (such as “scrub and carry”[16]) have been applied, though their efficacy has not been validated. Common analgesics such as

opioids and non-steroidal anti-inflammatory drugs (NSAIDs) have been trialled, but again, without proven efficacy. In the case of opioids, there are concerns of potential worsening of the condition from opioid induced central sensitisation. Intravenous regional analgesia (CRPS Bier blocks) has now been discontinued due to limited evidence of their lack of efficacy in this condition[17]. Calcitonin infusions have been mostly discontinued due to lack of sustained benefit in more modern studies[18]. Early use of oral corticosteroids (six-week course) and single infusion of IV bisphosphonates has the strongest evidence base and continues to be a component of modern therapy[3].

In the absence of specific CRPS validated treatments it is commonplace to see standard treatments for neuropathic pain applied to the condition. This includes anti-neuropathic medications such as gabapentin, pregabalin, duloxetine, tricyclic antidepressants, intravenous lignocaine and ketamine infusions. The efficacy of this approach is under question with low level evidence supporting consideration of its use.

Aggressive multimodal rehabilitation, including the use of cognitive behavioural therapy, has had widespread support from clinicians in terms of reasonableness of expectation of benefit and positive risk/return benefit, with limited evidence of efficacy[15]. More recently, motor imagery therapy has had documented benefit and has replaced more traditional forms of physiotherapy input to the condition[3]. Sympathetic nerve blocks (and the more modern variants of radiofrequency and pulsed radiofrequency lesioning of the sympathetic chain) have limited evidence of efficacy in early (<12 months of symptoms) CRPS and appear to be well supported by clinician personal experience since its introduction more than 40 years ago[3].

ANIMAL MODELS OF COMPLEX REGIONAL PAIN SYNDROME

Several animal models of CRPS have been developed in order to study different initiators and pathological mechanisms of the condition[19]. Two notable models are the rodent tibia fracture model (TFM) and the chronic post-ischemia pain (CPIP) model.

The TFM was developed to mimic the symptoms of CRPS due to distal limb fracture, the most common cause of CRPS-I. Under anaesthesia, a closed tibial fracture is performed and a cast is placed on the hindlimb for four weeks (rats) or three weeks (mice). This induces CRPS-like symptoms, including ipsilateral limb warmth, oedema, allodynia (mechanical), periarticular osteopenia, epidermal thickening, and limb unweighting[20,21]. This model has provided valuable insights into pain sensitisation, vascular changes and immune response as important CRPS mechanisms. Studies using the TFM have highlighted important roles for neuropeptides (such as substance P and calcitonin gene-related peptide), keratinocyte activation, inflammatory cytokine production (particularly interleukin-1 (IL-1) and tumour necrosis factor (TNF)) by endothelial cells, nerve growth factor (NGF) signalling, and mast cell proliferation in nociceptive sensitisation in CRPS[19-24]. The CPIP model is another rodent model that mimics CRPS-I features following ischemia/reperfusion injury[25]. Rodents are anaesthetised and a tight O-ring is fitted over the distal hindlimb for three hours. Reperfusion occurs immediately after O-ring removal. This produces an inflammatory cascade and subsequent neuropathic pain-like symptoms, including hyperalgesia and allodynia (cold and mechanical), and CRPS-like changes in skin appearance[25]. Studies using the CPIP model have provided evidence of macrophage and neutrophil recruitment, increased inflammatory cytokine production, and oxidative stress in CRPS[26].

While these animal models do well to mimic many of the key features of CRPS, and have been invaluable instruments for studying CRPS pathophysiology and testing potential new treatments, they fail to reproduce all of the classical symptoms. Additionally, the most commonly used models focus on physical trauma (fracture, casting) as the cause of CRPS, however, up to 10 per cent of CRPS cases are not attributable to trauma/injury[27]. Furthermore, the acute and chronic phases of CRPS differ considerably in terms of clinical presentation and disease mechanisms, for which animal models provide limited accuracy[28].

HYPOTHESES

CRPS has defied a clear, unified pathological explanation to date. Many observations have been made of physiological abnormalities, however, how these explain the condition and who does and doesn't develop CRPS remains unclear[29]. Not surprisingly, treatments for the condition are limited in number, efficacy and their ability to enact a cure. There is a need for a valid hypothesis that accounts for the fundamental aspects of the condition and suggests new treatment avenues based on confirmed pathophysiological mechanisms.

Kingery/Birklein

The work of Kingery, Clark and colleagues has been paramount to our understanding of inflammation and immune system involvement in CRPS. Their latest review focuses on autoinflammatory and autoimmune contributions to CRPS pathophysiology[30]. Autoinflammation involves dysfunction of the innate immune system while autoimmunity involves the adaptive immune system, both of which are driven by dendritic cells (DCs – a

class of immunosurveillance cells), Langerhans cells (LCs – epidermal dendritic cells), and mast cells, among other immune cells[30].

Evidence of autoinflammation in CRPS comes from observations of elevated levels of pro-inflammatory cytokines (TNFα, IL-1ß, IL-6), accumulation of mast cells, DCs/LCs and keratinocytes, and non-pathogenic activation of DCs (such as by damage products, tissue hypoxia) in the affected limbs of acute CRPS patients and/or animal models[22,31-33]. Dysfunction of the autonomic nervous system may also contribute to this excessive inflammation. Schlereth, Drummond and Birklein reviewed the role of sympathetic overactivity in CRPS inflammation[34]. Norepinephrine activates DCs and LCs via α1-adrenoceptor stimulation which is expressed under inflammatory conditions[35].

Besides B-cells, a normal adaptive immune response may be initiated by DCs and LCs upon presenting antigen to T-cells in regional draining lymph nodes[36], however, under certain conditions, DCs and LCs may present self-antigens, resulting in autoantibody production[37]. Much of the evidence of autoimmunity in CRPS comes from investigations of the sera of CRPS patients. One study found that some CRPS patients have autoantibodies against autonomic neurons[38], and others found that many patients have autoantibodies to M2 muscarinic receptors, α1-adrenoceptors, or ß2-adrenoreceptors[39, 40]. Autoantibody involvement has also been supported by studies in which serum-IgG from CRPS patients was injected into rodents and produced CRPS-like symptoms (such as hyperalgesia, oedema)[41,42].

Birklein and colleagues recently published a review on potential biomarkers and proposed two conceptual frameworks for CRPS: 1) augmented neuro-immune activation; and 2) autoantibodies[43]. Their first hypothesis suggests that an increased production of inflammatory mediators by mast cells, keratinocytes, osteocytes and sensory nerve cells after trauma drives acute CRPS signs and peripheral nociceptive sensitisation, which may lead to spinal dorsal sensitisation. Chronic CRPS represents a centralised state upon which peripheral inflammation subsides and central mechanisms (neuroplasticity, cortical reorganisation) drive persistent symptoms, such as pain and motor dysfunction[44]. The second proposes that if limb trauma occurs during a vulnerable time in which antibody production is elevated, an exaggerated inflammatory response can result in autoantibody production to neuronal structures, which can cause nociceptive sensitisation. In chronic CRPS, autoantibody production persists.

Cortical reorganisation

The first indications of cortical involvement in CRPS came from the work of Maihofner and colleagues, who observed referred sensations in the affected limbs of CRPS patients when the unaffected limb or another area of the body was stimulated – distortions in spatial representation indicative of cortical reorganisation[45,46]. They also reported correlations between the degree of cortical reorganisation, pain intensity and mechanical hyperalgesia.

Moseley and colleagues also provided evidence of cortical involvement in CRPS through reports of distorted body perception CRPS-I patients[47-50]. Their studies demonstrated that 1) CRPS-I patients may perceive their affected limbs to be larger, and this is correlated with symptom duration[47]; 2) CRPS-I patients take longer to recognise their affected limbs, and this is related to symptom duration and the level of pain they predict they would experience if performing different limb postures (as shown in photographs)[49]; and 3) imagining postures in the affected limb can increase pain and swelling[48,50]. They hypothesised that maladaptive neuroplasticity and cortical reorganisation of the motor M1 and somatosensory S1 cortices as likely contributors to functional impairments in CRPS and chronic pain patients[51-53].

In 2011, Marinus, Moseley, Birklein, Maihofner, Kingery and van Hilten jointly reviewed CRPS, focusing on aberrant inflammatory pathways, vasomotor dysfunction, and maladaptive plasticity, as three major pathophysiological mechanisms driving the development and maintenance of CRPS[53].

Basal ganglia dysfunction

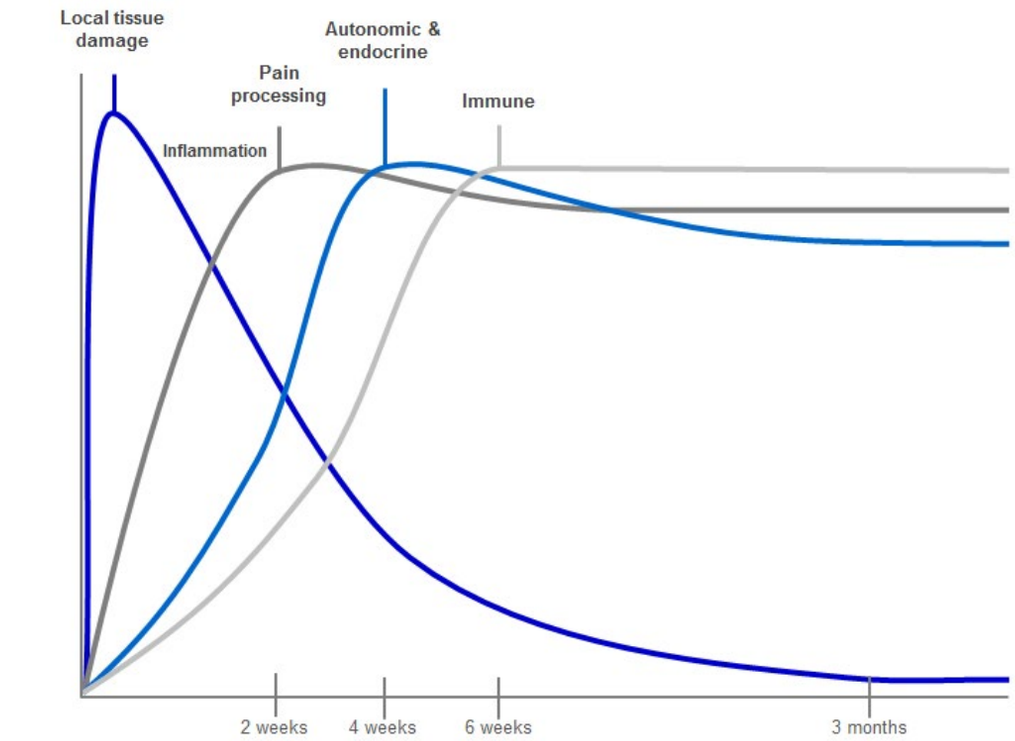
Subcortical contributions to pain processing (including the basal ganglia) have also been studied[54,55]. Azqueta-Gavaldon and colleagues proposed a hypothesis of basal ganglia dysfunction in CRPS[56]. Neuroinflammation of the basal ganglia due to microglial activation has been observed in CRPS patients, and this is positively associated with pain intensity[57]. It is possible that an inflammatory/immune response can induce pathological changes in basal ganglia (for example, increased activity, altered dopamine neurotransmission)[58]. Insights gained from these studies, together with the implied roles of the basal ganglia in CRPS-associated motor dysfunction (such as dystonia) and mood disturbances (such as reward behaviour)[59], provide hypothetical grounds for involvement of basal ganglia dysfunction in CRPS pathophysiology[56].

Russo/Georgius (Authors)

Inspired by the work of those above is our most recently proposed hypothesis[29] which describes a four-component model and timeline of tissue trauma, pathological pain processing, autonomic dysregulation and

immune dysfunction, as shown in Figure 1[29]. We propose that interactions between these components, which may vary in degree of homeostatic disturbance, involvement, and time course between individuals, may form the basis of activation, development and maintenance of the condition. The focus of our hypothesis is on the immune component.

Figure 1. The proposed four component model of CRPS depicted as a time course of homeostatic disturbances. Adapted from Russo et al[29].



The authors propose that DCs are the primary drivers of CRPS. Activation, maturation/migration and/or expansion of DCs may occur in the acute phase of CRPS as a result of specific processes/pathways that come under the components of the model; 1) activation by damage-associated molecular products (DAMPs), which are released following tissue trauma[36]; 2) activation by tissue hypoxia caused by trauma[60]; 3) loss of DC inhibition in the regional lymph node due to loss of vagal control via the cholinergic anti-inflammatory pathway, leading to loss of immune tolerance and the initiation of an adaptive immune response[61]; 4) activation by norepinephrine due to excess sympathetic activity/stress response[35]; 5) loss of DC inhibition due to altered motor feedback (motor cortex, basal ganglia) as a result of limb immobilisation[52]. The downstream, chronic effects of this may include endothelial and vasomotor dysfunction, neuroinflammation due to microglial activation, central sensitisation, autoimmunity, and pathological pain processing due to basal ganglia dysfunction[29].

Recently, Russo, Austin and colleagues published the results of an immune profiling study of the serum of CRPS patients which complement this hypothesis[62]. In this study, expansion and activation of multiple central memory T cell populations compared to healthy matched controls was found. A decreased population of myeloid DCs was observed, but with increased p38 phosphorylation, which was correlated with increased activation of central memory T cells. The decreased number of DCs might indicate migration to peripheral tissue and regional draining lymph nodes, where they activate T-cells and induce an adaptive immune response[63].

IMPLICATIONS OF THE HYPOTHESES

Formerly, there existed a scatter of seemingly disparate fields of research and schools of thought on the pathophysiology of CRPS. It was largely believed that CRPS was primarily a neurological disorder. This belief has since shifted towards CRPS as an immunoneurological disorder.

The hypotheses reviewed above cover the most notable biological systems for which there exists substantial evidence for involvement in CRPS: the immune system, autonomic nervous system, and the peripheral and central nervous systems. They attempt to explain how the proposed pathophysiological mechanisms support, rather than contradict, each other. Furthermore, these hypotheses provide directions for future research and fertile grounds for testing existing non-CRPS therapies, trialing new multimodal methods, and developing new therapies that have the potential to target multiple underlying factors of this complex condition.

CURRENT STATE-OF-THE-ART RECOMMENDATIONS

Timeliness of diagnosis and intervention is critical for improving prognosis. The majority of mild cases will resolve within the first year, however, those who progress to the chronic phase have a poor prognosis[3]. Additionally, psychological symptoms present within the first year are associated with worse outcomes if left untreated[64]. Treatment of chronic CRPS is especially challenging and requires a different management approach as the disease becomes more centrally driven and cortical changes may predominate.

As a multifactorial, heterogeneous disease, there is no “one size fits all” approach to treating the CRPS patient. A mechanism-based approach that considers the individual’s clinical presentation and suspected pathophysiology is recommended. Table 1 presents treatment options based on presenting signs and proposed mechanisms as suggested by Gierthmühlen and colleagues[65], and additional recommendations adapted from the most up-to-date report by Birklein and Dimova[3].

Table 1. Recommendations for treatment of CRPS based on clinical signs, mechanisms and disease phase.

Clinical signs	Treatment options
Inflammatory symptoms (acute CRPS; oedema, redness, heat, acute pain)	▪ Short-term corticosteroids
Regional osteopenia (acute CRPS)	▪ Bisphosphonates ▪ Or corticosteroids + DMSO cream
Psychological symptoms	▪ Behavioural therapies (CBT)
Distorted body representation	▪ Physical and occupational therapy ▪ Mirror therapy (acute CRPS) ▪ Graded motor imagery (chronic CRPS)
Spontaneous pain, hyperalgesia, allodynia	▪ Analgesics (including topical creams and combinations) ▪ Tricyclic antidepressants (amitriptyline, nortriptyline) ▪ Gabapentin ▪ Pregabalin
Sympathetically-maintained pain (acute – intermediate CRPS)	▪ Sympathetic nerve blocks ▪ Intravenous ketamine infusion
Chronic refractory pain	▪ Spinal cord stimulation ▪ Dorsal root ganglion stimulation (lower limb CRPS)
Central motor symptoms (dystonia)	▪ Intramuscular botulinum toxin type A (intermediate CRPS) ▪ Intrathecal baclofen pump (chronic CRPS)

More recently, the European Pain Federation established a task force of CRPS experts and published a position paper on standards for the management (and diagnosis) of CRPS[15]. These standards cover diagnosis, referral and education, pain management, physical and vocational rehabilitation, and treating distress.

FUTURE RESEARCH AREAS

For each target area of dysfunction (immune, autonomic, central pain processing, autoantibody production) there are several candidate treatments that will need to be evaluated both in animal models and human trials. The complexity of combining treatments in different areas will challenge clinical trial design. A more robust animal model that more closely mimics the human CRPS condition may need to be developed and will likely involve a refinement of the rodent tibia fracture/casting model (possibly with central sensitisation induced by initial opioid therapy/nicotine exposure).

On a systems front, there needs to be research conducted on how patients presenting with acute CRPS can be navigated through the health care system to achieve timely therapy, often alongside treatment of their primary limb injury.

Further detailed examination of immune system changes in a serial real time manner would help elucidate cause and association effects and determine critical immune processes for blockade/augmentation.

CONCLUSIONS

CRPS has remained both an enigma and a frustrating condition to treat for generations of pain physicians. Very recently, there is good evidence of the immune, autonomic and central pain processing abnormalities of the condition, and this should allow effective treatment options to emerge over the next few years. It is clear to researchers in the field that no single “magic bullet” treatment will likely be developed. Rather, it is likely that a suite of treatments aimed at bringing the various disturbed body systems back into homeostasis is likely to be required, and that the earlier this suite of treatments can be deployed, the more likely the true resolution of the condition will occur. This will require neurohumoral treatments that employ both a top down and a bottom up approach wedded to multimodal rehabilitation involvement.

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Brain/Neuro

Postoperative delirium

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INTRODUCTION

"Now it is useless to adopt remedies when the delirium is at its height… there is nothing else to do than to restrain the patient, but when circumstances permit, relief must be given with haste…"

It is believed that the term delirium first appeared in medical literature in De Medicina by Aulos Cornelius Celsus during the reign of the Roman Emperor Tiberius (14–37 AD)[1]. In modern times the World Health Organization (WHO) has defined delirium as "an etiologically nonspecific organic cerebral syndrome characterized by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion, and the sleep-wake schedule. The duration is variable and the degree of severity ranges from mild to very severe."

Postoperative delirium (POD) has been incorporated into the new 2018 nomenclature for Perioperative Neurocognitive Disorders[2]. This replaces the old terminology for "postoperative cognitive dysfunction" and more clearly highlights delirium as a distinct condition in line with DSM-V diagnostic criteria and the diagnostic lexicon used by physicians and other medical specialists. The new nomenclature defines POD as that which occurs in hospital up to 1 week post procedure or until discharge (whichever occurs first) and meets DSM-V diagnostic criteria[3].

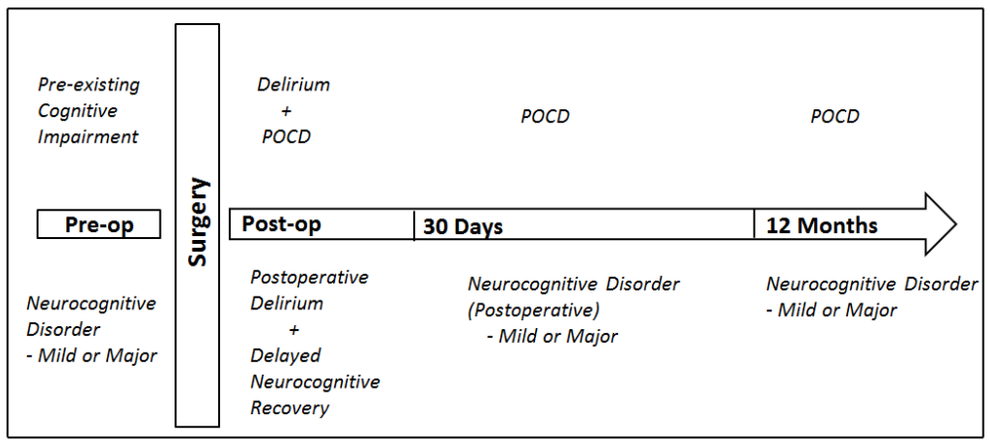
DSM-V diagnostic criteria for delirium is as follows:

- Disturbance in attention (that is, reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
- The disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
- An additional disturbance in cognition (for example, memory deficit, disorientation, language, visuospatial ability, or perception).
- The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.
- There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (that is, due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies.

POD is a postoperative complication that can occur in patients of any age. It represents a different syndrome to emergence delirium, which can occur in up to 20% of cases, particularly in children. Older patients are at particularly high risk of POD due to their increased rates of predisposing risk factors such as pre-existing cognitive impairment, comorbidities, malnutrition, sensory deficits, impaired functional status and frailty.

Perioperative neurocognitive disorders, previously referred to as postoperative cognitive dysfunction, have been the subject of much contemporary research. The International Perioperative Cognition Nomenclature Working Group has recently published its recommendations[2]. They recommend that the term "perioperative neurocognitive disorders" be used for cognitive impairment identified in the preoperative or postoperative period. This term is inclusive of cognitive decline diagnosed preoperatively (neurocognitive disorder), any acute event (POD), cognitive decline diagnosed up to 30 days following a procedure (delayed neurocognitive recovery) and up to 12 months post procedure (postoperative neurocognitive disorder), see Figure 1. It is hoped that adoption of this terminology, which is similar to that used outside of anaesthesia, will improve consistency in the way perioperative cognitive disorders are communicated and reported.

Figure 1. Diagram of old versus new nomenclature.



In Australia there are approximately 11 million hospitalisations per annum. One in four of these involve a surgical procedure and almost one third of these are in patients aged over 60 years. It is estimated that by 2050, those aged over 60 will comprise 25% of the population and receive 50% of all anaesthetics. Rates of POD and postoperative neurocognitive disorders vary widely depending on the patient's age, surgical procedure and comorbidities, with some studies suggesting rates of up to 87% in high risk populations[4].

An episode of POD has a huge impact on individual patients and their families but also on the healthcare system. The Australian Commission on Quality and Safety in Healthcare estimates that each hospitalisation involving hospital-acquired delirium is associated with $27,791 in extra costs. Postoperative delirium is an independent risk factor for increased morbidity and mortality[5]. Studies have shown that mortality is increased at 6-month and 5-year follow-up[6].

In this article we will review recent literature on POD.

PATHOPHYSIOLOGY

The exact pathophysiology of delirium is not yet completely understood. It is widely accepted that acute central cholinergic deficiency plays a key role. Other theories suggest that decreased GABA-ergic activity, abnormalities in serotonin and melatonin pathways, noradrenergic hyperactivity and cerebral hypoperfusion are other potential mechanisms. Surgery itself is associated with cholinergic inhibition, serotonin deficiency and cortisol excess which may contribute specifically to post operative delirium[7,8].

In older but otherwise healthy patients, activation of the peripheral immune system causes an exaggerated cerebral inflammatory response. This may explain why older adults are more prone to delirium even after an apparently trivial precipitating event. The ageing process seems to serve as a "priming" stimulus for microglia via toll-like receptor 4, which then release large quantities of proinflammatory cytokines when stimulated by peripheral inflammatory signals.

Recent research has shown that acute systemic inflammation induces both transient, reversible cognitive deficits (which resembles delirium) and lasting brain injury, and that interleukin 1 contributes to both processes, but via differing mechanisms[9].

A 2019 systematic review[10] of preoperative biomarkers and imaging tests as predictors of POD in non-cardiac surgical patients found that C-reactive protein is currently the most promising biomarker associated with POD. The search for a reliable biomarker is ongoing and there is currently no standard biomarker for diagnosis or prognosis of postoperative cognitive issues. The findings of some research on biomarker association with POD and postoperative neurocognitive disorders are contradictory and thus further research including the use of medical imaging and metabolic and genomic testing is required.

CLINICAL PRESENTATION

Delirium can present in a hyperactive, hypoactive or mixed form. The American Geriatrics Society identified several symptoms associated with POD in their best practice statement in 2015[11]. These symptoms include: an abrupt change in cognitive function (worsening confusion over hours or days) including problems with attention, difficulty concentrating, new memory problems and new disorientation. Patients may have difficulty tracking conversations, following instructions and have quick changing emotions, easily irritated, appear hypervigilant and have uncharacteristic refusals to engage with postoperative care. Other features that may be present include expression of new paranoid thoughts or delusions or new perceptual disturbances such as illusions and hallucinations. Symptoms specific to hypoactive delirium include slowed speech, which is more disorganised and difficult to follow, slowed or decreased movements, decreased appetite, new incontinence and changes to the sleep wake cycle such as sleeping during the day. Symptoms and level of arousal fluctuate over the course of minutes to hours.

It is essential that patients with these symptoms are identified early and appropriately managed. There are several tools available to monitor for delirium including the confusion assessment method and the 4AT. The 4AT is a validated tool that is frequently used to screen hospital inpatients for delirium[12]. Table 1 outlines this assessment. A score of 4 or above indicates possible delirium +/- cognitive impairment, 1-3: possible cognitive impairment and 0 represents that delirium or cognitive impairment is unlikely.

Table 1. 4AT Rapid clinical test for delirium.

Alertness	Normal	0 points
	Clearly abnormal	4 points
AMT4	0 mistakes	0 points
Age, date of birth, place (name of the hospital or building), current year	1 mistake	1 point
	≥2 mistakes or untestable	2 points
Attention	Lists more than 7 months correctly	0 points
Instruct patient to list months in reverse order, starting at December	Starts but lists less than 7 months or refuses to start	1 point
	Untestable (cannot start because unwell, drowsy or inattentive)	2 points
Acute change or fluctuating course	Yes	4 points
	No	0 points
Evidence of significant change or fluctuation in mental status		

Families and carers can play a key role in identifying a change in a patient's behaviour if they are educated in what to look for. Currently in our institution, we are trialling the introduction of an information sheet for families of patients who are identified as at risk of POD. We hope that this intervention will help to decrease the frequency of delirium but also lead to earlier diagnosis and management for patients who develop POD.

IDENTIFYING THE AT-RISK PATIENT

Throughout the literature one of the most common independent risk factors for POD is pre-existing cognitive impairment. Screening patients for cognitive impairment in the preoperative setting can not only help to assess risk of POD, but also provide a baseline performance when screening for delirium postoperatively.

Formal cognitive assessments such as the AMT-4 (age, date of birth, place and year) and Mini-Cog© are a brief and accurate way of assessing cognition which can be easily incorporated into the anaesthetic preassessment

clinic or the standard admission documentation[8]. The Mini-Cog© consists of 2 components, a 3-item recall test for memory and a simply scored clock drawing test.

The Montreal Cognitive Assessment (MoCA) tool is another frequently used assessment tool. It was initially validated to screen for mild cognitive impairment, but is now used more broadly to assess cognitive impairment. The MoCA assesses multiple cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. It has greater sensitivity than the mini mental state examination (MMSE), so may detect cognitive impairment in patients with memory complaints who score within the normal limits of MMSE[13]. Telephone-based screening tools can also be used as part of the preoperative workup. The Telephone Interview for Cognitive Status (TICS) and Telephone Interview for Cognitive Status—Modified (TICSM) are validated tools that have been shown in epidemiological studies to detect a range of mild to moderate cognitive disorders[14]. If cognitive impairment is diagnosed in the preoperative setting, patients can then be referred to a geriatrician, neurologist or psychiatrist for a more detailed work up and ongoing management.

The European Society of Anaesthesiologists and the American Geriatrics Society have both recently published guidelines that identify key risk factors for the development of POD. These can be divided into predisposing and precipitating factors and are summarised in Table 2.

Table 2. Risk factors for POD.

Predisposing factors	Precipitating factors
Age greater than 65 years. Cognitive impairment. Hearing or vision impairment. Severe illness or comorbidity burden, especially: ▪ Cerebrovascular events. ▪ Cardiovascular disease. ▪ Peripheral vascular disease. ▪ Diabetes. ▪ Anaemia. ▪ Parkinson's disease. ▪ Depression and anxiety disorders. Poor functional status, immobilisation or limited mobility. Polypharmacy and use of psychotropic medications, especially: ▪ Benzodiazepines. ▪ Anticholinergics. ▪ Antihistamines. ▪ Antipsychotics. ▪ Low albumin.	Procedure related factors: ▪ Hip fracture surgery. ▪ Aortic surgery. ▪ Prolonged procedures. Medical/Physiological factors: ▪ Hypoxia or hypercarbia. ▪ Renal insufficiency. ▪ Dehydration and prolonged preoperative fluid fasting. ▪ Presence of infection. ▪ Hypothermia on admission to the Post-Anaesthesia Care Unit. ▪ Electrolyte abnormalities (hyper- or hyponatremia). Other factors: ▪ Alcohol use. ▪ Sleep deprivation or disturbance. ▪ Presence of urinary catheter. ▪ Poor nutrition. ▪ Risk of urinary retention or constipation.

The risk of developing delirium can be thought of as a product of these predisposing and precipitating factors. A patient with multiple predisposing factors is more likely to develop delirium after a trivial precipitating event, whereas a substantial precipitating event would be required for a patient with no predisposing factors to develop POD.

There are no definitive laboratory tests to diagnose POD, and acute abnormalities of attention and cognition have a large list of differential diagnoses. A full workup including full blood count, renal profile, blood glucose, blood gas, urinalysis and ECG should be considered in all patients with an acute change in their cognitive status to out rule reversible cause such as hypoxia, hypoglycaemia, or electrolyte abnormalities. Alcohol withdrawal and conditions such as meningitis or status epilepticus can also cause an acute change in consciousness and should be considered if appropriate. There are currently no known neuroimaging findings which correlate to POD. As a result, imaging studies should only be requested if there is clinical suspicion of a specific finding, for example, stroke.

MANAGEMENT OF THE AT-RISK OR DELIRIOUS PATIENT

Preoperative

Screening patients preoperatively to assess their risk for POD is key to good management of these patients. Although formal neurocognitive testing can be time consuming, brief assessments can add valuable information, with the aim of counselling patients on perioperative risk and implementing targeted strategies to prevent POD[15].

The addition of the AMT-4, Mini-Cog© or clock draw tests to admission documentation provides a fast and effective screening tool for cognitive impairment. Staff education in other risk factors for POD is also key. Guidance from the European Society of Anaesthesiology[16] and the Brain Health Initiative[15] in the United States also recommend that any modifiable risk factors for POD should be addressed in the preoperative period if possible. This may include optimising pain management plans, alcohol reduction, minimising polypharmacy and limiting preoperative fluid fasting. Patients and their families should also be educated about the risk of delirium, and what they can do to reduce these risks postoperatively, such as regular reorientation, presence of familiar faces and help to correct sensory impairments. As the concept of shared decision-making takes greater importance, understanding all of the risks is important in the consent process.

A referral to a geriatrician for further assessment and management may also be warranted in the preoperative period. Indeed, a meta-analysis of perioperative interventions to reduce delirium found that a geriatrics consultation before surgery was one of only two perioperative interventions that were associated with a reduction in delirium[17].

Studies considering the effect of premedication on the incidence of POD have not yet found any agents that prevent POD[18].

Intraoperative

Choice of Anaesthetic Technique

The European Society of Anaesthesiology was unable to make a recommendation about the choice of anaesthetic agent to be used intraoperatively to reduce risk of POD, due to a lack of conclusive evidence. A Cochrane review published in 2018[19] also found little or no difference in POD according to the type of anaesthetic maintenance agent in non-cardiac surgery patients. This group did however find that total intravenous anaesthesia (TIVA) with propofol may reduce postoperative neurocognitive disorders. It remains unclear whether the choice of anaesthetic technique plays a significant role in the development of POD. Animal data suggests that cognitive impairment is triggered by the combination of anaesthesia and surgery and not by anaesthesia alone.

Light versus deep sedation has not been shown to have effect on rates of delirium in older adults presenting for hip fracture repair under spinal anaesthesia[20]. This randomised clinical trial did however show that in patients with low baseline comorbidities (Charlson comorbidity index score 0), lighter sedation halved the risk of POD.

There is currently insufficient evidence as to whether neuraxial anaesthesia reduces the development of delirium compared to general anaesthesia. A recent Australian trial was unable to demonstrate a difference between patients who received a general versus a spinal anaesthetic during neck of femur fracture surgery[21].

Depth of anaesthesia monitoring

The use of bispectral index (BIS) guided anaesthesia techniques was shown by Radtke et al[22] to be associated with a reduced incidence of POD. By avoiding excessively deep anaesthesia (that is, target BIS of 40-60) there was a reduction in the amount of anaesthetic agent (propofol or volatile) delivered and subsequently a reduction in POD. While the exact mechanism linking the depth of anaesthesia to POD remains unclear, this study does suggest that avoiding excessively deep anaesthesia is an important strategy for the prevention of delirium.

In its guideline on risk reduction and management of delirium published in March 2019 the Scottish Intercollegiate Guidelines Network[23] recommend that depth of anaesthesia should be monitored in all patients aged over 60 years under general anaesthesia for surgery expected to last for more than 1 hour, with the aim of avoiding excessively deep anaesthesia. Similarly the Perioperative Neurotoxicity Working Group recommend that anaesthetists should perform electroencephalogram-based anaesthetic management in older adults[15].

A 2018 Cochrane review[24] has also concluded that there is moderate quality evidence that anaesthesia guided by processed EEG indices could reduce the risk of POD in patients aged over 60, undergoing non-cardiac and non-neurological surgical procedures. The benefit of EEG-guided anaesthesia in reducing POD has more recently been drawn into question, however, following the ENGAGES study published in February 2019[25]. This randomised control trial of 1232 older adults undergoing major surgery found that EEG-guided anaesthetic administration did not decrease the incidence of POD when compared to usual care. This study also found

that there was an increased risk of undesirable patient movement in the EEG-guided group and similar rates of serious adverse effects in the usual care and EEG-guided groups.

Hypotension

Intraoperative blood pressure fluctuation has been shown to be significantly associated with delirium. While a recent Italian pilot study has also demonstrated that intraoperative hypotension is not associated with postoperative neurocognitive dysfunction[26,27] the Neurotoxicity Working Group recommend that intraoperative hypotension be avoided in an effort to maintain cerebral perfusion[15].

Dexmedetomidine

The use of intraoperative dexmedetomidine has been shown to decrease the risk of POD in cardiac and non-cardiac surgery patients[28]. A systematic review and metanalysis published in the *British Journal of Anaesthesia* in 2018 found that POD was also reduced if dexmedetomidine was administered during the postoperative period. Optimal dosing of dexmedetomidine is still under investigation but the authors of this metanalysis suggest starting with no loading dose or up to 0.5 micrograms per kilogram followed by a maintenance dose of 0.2 micrograms per kilogram per hour[29].

The 2019 SIGN guideline on delirium does not recommend the use of dexmedetomidine in the perioperative setting, citing potential physiological concerns and cost implications.

Ketamine

Ketamine has been used intraoperatively as part of a multimodal analgesia approach and in an effort to reduce opioid consumption. It had been suggested that intraoperative ketamine in subanaesthetic doses may also reduce the incidence of POD.

The PODCAST study[30] published in *The Lancet* in 2017 found that a single subanaesthetic dose of intraoperative ketamine has did not decrease the incidence of delirium in older patients after major surgery and also highlighted that intraoperative ketamine may cause harm by inducing negative experiences for patients.

Other interventions

Guidelines from the European Society of Anaesthesiology, the American Geriatrics Society and the Australian Commission on Quality and Safety in Healthcare suggest other interventions that may reduce the incidence of POD. These include implementation of fast track surgery, avoidance of routine benzodiazepine premedication (except in acute withdrawal) and adequate pain assessment and treatment[5,16,11].

The role of dexamethasone is also currently under investigation. One phase three double blind randomised control trial found that a single low dose of dexamethasone before non-cardiac and non-neurological surgery reduced the incidence of postoperative neurocognitive disorders[31].

Postoperative

The majority of the recommendations from the Australian Clinical Care Standards, the American Geriatrics Society Delirium Guidelines Panel and the European Society of Anaesthesiology relate to the postoperative period. The strongest recommendations involve postoperative multicomponent non-pharmacological interventions by an interdisciplinary team; and optimisation of analgesia and medications (in particular avoidance of Beers list medications)[32].

Prompt diagnosis and treatment are also key to best management of POD. Regular screening for delirium should begin immediately postoperatively and continue ideally until day 5 using the same tool as was used preoperatively. A careful assessment to identify any predisposing and precipitating factors, particularly those that are reversible should be undertaken. The impact of new medications, polypharmacy and analgesic agents should also be assessed.

A 2018 systematic review[33] showed that the Hospital Elder Life Program (HELP), which focuses on multimodal non-pharmacological interventions by an interdisciplinary team, is effective in reducing incidence of delirium and rate of falls, with a trend toward decreasing length of stay and preventing institutionalisation. HELP have also been shown to reduce costs. In nine studies of cost-effectiveness, the program saved $US1600-3800 per patient in hospital costs and more than $US16,000 per person-year in long-term care costs in the year following delirium.

In its best practice statement on delirium, the American Geriatrics Society[11] highlights that non-pharmacological multicomponent strategies are effective in the prevention and management of delirium. Such strategies include orientation, therapeutic activities for cognitive impairment, early mobilisation, non-pharmacologic approaches to minimise the use of psychoactive drugs, prevention of sleep deprivation, communication methods, eyeglasses and hearing aids, and early intervention for volume depletion. The statement also emphasises the importance of a multidisciplinary team approach to the management of these patients.

The role of antipsychotics in the management of POD is controversial. In its clinical care standard for delirium the Australian Commission on Quality and Safety in Healthcare recommends minimising the use of antipsychotic medications as they have a number of adverse effects for older people and can worsen delirium. If non-pharmacological interventions have not been effective the commission suggest that antipsychotics be introduced at low doses and that response be closely monitored.

The best practice statement from the American Geriatric Society also makes recommendations about drug prescribing in patients at risk of delirium. These include that healthcare practitioners should avoid the use of medications that induce delirium postoperatively. These medications include drugs with anticholinergic properties such as tricyclic antidepressants, corticosteroids and sedative hypnotics such as benzodiazepines. The introduction of multiple new medications has also been shown to increase delirium postoperatively. The American Geriatric Society also highlights the importance of formal and informal education programs for staff to improve understanding of delirium.

WHERE DO WE GO FROM HERE?

The concept of enhanced recovery after surgery (ERAS) has been suggested as a framework for developing care pathways for those at risk of POD and or postoperative neurocognitive disorders. Our institution is developing an “ERAS for the Brain” pathway incorporating many of the factors discussed in this article:

- Comprehensive screening of patients preoperatively.
- Identification of screen-positive patients as “at risk” and elevation to “ERAS for the Brain” perioperative pathway.
- A discussion with patient and family (and provision of written information sheet) about the risk of POD and postoperative neurocognitive dysfunction, highlighting strategies which will minimise this risk.
- Information sheet for anaesthesia care providers regarding intra-operative best practice, including avoidance of high-risk medications, and consideration of processed EEG and TIVA.
- Information sheet for ward-based care providers regarding postoperative best practice (prevention), including pharmacological optimisation and non-pharmacological approaches (medication management, early mobilisation and exercise, cognitive stimulation, support of circadian rhythms with sleep protocols and hygiene, vision and hearing aids, maintenance of electrolytes, early removal of the urinary catheter) and education for nurses.
- Early detection and optimal management using our hospital’s confusion protocol.

This pathway would also encourage a multidisciplinary approach to care of these patients with early involvement with allied health services and geriatricians.

In conclusion, POD and postoperative neurocognitive disorders are a common issue for older patients presenting for elective and emergency surgery. While there is not currently enough evidence to recommend a specific anaesthetic technique to avoid this, there are several interventions throughout the patient’s hospital journey which can mitigate the risk for development of POD and postoperative neurocognitive disorders.

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The psychedelic renaissance: Ethnopharmacology, neuroscience and clinical efficacy

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INTRODUCTION

After a period of dormancy there is a "psychedelic renaissance" in neuroscience research. Evidence of benefit is accumulating for refractory depression, psychoneurosis, addiction, suffering in terminal illness and analgesia. They may alleviate pain indirectly through the psychedelic experience on the interpretation of pain. They may work directly on medullary 5-HT_{2A} receptors enhancing descending pain inhibition.

Classical hallucinogens or psychedelics are drugs that produce similar discriminative stimulus effects on thought, perception and mood without producing memory impairment, delirium or addiction. They act primarily as agonists of the 5-HT_{2A} subtype of serotonergic receptor[1]. This partly includes a range of drugs such as MDMA, cannabinoids, arylcyclohexamines (PCP and ketamine), or kappa opioid agonists (Salvinorin A). These are not usually considered as "classical hallucinogens" and beyond the full scope of this review, which will focus on Mescaline, Psilocybin, DMT and LSD. Pseudohallucinogens are toxic compounds producing a delirious state through altered physiology. Although descriptors such as hallucinogen, phantastica, psychotomimetic, phanerothyme (visible soul), entheogen (god within), are used for these drugs, this review will call them psychedelic (mind revealing)[1], as they do more than hallucinate.

This article will cover ethnopharmacology, recent history, pharmacology, receptor mechanisms, neuroscience, "psychedelic experience", and clinical efficacy.

ETHNOPHARMACOLOGY AND RECENT HISTORY

Ethnopharmacology studies the pharmacological qualities of traditional medicinal substances and allows us to "pre-screen" potential therapeutics. Psychedelics have been used by primitive cultures as a medicine, rite of passage, for divination, self-reflection or entertainment. They were used in a "prosocial" way to connect people to their culture and the universe.

Common traditional sources of these compounds are plants. Psychoactive plants contain chemicals that appear to have evolved as allelochemicals, that is, a chemical that usually exerts a detrimental physiological effect on individuals of other species[2]. There is a wide phylogenetic distribution among plants which shows multiple evolutionary origins of psychoactive families. Unrelated plant families exert similar psychoactive effects and modulate similar neurotransmitters (mechanistic convergence). Chemically similar psychoactive chemicals may also exist in phylogenetically unrelated plant lineages[2]. It has been hypothesised that animals have sought plants with phytochemicals chemically similar to their endogenous neurotransmitters to augment nutrition, facilitate survival, and alleviate pain and hunger. Whether this represents a co-evolutionary mutualism is uncertain.

In the "Old World" (Europe, Africa, Asia and Oceania) only 20 psychedelic plants occur. The "New World" (Americas) has more than 100 hallucinogenic plants, where there was a greater emphasis on the psychedelic experience by traditional cultures[4-6]. Psychedelics have been used by some indigenous Americans to enhance the hunting ability of dogs, possibly by enhancing sensory perception (most likely olfaction) possibly by diminishing extraneous signals[3]. See Table 1 for examples.

Table 1. Ethnopharmacology[3-6].

Source/ Family	Genus	Origin	Drug	Common name	Ethnopharmacologic use
Fungi	Psilocybin Strophophora Conocybe	Mexico Guatamala	Psilocybin prodrug > Psilocin	Teonanacatl (flesh of the gods)	3000 yr use – divinatory rites. Now in modern Native- Christian ceremony

Source/ Family	Genus	Origin	Drug	Common name	Ethnopharmacologic use
Fungi	Amanita-muscaria	Temperate – Globe	Muscimole Ibotenic acid NMDA agonist	Fly agaric	Siberian Finno-Ugrian people. ? God-narcotic Soma. Ingest urine to prolong effect
Cactacae	Lophophora Trichocereus	Dry tropical America	Mescaline and alkaloids	Peyote Mescal button	Sacrament Native American Church ^{14}C dated button 5700 yr
Giant Liana Jungle Vines	Banisteriopsis	Amazonia Brazil Columbia Ecudaor Bolivia	β Carbolines Harmine Harmaline (MAOIs)	Ayahuasca tea, oce-yaje	Divinitory rites "telepathic properties". Purgative. Antihelminthic.
Rubiacae	Psychotria	As above	DMT	Chacruna	Mixed with above Ayahuasca Eye drops for migraine
Myristicacae (Nutmeg family)	Virola	Orinoco basin: Columbia Venezuala	DMT β Carbolines	Epená Patricá cumala	Snuff of Waika tribe used for endocannabilsm rite. Arrow Poison
Morning Glory	Concolvulus Argyreia	Widespread	Lysergides like LSD	Numerous	Chinese medicine – laxative Aztec – seeds – divination
Iboga (Dogbane family)	Tabernathe	Gabon Congo	Ibogaine Mild 5HT$_{2A}$ CVS toxicity		Pygmy, later Bwiti initiation rite marketed in France as Lambarene (Stimulant). R$_x$ alcohol addiction 1:300 fatality – unsupervised addiction therapy
Solonacae (Nightshades)	Hyoscyamus Atropa Dhatura Mandragora	Europe central Asia	Belladona Alkaloids Hyoscyamine Scopolomine	Henbane Mandrake Jimsonweed Deadly-Nightshade	Poison, hypnotics, analgesia, "witches brews" More – pseudohallucinogen
Cannabacae	Cannabis	Central and south Asia	THC	Numerous "Ta Ma" first Chinese term	Euphoriant, mixed stimulant-sedation, analgesic.
Amphibian	Bufo	Nth Mexico SW USA Australasia	Bufotenin DMT Cardiac glycosides	Colorado, Sonoran, Desert, Cane Toads	Chinese folk medicine for cancers. ? Haitian Zombie poison
Amphibian	Phyllomedusa species	Amazonia	Opioid peptides deltorphin	Giant leaf frog	"Cleansing" rituals – Intense purgative
Insect	Pogonomyrmex	Sth California	Variety toxins Haemolysins Nicotinic effect	Red Harvester Ants	Visionary rites. Often combined jimsonweed (pseudohallucinogen)

Figure 1. Ethnopharmacology[4].

Magic mushrooms

Peyote cactus – Mescal

Assisted Virola snuff inhalation

"All fungi are edible. Some fungi are edible once." – Terry Prachett (mid-European proverb)

Recent history

In 1887 Berlin pharmacologist Louis Lewin analyses dried mescal buttons sent from Parke Davis in Detroit, sourced by Dallas physician Joseph Briggs[8]. Mescaline first isolated in 1895 by Arthur Heffter from peyote. Self-assessments by Prentiss and Morgan 1895, Weir Mitchell (described Causalgia – CRPS and "Phantom Pain") 1896, and Havelock Ellis 1896 were reported in medical literature[7-10]. Early volunteer physicians noted that hallucinations induced by Mescaline bore similarity to psychotic states. Heinrich Kluver in 1926 described changes in "Gegenstandsbewusstsein und Ichbewusstsein", that is, object awareness and self-awareness, now described as disintegration of ego boundaries or the sense of "self"[11]. Kluver influenced Richard Evans Schultes, an ethnobotanist from Harvard who spent much time with American Amazonia and Mexican tribes studying their psychedelic use. In 1936 Erich Guttman and Walter Maclay from Maudsley Hospital used

Mescaline on: medical students, undergraduates, “normals”, psychopathic patients, manic depressives, schizophrenics, depressives, “morphinists”, and those suffering derealisation and depersonalisation[12]. They noted potential therapeutic use.

The parasitic Ergot fungus, Claviceps purpura grows on the ears of rye and related cereals. Linked to cold winters followed by wet springs. Ergotism was responsible for mass poisoning with psychoses; mania and gangrene in Medieval Europe from spoiled grain stock (St Anthony’s fire). Lysergic acid diethylamide (LSD) was first synthesised in 1938 by Albert Hoffman of Sandoz laboratories, while systematically studying derivatives of ergot alkaloids for a respiratory and circulatory stimulant[13,14]. LSD was abandoned because it caused restless lab animals. Hofmann accidentally contaminated himself in 1943 with LSD. First intentional “trip” was associated with a difficult bicycle ride home, on April 16 now known as “Bicycle Day”! His initial experience was fear and paranoia, the next day he had a sensation of wellbeing and renewed life.

It was recognised as an extremely potent psychoactive substance. Commercially it was introduced under trade name Delysid in 1948 for analytical psychotherapy and experimental psychoses. Covertly the military explored the use of these drugs for psychochemical warfare, and by some authorities as adjunct to interrogation. In 1953 CIA Project MKUltra researched mind control[15,16]. They were considered unpredictable and unreliable, as a “truth drug”, or for tactical use[17]. LSD was initially perceived as a model psychotomimetic. Hofmann also isolated Psilocybin in 1958, marketed as Indocybin. Physiological toxicity was not noted with LSD even in large overdose. Psychedelics were not helpful in schizophrenia, often exacerbating psychosis. But trials in depressive, anxious, obsessive and addictive disorders were more encouraging, especially within a psychologically supportive environment, with low risks of toxicity.

Between 1950 and the mid-1960s there were more than 1000 clinical papers discussing 40,000 patients, several dozen books and six international conferences on psychedelic drug therapy[18]. Sidney Cohen (1960) investigated the incidence of adverse events with 44 researchers and over 5000 patients (and 25,000 dosing). A low incidence of serious events occurred[19,20]. Harvard psychologist Timothy Leary advocated widespread use, and suggested to “turn on, tune in and drop out”. US president at the time Richard Nixon described him as the most dangerous man in America! Evidence of psychotic reactions in sensitive individuals accumulated with occasional tragic cases. Reports of a Hallucinogen Persisting Perception Disorder with “flashbacks” visual distortions long after the drugs were ingested. Sandoz stopped LSD production in 1968. “Street” LSD is often impregnated into blotting paper, and numerous designs exist. Figure 2 shows an example.

Figure 2. LSD blotter art[14].

Legal status

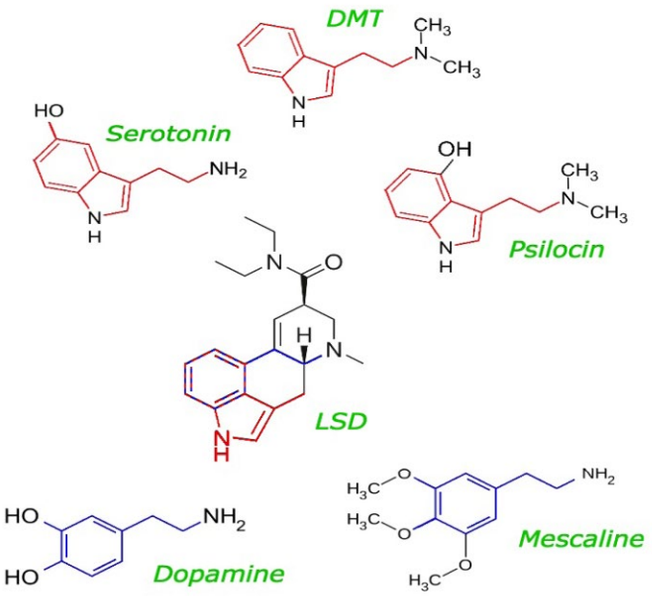
The UN convention on psychotropic substance (1971) requires signing parties to prohibit LSD. It is therefore illegal in those signatories, but enforcement varies from country to country[7,21]. In Australia it is a Schedule 9 substance prohibited under the Poisons Act 2017. It is prohibited by law, except when required for medical or scientific research, or for analytical, teaching or training purposes with Commonwealth and/or State or Territory Health Authority. Post-convention research was scant for many years, and is still challenging. In Denmark an LSD damages law was enacted in 1986 with 151 patients gaining compensation for a variety of psychological symptoms presumed but not proven to be due to LSD given supposedly under coercion or without informed consent[22].

PHARMACOLOGY OF PSYCHEDELICS[18,23]

Tryptamines

(Indolamines) include natural agents: 4-phosporyloxy-DMT (Psilocybin), N,N-dimethyltryptamine (DMT), N,N-dipropyltryptamine (DPT), 5,-methoxy-DMT (5-MeO-DMT), Bufotenin (5-OH-DMT). Simple tryptamines are structurally related to serotonin[23-27]. See Figure 3.

Figure 3. Classic structures.



Phenylalkylamines

The most widely explored class, research chemicals with abuse concerns. A rapidly expanding group subdivided into Phenylethylamines: mescaline has low potency, 2,5 –dimethoxy-4-iododphenethylamine (2C-I), phenylisopropylamines (amphetamines), including 2,5 –dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4bromoamphetamine (DOB), DOM (MDMA and MDE are structurally within this group). New class N-benzyphenylethylamine (25I-NBOMe), (25B-NBOMe). bromoDragonFLY, TCB-2methylamine. The list is incomplete[18]. Substitution of ring or sidechains can affect potency of all psychedelics.

Ergolines

Tetracyclic molecules derived from ergot (and in morning glories). They have a more rigid ring structure (includes LSD and related compounds).

Table 2. Comparative Psychedelic Pharmacokinetics[24,29,42].

Pharmacokinetics	LSD oral	PSILOCYBIN	DMT Inhaled	DMT oral Ayahuasca	MESCALINE
Oral Bioavailabilty	70%	? 50%		Not without MAOI harmine 0.2 mg/kg	Rapid ? %
Dose micro/ threshold	10-20 mcg	3-4 mg	Smoke/vaporise 2-5 mg		< 100 mg
Light	20-75 mcg	4-8 mg	10-20 mg	DMT 30 mg	100-200 mg

Common	50-150 mcg	6-20 mg	20-40 mg	DMT 50 mg	200-300 mg
Strong	150-400 mcg	20-40 mg	40-60 mg	DMT 70 mg	300-500 mg
Onset	50 min	15-20 min S/L 30-60 min oral	15-60 seconds	60 min 0.6-0.85 mg/kg DMT	45-60 min
Peak effect	170 min	90-180 min	5-20 min	90 min	T + 4 hrs
Duration of effect	8-12 hrs	2-6 hrs	60-70 min	4 hrs	4-8 hrs
Site effect conc.	> 0.75 ng/ml	4-6 mcg/ml	60 ng/ml (IV)		
T 1/2	2.9 hrs	1.5-2.25 hrs			
Metabolism	Cyp2D6, 2E1, 3A4	Glucuronidation, MAO	MAO, Cyp2D6	MAO, Cyp2D6	MAO
Excretion	Renal 1% unchanged	Renal 3-5% unchanged	Renal 0.16% unchanged		Renal 80-90% unchanged
Plant Source Drug Content		Mushrooms 0.16 -1.78% dry wt	Virola. Shoots 0.1-0.5 mg/100g	Av.24 mg DMT/ 100 ml Ayahuasca	Mescal Button 25 mg av.

Somatic symptoms and signs

Mild sympathetic effects, dose dependent: A gastrointestinal phase initially is common and more in the less potent varieties. Loss of appetite, nausea and vomiting may be accompanied by diaphoresis, which precede the psychedelic effects[29]. Associated features of Mydriasis, facial flushing, hyper-reflexia, salivation, palpitations, mild elevated BP, respiratory rate and temperature.

Toxicity

Low toxicity occurs, but more in those with greater noradrenaline release, for example, phenylalkylamines. Cardiovascular toxicity is rare, but may occur with premorbid disposition. Accidentally choosing poisonous fungi is a more common problem[30]. Toxicity from excipients in "street" formulations is more common. Massive overdose of LSD associated with hyperthermia and reversible coagulopathy from platelet inhibition[31]. Hyperthermia causes may include HPA dysregulation, serotonin syndrome, neurolept malignant syndrome, depending on class. Hallucinogen persistent perception disorder has been noted in a small group of regular high dose users with visual disturbance and anxiety. Successful treatment has been with atypical antipsychotics, clonazepam and lamotrigine[18]. Prolonged psychotic reactions were noted at a rate of 0.8 per 1000 in 1962[20]. Two large retrospective studies, each more than 130,000 adults showed reduced use of mental health facilities or suicide following psychedelic use compared to non-users[32,33].

Death

Is rare, usually by "misadventure" from a behavioural cause. Suicide though rare, is more common with premorbid psychiatric problems in an unsupported environment[20]. Deaths are more common with "designer" psychostimulant phenyalkylamine "research chemicals" taken illicitly[18].

Addiction

Compared to all other drugs of use and abuse these have a very low potential for addiction. Acute tolerance and tachyphylaxis have been well described after repeat high dose use, with cross tolerance from similar drugs probably by 5-HT_{2A} downregulation[18,42].

Serotonin and psychedelics

The serotonin system is a remarkably evolutionary conserved neuromodulator/neurotransmitter. It regulates not only psychophysiological function like sleep, food intake, body temperature, depression/anxiety, alcohol/drug reinforcement, emotional behaviour, environmental sensitivity and adaptive responsivity but also modulates cognitive capacities such as learning and memory. Reduced 5-HT transmission or precursor intake leads to impulsive and aggressive behaviours.

Serotonin (5HT) is localised to three key systems, platelets, gut enterochromafin cells and brain. It does not pass the blood brain barrier[34,35]. Synthesis of 5-HT is from dietary tryptophan. The release of 5HT from vesicles into synaptic cleft, and termination of effect is by Serotonin Transporter (SERT), which is found peri-synaptically along axons, not just in terminals. Catabolism of 5-HT, noradrenalin and some psychedelics occurs preferentially by Monoamine-oxidase type A (MAOA). Classical MAO inhibitors (MAOI) phenelzine or tranylcypromine are

irreversible nonselective MAOI (MAOA and MAOB). Hence DMT in Ayahuasca tea survives hepatic first pass effect from its reversible MAOA inhibitors, β carbolines.

A key mechanism of action is activation of neocortical layer V, pyramidal cell glutamate transmission secondary to 5-HT_{2A} receptor stimulation[28,42]. 5-HT_{2A} is a $G_{q/11}$ protein-coupled receptor that is functionally coupled to phospholipase C and A_2, leading to production of Inositol phosphates, diacylglycerol, and arachidonic acid as second messengers and raising intracellular Ca^{2+}. Abnormalities of 5-HT_{2A} are associated with schizophrenia and depression. 5-HT subtypes of interest in pain are 1A,1B/D,2A,2C,3-7[35].

Table 3. Receptor Affinity[36].

		LSD[a]	Psilocin[b]	DMT[b]	Mescaline[a]
5-HT_{1A}	Receptor binding $K_i \pm SD$ (μM)	0.003 ± 0.0005	0.123 ± 0.02	0.075 ± 0.02	4.6 ± 0.4
5-HT_{2A}	Receptor binding $K_i \pm SD$ (μM)	0.004 ± 0.001	0.049 ± 0.01	0.237 ± 0.04	6.3 ± 1.8
5-HT_{2A}	Activation potency $EC_{50} \pm SD$ (μM)	0.261 ± 0.15	0.721 ± 0.55	0.076 ± 0.03	10 ± 1.8
5-HT_{2A}	Activation efficacy % maximum ± SD	28 ± 10	16 ± 8	40 ± 11	56 ± 15
5-HT_{2B}	Activation potency $EC_{50} \pm SD$ (μM)	12 ± 0.4	> 20	3.4 ± 3.2	> 20
5-HT_{2B}	Activation efficacy % maximum ± SD	71 ± 31		19 ± 6	
5-HT_{2C}	Receptor binding $K_i \pm SD$ (μM)	0.015 ± 0.003	0.094 ± 0.009	0.424 ± 0.15	17 ± 2.0
α_{2A}	Receptor binding $K_i \pm SD$ (μM)	0.67 ± 0.18	6.7 ± 1.1	1.3 ± 0.2	> 15
α_{1A}	Receptor binding $K_i \pm SD$ (μM)	0.012 ± 0.002	2.1 ± 0.01	2.1 ± 0.4	1.4 ± 0.2
D_1	Receptor binding $K_i \pm SD$ (μM)	0.31 ± 0.09	> 14	6.0 ± 0.9	> 14
D_2	Receptor binding $K_i \pm SD$ (μM)	0.025 ± 0.0004	3.7 ± 0.6	3.0 ± 0.4	> 10
D_3	Receptor binding $K_i \pm SD$ (μM)	0.10 ± 0.01	8.9 ± 0.8	6.3 ± 2.1	> 17
H_1	Receptor binding $K_i \pm SD$ (μM)	1.1 ± 0.2	1.6 ± 0.2	0.22 ± 0.03	> 25
$TAAR_1$[c]	Activation potency $EC_{50} \pm SD$ (μM)	> 20	> 30	> 10	> 10
NET	Receptor binding $K_i \pm SD$ (μM)	> 30	13 ± 1.7	6.5 ± 1.3	> 30
NET	Inhibition potency IC_{50} (μM) (95% CI)	> 100	14 (10–19)	3.9 (2.8–5.3)	> 100
DAT	Receptor binding $K_i \pm SD$ (μM)	> 30	> 30	22 ± 3.9	> 30
DAT	Inhibition potency IC_{50} (μM) (95% CI)	> 100	> 100	52 (37–72)	> 100
SERT	Receptor binding $K_i \pm SD$ (μM)	> 30	6.0 ± 0.3	6.0 ± 0.6	> 30
SERT	Inhibition potency IC_{50} (μM) (95% CI)	> 100	3.9 (3.1–4.8)	3.1 (2.4–4.0)	> 100
Dose[d]	Mg	0.1	12	40	300

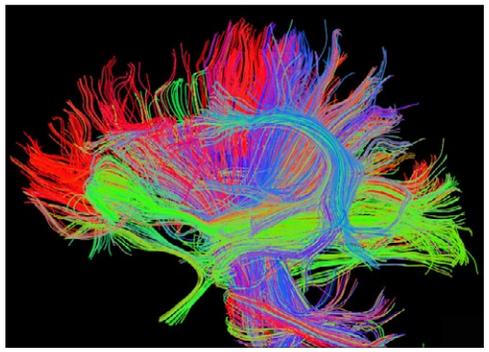
Abbreviations: DAT, dopamine transporter; NET, norepinephrine transporter; SERT, serotonin transporter.
All data were generated using the same assays across substances to allow for direct comparisons.
[a]Rickli *et al*, 2015.
[b]Rickli *et al*, 2016.
[c]Simmler *et al*, 2016.
[d]Estimated average psychoactive dose in humans from Passie *et al*, 2008 and Nichols, 2004.

Psychedelics bind to many receptors with varying affinities[23,36]. They may not produce a selective serotonergic state, but more likely a nonselective multisystem neurochemical perturbation via direct and indirect means. LSD is a mixed partial agonist at $5HT_{2A/1A}$ receptors. The subjective hallucinatory effects can be blocked by pre-treatment with antagonists Ketanserin and Volinanserin[18]. Atypical antipsychotics clozapine, risperidone, olanzapine and so on are antagonist at the $5HT_{2A}$ and D_2 receptors. Ketamine also acts at NMDA, $5HT_{2A}$, D_2 and κ opioid receptors, and its psychic effects are blocked by atypical $5HT_{2A}$/ D_2 antagonist clozapine and in Rat brain by highly selective 5-HT_{2A} antagonist Volinanserin[44].

Despite different structures, psychedelics produce very similar subjective effects. However subtle changes in the receptor interactions with each molecule may cause differing signalling. In vitro correlation of hallucinogenic effect to in vivo is often poor.

Exploration of Neural Correlates of Consciousness with psychedelics was originally by careful dissection and cellular mapping, later with molecular techniques, radiolabelling and colour labelling. Structure activity relationships are based in part on drug discrimination with animal behavioural models and newer receptor binding by displacement of potent radiolabelled 5-HT_{2A} agonists such as [^{125}I] DOI in brain sections[18,42]. This is complemented by functional neuroimaging, for example, MEG,PET, SPECT, fMRI, Arterial Spin Labelling, BOLD and White Matter Tractography (see Figure 4)[38,39].

Figure 4. White Matter Tractography[47].



SITES OF 5-HT$_{2A}$ EXPRESSION AND PSYCHEDELIC EFFECTS ON NEURONAL SYSTEMS

5HT$_{2A}$ agonists produce acute psychedelic effects by excitation of brain regions involved with emotion, cognition, memory and self-awareness including the medial and lateral frontal cortex and medial temporal lobe. A key function of brain 5-HT is to moderate anxiety and stress and promote patience and coping. It appears to enhance two distinct adaptive responses to adversity mediated by 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors. It is proposed that passive coping (tolerating a source of stress) is mediated by 5-HT$_{1A}$, enhanced by conventional reuptake inhibitors (for example, SSRIs) and appears linked to chronic adversity. Conversely active coping (actively addressing a stress), is mediated by 5-HT$_{2A}$ and enhanced by 5-HT$_{2A}$ agonist psychedelics. 5-HT$_{2A}$ is more relevant as the severity of adversity reaches a critical point. This leads to complementary adaptive and potentially therapeutic options[40]. 5-HT$_{1A}$ is densely found in limbic cortex, especially hippocampus. 5-HT quells limbic activity. 5-HT$_{2A}$ is crucial in regulating 5-HT release in cortex by top down modulation of cortical – raphe inhibitory feedback circuit. 5-HT$_{2A}$ receptors are most dense on dendrites of excitatory glutamatergic pyramidal neurons of layer V in the cortex. Endogenous DMT has been detected in humans, and is formed by metabolism of tryptamine. The enzyme that produces it is found throughout the body, but in high concentrations in anterior horn of spinal cord, uncus, medulla, amygdala and frontal cortex. Although the raised DMT levels seen in high stress was suggested as the psychedelic effects seen in near death experiences, this has been recently challenged with alternate explanation[24,41]. It doesn't appear associated with schizophrenia[24].

Ascending Arousal System

Consists of monoaminergic and cholinergic neurons in the brainstem. Locus Coeruleus (LC) with noradrenergic neurons (the site of action of α2 agonist clonidine). Dorsal and Medial Raphe Nuclei are mainly 5-HT but some dopamine (DA). Pedunculopontine and laterodorsal tegmental nuclei are cholinergic. Tuberomammilary nucleus contains histaminergic neurons. The LC neurons are very responsive to sensory stimuli, especially novel or arousing. Psychedelics through 5-HT$_{2A}$ profoundly enhance response of LC neurons to sensory stimuli by excitatory input from the Prefrontal Cortex (PFC)[42].

Prefrontal Cortex

The PFC is involved with "executive control" planning complex cognitive behaviour, personality expression, decision making and moderating social behaviour. The PFC is an important site of psychedelic action by disrupting oscillatory activity of cortical networks, reducing the likelihood that individual pyramidal cells will fire in synchrony[36]. The PFC exerts top down control over processing in temporal and parietal cortices, and psychedelics increase metabolic rates in these areas. Body image changes of derealisation and depersonalisation (ego disintegration), are specifically linked to altered fronto-parietal and occipital cortex. The posterior parietal cortex is part of the dorsal visual stream and generates multiple egocentric representations of space.

Limbic Cortices

Include hippocampal complex, septal area, amygdala, cingulate gyrus and insula. They directly or indirectly communicate and regulate (PAG) peri aqueductal gray, (important in pain modulation) and hypothalamic function[43]. The Amygdala is involved in generating fear responses and processing the emotional context of sensory input. Processing appears to be regulated by 5-HT$_{2A}$. LSD and Psilocybin have the ability to reduce emotional processing, facilitating the "extinction of fear", secondary to enhanced inhibitory top down control from PFC [42,45]. Psilocybin switches off anterior and post-cingulate gyrus and its thalamic connection reducing sensorimotor and cognitive connection.

Cortico–Striato-Thalamo-Cortical (CSTC) loops

CSTC loops are parallel, anatomically segregated circuits relaying information between the basal ganglia, thalamus and cortex[37,42]. In each circuit, projections from multiple cortical regions converge on specific subregions of the striatum. This in turn projects to the pallidum sending feedback to the cortex via the thalamus. The thalamus serves as a filter that "gates" the flow of sensory and cognitive information. At least five loops have been identified. Psilocybin and LSD reduce filtering resulting in excessive stimulation of frontal regions, "hyper-frontality" and symptoms of sensory overload and hallucinations[36]. The psychedelic experience can be hard work!

Visual Cortex

The primary visual cortex (V1) has high 5-HT$_{2A}$ levels. Psychedelics reduce retino-cortical transmission. This coupled with increased excitability of pyramidal neurons in V1 probably destabilises network activity resulting in patterns of firing perceived as geometric form constants[42]. The spreading wave of depolarisation in migraine aura produces a similar effect.

Functional Brain Networks

The brain is a complex network of anatomically segregated groups of hubs and subsections. They interact in relatively fixed ways and offer a framework to understand cognitive function. They have been studied extensively with functional techniques and LSD[36,44]. Altered hub topology in widespread body pain (fibromyalgia) has recently been reported[49,50]. Network overactivity and disruption is hypothesized to be relevant to a variety of disorders, including chronic pain, PTSD, Alzheimer's, autism, ADHD, depression, schizophrenia and bipolar disorder[46,47]. Network examples include:

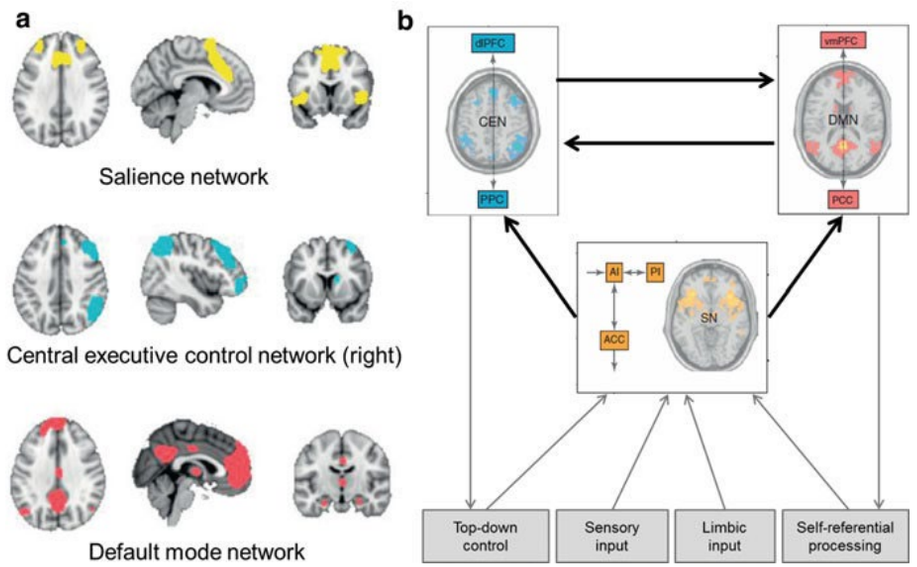
Default Mode Network (DMN)

This is active when an individual is awake and at rest[46]. It preferentially activates during focus on internally orientated tasks, for example, self-referential thought, mind wandering, internal-orientated cognition and autobiographical memory. The Default Mode Network and frontal-parietal connections represent overarching systems of the brain. It is overactive in depression and PTSD. LSD decreases DMN integrity[36,48]. Pain disrupts activity in the DMN, LSD and psilocybin may alleviate intrusive cognition and breakdown of normal self, associated with chronic pain.

Salience Network: Monitors salience of external inputs and internal brain events. The transition between increased synchrony (task negative) DMN and (task positive) Central Executive Network is likely mediated through Salience Network.

Executive Control Network: Helps keep focus on useful ideas while discarding those that don't work. People with more creativity seem to engage brain networks that don't typically work together.

Figure 5. Network Relationships[79].



Pain[53]

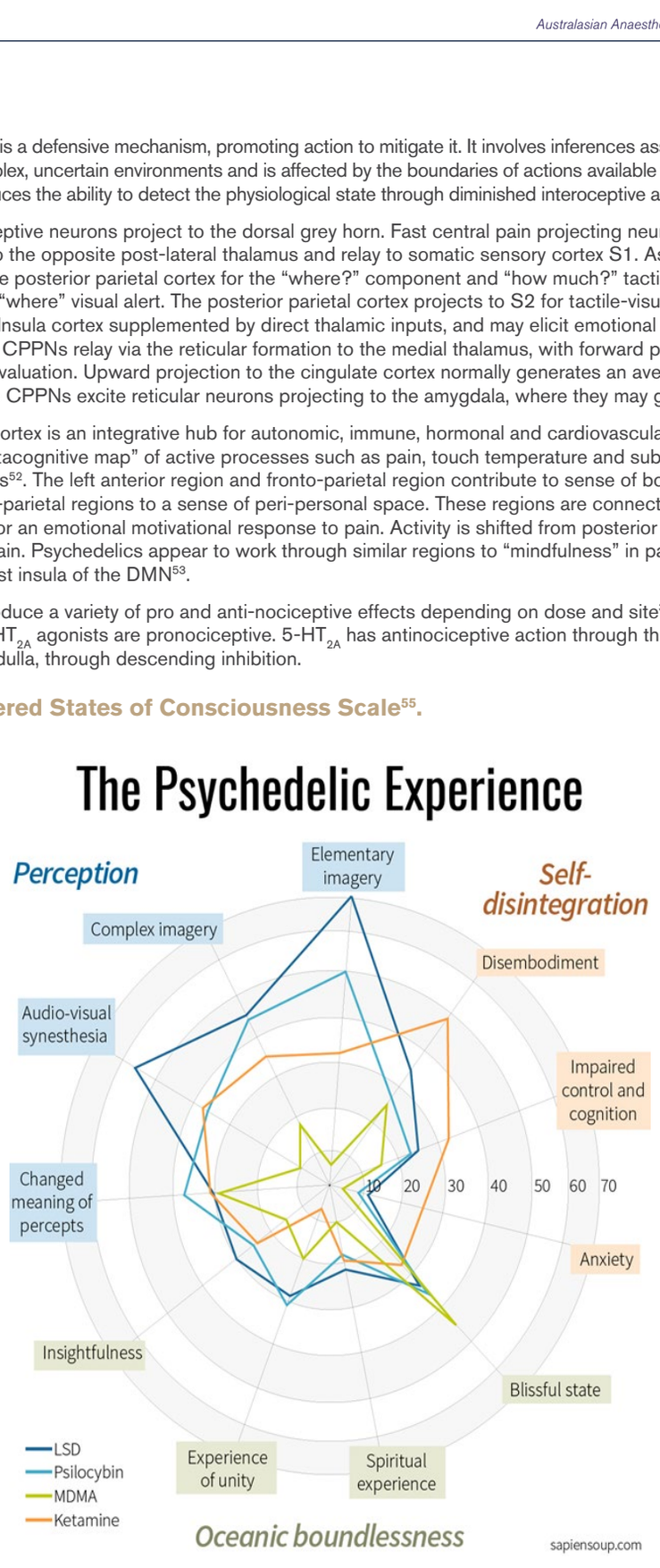
Detection of pain is a defensive mechanism, promoting action to mitigate it. It involves inferences associated with rationalising complex, uncertain environments and is affected by the boundaries of actions available to the person[51]. Chronic pain reduces the ability to detect the physiological state through diminished interoceptive awareness[52].

Peripheral nociceptive neurons project to the dorsal grey horn. Fast central pain projecting neurons (CPPNs) project directly to the opposite post-lateral thalamus and relay to somatic sensory cortex S1. Association fibres connect S1 to the posterior parietal cortex for the "where?" component and "how much?" tactile analysis and to provide a "where" visual alert. The posterior parietal cortex projects to S2 for tactile-visual integration. Onward relay to Insula cortex supplemented by direct thalamic inputs, and may elicit emotional and autonomic responses. Slow CPPNs relay via the reticular formation to the medial thalamus, with forward projection to the PFC for overall evaluation. Upward projection to the cingulate cortex normally generates an aversive emotional evaluation. Some CPPNs excite reticular neurons projecting to the amygdala, where they may generate fear[43,45].

The right insula cortex is an integrative hub for autonomic, immune, hormonal and cardiovascular systems producing a "metacognitive map" of active processes such as pain, touch temperature and subjective and emotional feelings[52]. The left anterior region and fronto-parietal region contribute to sense of body ownership and the temporo-parietal regions to a sense of peri-personal space. These regions are connected with anterior cingulate gyrus for an emotional motivational response to pain. Activity is shifted from posterior to anterior insula with persistent pain. Psychedelics appear to work through similar regions to "mindfulness" in pain mPFC, post cingulate and post insula of the DMN[53].

Psychedelics produce a variety of pro and anti-nociceptive effects depending on dose and site[35]. In the periphery 5-HT_{2A} agonists are pronociceptive. 5-HT_{2A} has antinociceptive action through the rostral ventromedial medulla, through descending inhibition.

Figure 6. Altered States of Consciousness Scale[55].



PSYCHEDELIC DRUG EFFECTS

There are qualitative inter drug differences between the four classic drugs. Drug dose is a primary factor in predicting types of effects that will occur[54,55]. Effects unfold temporally over a drug session and some effects have a higher probability of occurring at specific time points. The psychedelic experience is particularly context sensitive, traditionally referred to as set and setting, for example, personality, pre-dose mood, drug session environment and external stimuli. Validated psychometric tools are used to evaluate the psychedelic experience, for example, 11 dimensional altered states of consciousness (5D-ASC). Three core dimensions are Oceanic Boundlessness, Anxious Ego Dissolution, and Visionary Reconstructuralization[55].

Perceptual effects

Occur along a dose dependent range from subtle to drastic. Perceptual intensification, for example, colours, textures, contour definition, light intensity, sound, timbre variation, higher resolution, crispness, clarity, "newness". Distortion and illusions: sense of size edges warped or moving boundaries wrap around undulating rhythmic movements, mental imagery altered motor perception object completion, binocular rivalry. Elementary hallucinations: for example, geometric patterns latticework other geometric visuospatial form constants (see Figure 7). Complex hallucinations, visual scenes with structural motifs, landscapes animals and people often with imbued personal meaning. They typically follow elementary hallucinations and are more likely at higher doses especially with DMT. Both more commonly with eyes closed, but can occur with eyes open. Sometimes sensible "film like" scenes appear often indescribable in ordinary language. Mental imagery is often modulated by verbal and musical auditory stimuli. Synaesthesia especially visual phenomena are driven by auditory stimuli.

Figure 7. Elementary Geometric Hallucination.

Emotional effects

General intensification of feelings, increased conscious access to emotions. Euphoria involuntary grinning and laughter. Negative experiences with fear paranoia and sense of loss of control. The majority of psychedelic effects in supportive contexts are experienced as positive. Both LSD and Psilocybin can bias emotion toward positive responses to social environmental stimuli. Spontaneous feelings of awe, wonder, bliss and joy. In supportive environments they can promote trust, empathy bonding, connectedness. Music especially can modulate this (the hidden therapist!).

Cognitive effects

Acute changes in linear thought process. Free flowing thoughts. Altered time perception. Reduced performance of standard working memory occurs, but less in experienced uses. Cognitive flexibility and optimism can remain for two weeks after the acute effects gone. Micro-dosing may enhance cognitive performance.

Ego effects and dissolution

Dose dependent change of effects on sense of self from subtle to drastic. Loss of self and identity. The frightening description "I felt I was merging with my surroundings" can morph into "I felt at one with the universe" when appropriately guided. Psilocybin thought to produce the effect more reliably than LSD. Some workers believe more positive psychedelic assisted therapy outcomes when complete ego dissolution occurred. Psychedelics may induce a sense of connectedness, enhancing therapy.

Long term effects have been studied with a variety of agents after supportive therapeutic trials. Although some experienced fearful episodes, almost all felt it was a profoundly meaningful experience that had long lasting subjective positive effects.

CLINICAL EFFICACY

Clinical research

These new studies with good initial safety and efficacy give encouragement to further larger studies. However regulatory and legal hurdles to licencing psychedelics as medicines are formidable. Guidelines for safety in psychedelic research have been suggested by the Johns Hopkins group[56]. Pain research is limited.

Headache

Trials for cluster and vascular migraine. Microdosing studies in patients result in termination of cluster attacks and cluster period, (neurology 2006 Sewell 53 patients Schindler et al 496 patients)[57,58]. Currently a trial is in progress for cluster headache through Yale University. The non-hallucinogenic BOL-148 (2-bromo-LSD), given over three days in 10 days, reduced frequency of cluster headache. $5HT_{2A}$ may not be the only mechanism[59].

Phantom pain

Fanciulla (1977) with sub-hallucinatory LSD (25 mcg daily for 1 week, then 50 mcg daily for two weeks) had good response in five out of seven patients[60].

End of life anxiety, depression – existential crisis and pain

Kast and Collins (1964) gave randomly 2mg of hydromorphone then 100mg pethidine, if unhelpful LSD 100 mcg, to cancer or gangrene patients. Analgesia lasted beyond 19 hours post LSD and patients were able to discuss their death freely and had a "disregard for the gravity of their situation"[61]. Kast (1967) gave 100 mcg LSD to terminally ill for pain with effects lasting 12 hours. Pahnke et al (1969) in 22 patients with terminal metastatic cancer gave LSD and psychotherapy which improved pain, mood anxiety and fear of death with no adverse effects for most patients[62]. Grof et al (1973) gave LSD assisted psychotherapy for 31 patients with pain, anxiety and depression associated with terminal metastatic illness and found significant improvement in pain severity, preoccupation with pain, suffering, anxiety depression and fear of death[63].

Recent studies

Grob et al (2011) gave a moderate dose psilocybin (0.2 mg/kg) and active placebo niacin to 12 advanced cancer patients with no difference in adverse events[64]. Gasser et al (2014) gave 12 patients LSD, 20 or 200 mcg with drug free psychotherapy. Significant reductions in state but not trait anxiety were seen[65]. Ross et al (2016) in 29 patients were given a single dose of psilocybin (0.3 mg/kg) or Niacin with psychotherapy crossover trial at seven weeks with no adverse effects. Immediate, substantial and sustained clinical benefits were seen which was sustained to completion at 6.5 months[66]. Griffiths et al (2016) in a similar double blind crossover with 51 patients used psilocybin low dose (1 or 3 mg/70kg) or high dose (22 or 30 mg/70 kg). There was support for nine month follow up (on average) with no adverse events. A significant effect of higher dose in primary outcomes was reported[67].

The potential efficacy in central, neuropathic and nociplastic pain states will be of interest.

Psychiatry

Classical psychedelic drugs were extensively used in psychiatry prior to UN convention. Trials show they were not helpful for established psychotic disorders, and should be avoided in those liable to develop them. Patients with "psychoneurotic" symptoms appear to benefit from the loosening of otherwise fixed, maladaptive, cognitive and behavioural process especially in a supportive therapeutic setting. The pre-prohibition studies are considered suboptimal[7]. Recent systematic reviews in unipolar mood disorder and meta-analysis in alcoholism suggest efficacy. Various pilot studies in non-psychotic psychiatric disorders provide encouraging results that provide evidence of safety and efficacy. Modern clinical research was heralded by three papers investigating the effects of DMT, mescaline, and psilocybin in healthy volunteers in the USA by Strassman and Qualls 1994, in Germany by Hermle et al 1998 and in Switzerland by Vollenweider et al 1997. These studies are the basis for a resurgence of studies focussing on neuroimaging, psychopharmacological and neuropsychological correlates of the psychedelic state[68].

Depression

Three pilot studies. Carhart-Harris et al (2016, 2017), used an open label in 20 patients with 2 doses of Psilocybin 10mg test and 25mg therapeutic dose one week apart in treatment resistant depression in moderately severely depressed without psychotic symptoms (withdrawn from antidepressants prior to study) with no adverse effects. Significant improvements in depression were noted for up to six months, maximal at five weeks[69,70]. Osorio et al (2015) in four patients and Sanches et al (2016) in 17 patients both used Ayahuasca given 2.2 ml/kg (containing 0.8 mg/ml DMT and 0.21 mg/ml harmine). Significant reductions in depressive symptoms after three weeks of follow up were seen[71,72].

Obsessive Compulsive Disorder (OCD)

Moreno et al 2006 in treatment resistant OCD in nine patients and no other major disorder, were given psilocybin (25, 100, 200 300 mcg/kg) in an open label design. Significant reductions in symptoms noted, but no difference which dose used. The trial was underpowered[73].

Tobacco addiction

Johnson et al 2014, open label trial in15 patients given Psilocybin in moderate (20 mg/70 kg) or high dose (30 mg/70 kg) with psychotherapy. Psilocybin at weeks five, seven and 13. Total of 19 meetings. 80% abstinence at six months[74].

Alcohol addiction

Bogenschutz et al 2015, gave psilocybin to 10 patients in addition to standard motivation therapy. Treatment for 12 weeks dose was 0.3 or 0.4 mg/kg. Immediate improvements in behaviour correlated with 1960s studies of LSD in alcoholics with no adverse effects[75,76].

Recreational and non-medical use

The lay press/blogosphere have interest in psychedelics, for entertainment, self-reflection, spirituality and management of a variety of ailments. Many naïve, some very sophisticated, but there is information to be exchanged, and the user groups can be of help. Unfortunately abuse of "research chemicals", with significant morbidities has the potential to derail current legitimate research.

Cognitive enhancement

Micro-dosing is currently very popular. Small doses of LSD (10 mcg) or psilocybin (1-3 gm of mushroom), on a daily basis. Enhanced creativity, and cognitive flexibility are described (some associated with headache!)[77]. The $5\text{-}HT_{2A/2C}$ receptor system has been investigated with antagonists on memory. In animal models specific antagonists Volinanserin and SB-242084 impair spatial reversal learning when infused into orbitofrontal cortex a site for potential obsessive-compulsivity. Novel $5HT_{2A/2C}$ agonists with pro-cognitive effects have been reported[78].

CONCLUSION

Psychedelics have been revered by "primitives", weaponised by intelligence agencies, adulated by hedonists and vilified by authorities. The social schism between "good medicines" and "bad drugs" has stifled research into a class of drugs that when used appropriately can have a positive and profound effect on the consciousness, disease states and suffering. Hopefully with good research and pragmatic laws, these agents will have a place in medicine before the cycle repeats itself.

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High hopes for dope: What role does medicinal cannabis play in current clinical practice?

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INTRODUCTION

Cannabis has a multitude of uses; hemp was used as a fibre and the seed as a source of nutrition as early as 10,000 years ago in Taiwan. Medicinal use came later, with earliest accounts dating back to 2700 BC in Central Asia by a number of Chinese herbal medicine practitioners. Hua Tuo (considered the father of surgery in China) performed surgery between 140 and 208 AD using a combination of wine and powdered cannabis to provide anaesthesia[1]. In India it has also been used for centuries in rituals to induce stupor and as an anaesthetic for surgery[2]. While some of its ancient uses as a wound dressing, antibiotic, and cure for “absent-mindedness” are not in practice[3], its use as an antiemetic and appetite stimulant for “the wasting diseases” and analgesic is a source of active research and use in modern medicine.

Its proposed wide-ranging medicinal properties have fuelled a resurgence in patient and community demand for its prescription which has been coupled with political will to enact legislative change to enable wider access. In this article we attempt to identify the current clinical place of medical cannabis in pain management and anaesthesia as well as outline some of the concerns associated with its use.

PHARMACOLOGY

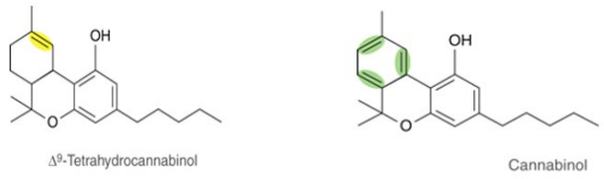
The cannabis genus consists of at least two commonly recognised species: *Cannabis sativa, Cannabis indica*. Cannabis plants may be male, female or both. It is the female plant which produces the resin-secreting flowers that are used medicinally.

Cannabinoids are the biologically active constituents of cannabis, or synthetic compounds that have an affinity for cannabinoid receptors. The cannabis plant consists of at least 60 or more other cannabinoids, and at least 500 other non-cannabinoid molecules including terpenes and flavonoids that may have a role in clinical effects of medical marijuana. Pharmacological focus has historically been on the two major cannabinoids: tetrahydocannabinol (THC) and cannabidiol (CBD)[4]. THC is psychoactive and is responsible for many of the favourable pharmacodynamic effects sought by patients and recreational users.

The greatest determinant of the THC content of cannabis is breeding and cultivation techniques. Cannabis cultivation is heavily dependent on the duration of daylight the plant receives, also known as the “photoperiod”. Juvenile plants respond to long day lengths by increasing vegetative growth in the first three months of life. Following this, flowering is enhanced by shorter day lengths with more flowers increasing the overall THC content of the crop. Unfertilised plants (in the absence of male plants to pollinate) also continue to grow more flowers and hence the THC content of the crop is also increased – a cultivation technique known as sinsemilla. Selective breeding of high-yield species has led to an increase in THC content from approximately 3% to up to 22% over the past decade[5].

Cannabis with minimal THC content (usually <0.3%) is referred to as hemp. Unlike cannabis, hemp is cultivated with the presence of both male and female plants allowing for fertilisation to occur. The predominant cannabinoid in hemp is CBD. CBD is purported to not have psychoactive effects[6].

Figure 1. Key structure-activity relationships of cannabinoids.



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CBD and THC are structurally similar however have marked differences in effect. The addition of a hydroxyl group and a double bond to THC (highlighted) to form CBD removes psychoactivity altogether.

The cannabinoid receptors are G-protein coupled receptors with CB1 receptors primarily located in key areas of the CNS related to descending pain pathways. Endogenous cannabinoids are released in relation to acute stress and pain to cause anti-nociception by acting on inhibitory CB1 receptors. CB1 receptors are also important for physiological processes relating to appetite, stress response, immune and inflammatory response, mood and metabolism[4] and to maintain homeostasis by inhibiting excessive neuronal excitation[8]. CB2 receptors are located primarily in the peripheral immune system with modification of the cytokine response providing a role for anti-inflammatory effects of cannabinoids[9].

Cannabinoids (both synthetic and endocannabinoids) are also active at a number of non-cannabinoid receptors that have a role in analgesia. For example, CBD is an agonist at vanilloid receptors (a receptor at which capsaicin is known to act)[9].

Preparations

Cannabis refers to the whole plant or parts thereof. Cannabinoids are classified as either synthetic or phytocannabinoids with a defined chemical composition. Most preparations available in pain management contain a fixed ratio of THC and CBD. Cannabidiol (CBD) displays neuroprotective effects and reduces the psychoactivity when combined with THC.

Table 1. Currently available preparations of medical marijuana. Examples of countries with approved indications are given[10,11].

Plant-derived cannabinoids

Nabiximols (THC/CBD standardised extract)

- Each 100mcg spray : 2.7mg of THC, 2.5mg of CBD
- Oromucosal spray

Approved indications

- Spasticity in multiple sclerosis refractory to conventional treatment (Australia, Canada, Europe)
- Adjunctive treatment in MS-related neuropathic pain and chronic cancer pain (Canada)

Synthetic cannabinoid analogues

Dronabinol (THC)

- Capsule containing either 2.5mg, 5mg or 10mg of THC

Approved indications

- Nausea and vomiting refractory to treatment in oncology/palliative care (Ireland)
- Cancer pain (Denmark)
- Appetite stimulation in HIV (Ireland)

Nabilone (THC)

- Oral capsule – 0.25mg, 0.5mg, 1mg

Approved indications

- Chemotherapy-associated nausea and vomiting refractory to conventional treatment (UK)

Medical Cannabis

- Use of the whole plant or extracts of part of the plant
- Up to 14 different cannabis flowers of varying THC content 1-22% and CBD content 0.05%-9%
- Oil extract for oral or sublingual ingestion (available in Israel)

Approved indications

- Any indication, for use in "severe diseases" (Germany)
- HIV and multiple sclerosis (Czech Republic)
- Neuropathic pain after 1yr of conventional treatment, MS-related spasticity (Israel)

In the UK, while there has been approval for nabiximols and nabilone for refractory spasticity and chemotherapy-induced nausea and vomiting for some time, medicinal cannabis was only approved in late 2018 and recreational use remains illegal[11].

Nabiximols is the only commercial cannabis product currently registered with the Therapeutic Goods Administration (TGA). It is approved for "symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis who have not responded adequately to other anti-spasticity medication". The other cannabis preparations may be prescribed subject to authorisation under the Special Access Scheme provided the product has been legally manufactured and imported to strict quality standards.

INDICATIONS

Chronic non-cancer pain

Stockings et al have performed the most comprehensive systematic review to date that analyses outcomes in relation to efficacy of cannabinoids for chronic non cancer pain[12]. While they found moderate evidence (after assessing 13 RCTs) that cannabinoids were more likely than placebo to produce a 30% reduction in baseline pain (a common indicator in studies looking at analgesic efficacy), this effect was modest. When assessing the 4 RCTs that assessed 50% reduction in pain, there was no statistically significant difference. Overall pooled data suggested on a visual analogue scale, the improvement was one tenth of the difference that would be normally be considered a clinically significant difference in pain intensity. The quality of evidence used for analysis ranged from moderate to very low quality[13]. They found a Numbers Needed Treat to Benefit across all cannabinoids to achieve a 30% reduction in pain of 24, and a Numbers Need to Treat to Harm (NNTH) for any adverse effect of 6. This NNTH was similar to opioids in the treatment of chronic noncancer pain. There was moderate-high grade evidence supporting the use of cannabinoids such as nabiximols as adjunctive therapy in MS-related pain. They concluded that cannabinoids were unlikely to be highly effective medicines for chronic non-cancer pain.

A meta-analysis by the TGA of all relevant randomised studies which predated the study by Stockings et al found similar outcomes. It found that there was moderate evidence that medicinal cannabis products reduce pain scores by 30% and 50% compared to placebo[6]. In MS-related chronic pain, there was a moderate decrease in pain scores.

Most authors relegate the use of medicinal cannabis to that of an adjuvant agent. The TGA does not support its use to replace conventional first line therapies. Furthermore when used as an adjuvant, caution should be taken for potential interactions with other analgesics[6].

In Israel, where medicinal cannabis is widely available, a study assessed baseline pain and pain-related quality of life indicators. Of note, 44% of participants ceased opioid use at seven months ($p<0.001$) and of those continuing opioid use, median oral morphine equivalent decreased from 60mg to 45mg though this was not statistically significant[14]. A similar study found a 64% decrease in opioid use in patients with chronic pain who have been prescribed medical cannabis[15].

Use in cancer pain and palliative care

Medicinal cannabis has a potential role in many aspects of palliative care incorporating antiemetic, appetite-stimulating, sedating and potentially analgesic properties.

Dosing may be difficult as trials have mostly been based on healthy subjects and therefore severe illness may affect the pharmacokinetic properties of this class of medication.

In one study, both low and medium doses of nabiximols had statistically significant differences in patients reporting 30% relief from baseline pain[16]. Interestingly there was no difference between high-dose nabiximols and placebo for a statistical reduction in pain. It was suspected that in these cases, the severe adverse

effects associated with higher doses which were poorly tolerated, negated any of the analgesic benefit of the cannabinoids. In lower dose and medium dose groups, there was no significant difference in adverse effects or study withdrawals.

Studies have shown statistically significant improvement in sleep in patients treated with low-dose nabiximols. Sleep disturbance is a large burden of disease in the severely ill, so this may further improve quality of life in this population[16].

The TGA recommends that given paucity of studies evaluating use and efficacy in palliative care, medicinal cannabis should only be introduced after standard treatments have failed. Furthermore there are concerns that it may interact with chemotherapy or other medications used in palliative care[17]. There was low quality evidence that medicinal cannabis produced clinically significant improvement in appetite and weight gain, but otherwise there was no discernible effect even among low quality trials of improvement in pain scores, nausea and vomiting, mood, and sleep.

Prescribing and the law

Cannabis is the most widely used illicit drug in Australia with 10.4% of the population using it in 2016[18]. There has been an increasing societal acceptance for its use both recreationally and for medicinal purposes. Public support for the use of marijuana to treat medical conditions rose from 74% in 2010 to 87% in 2016, along with support for legalisation of cannabis in general[18]. In 2016, legislation was passed in the Australian federal parliament allowing for the cultivation of cannabis and the manufacturing of cannabinoid products for medicinal and research purposes. Subsequently individual state legislation was passed to provide a regulatory framework in which medicinal cannabis can be prescribed and dispensed while preventing unauthorised use of the products.

In NSW, clinicians applying for authority to prescribe and supply an unregistered Schedule 8 Cannabis Medicine are required to complete an joint online application to NSW Health and the TGA[19]. "In this process, NSW Health relies on a single clinical assessment by the TGA and confines its review to checking the credentials of the prescribing doctor and the patient history, as with any other Schedule 8 drug authority". Prescription of nabiximols (a registered S8 product) requires the same form to be filled but it is assessed by NSW Health only. Doctors can also refer their patients to medicinal cannabis clinics which streamline the process and offer telehealth consultations to facilitate prescription.

Analysis of the total cannabinoid content of the product is used to determine its schedule as per the NSW poisons list. A cannabis medicine is classified as schedule 4 if the CBD content is >98% of total cannabinoid content (for example, cannabidiol). All other cannabis products are classified as schedule 8 (for example, nabiximols and nabilone). Cannabis products not approved for human therapeutic use or products derived from unregulated sources such as oils and plant materials "will not be authorised"[19].

Product information for THC-containing products and international advice for the most part suggests patients should not drive while on treatment as a small but significant increase in collision has been seen across a number of meta-analyses[20,21]. The risks of impairment are greatest with initiation of treatment and with dose changes in the week prior. Patients taking cannabidiol which does not have a psychoactive component can lawfully drive, provided they are not considered "impaired". Roadside surveillance tests for the presence of THC in saliva. In NSW it is considered an offence to drive "under the influence of THC", for which the legislation at present does not provide for any medical defence[20].

In New Zealand, cannabis remains an illicit drug under the Misuse of Drugs Act 1975[22]. Under this act, Ministry of Health approval is required for most medicinal cannabis products except for nabiximols (when prescribed for MS-related spasticity) and cannabidiol products. However this is an area of rapid legislative change. In 2018, an amendment was passed allowing palliative patients an exemption to the charge of possession and use of illicit cannabis. A patient is provided with a statutory defence and will not receive a criminal conviction if diagnosed as requiring palliation by a medical or nurse practitioner. This is a compassionate measure while the NZ government establishes a medicinal cannabis scheme[22]. The medicinal cannabis scheme due in 2020 aims to enable domestic commercial cultivation of medicinal cannabis and incorporates a licencing scheme, quality standards and a medicinal cannabis agency. Furthermore, during the 2020 general election, a non-binding referendum will be held allowing voters an opportunity to decide on legalising the personal use of recreational cannabis.

Potential for dependency and adverse effects

Compared to inhalation, oral THC has a much lower bioavailability with peak concentrations reached 1-3 hours later for oral THC (dronabinol)[8]. Inhalation routes are rapidly absorbed with THC concentrations detected in plasma within seconds[23]. Dronabinol has a 10% oral bioavailability due to extensive first pass metabolism. Subjective psychoactive effects peak at 30 minutes following inhalation of marijuana compared with dronabinol which peaks at 2 hours for the same effect[24]. While pharmaceutical preparations may have a similar ability to

produce a "high", there is a suggestion that this may not translate to addictive, abusive or diversion potential due to the slow and gradual onset action resulting in a weaker reinforcement of reward pathways[24].

Table 2. Adverse effects of cannabinoids and cannabis[4,16,25].

Central nervous system	Cardiovascular
▪ Dizziness ▪ Drowsiness, somnolence ▪ Slurred speech ▪ Visual disturbance ▪ Mental clouding, confusion ▪ Psychosis ▪ Paranoia ▪ Fatigue	▪ Tachycardia ▪ Palpitations ▪ Increased myocardial oxygen demand, increased risk of myocardial infarction within 1 hour of use **Gastrointestinal** ▪ Nausea and vomiting ▪ Dry mouth ▪ Increased appetite

While most of the described adverse effects are relatively mild, more serious cases of suicidal and homicidal ideation, paranoia, agitation and psychosis have been described in studies evaluating cannabis use in average and at-risk populations. Persistent cannabis use, particularly during adolescence was associated with neurophysiological decline which persisted despite cannabis cessation[26].

Product information for nabiximols warns not to exceed maximum dosage as it increases the risk of these serious psychiatric events. However when used in patients with chronic pain, low quality evidence suggest that there was no difference between cannabis group and control groups[21].

Smoking medicinal cannabis isn't recommended due to the harmful effects of smoking itself. Respiratory effects include chronic bronchitis, chronic obstructive pulmonary disease and airway irritation. In countries where herbal cannabis is available it is recommended to inhale via a vaporiser rather than smoking.

The Faculty of Pain Medicine statement notes their concerns "about the adverse event profile in cannabis users, especially in young people, including impaired respiratory function, psychotic symptoms and disorders and cognitive impairment"[10].

Responsible prescribing

Contraindications to prescription include personal or family history of psychosis, schizophrenia, active substance use disorder or previous cannabis use disorder, unstable cardiovascular or respiratory disease[25]. Relative contraindications include a concurrent active mood or anxiety disorder and concurrent users of high-dose alcohol, opioids and/or benzodiazepines. It is a category B2 for use in pregnancy and is not recommended for use unless the benefit of treatment is considered to outweigh potential risks to the foetus. There is a high concentration of THC and CBD transfer in breast milk, probably due to the lipophilic nature of cannabinoids[27]. It is therefore contraindicated in breast feeding.

The constituents of cannabis are metabolised by a number of pathways, primarily CYP450 in the liver. THC is primarily metabolised by CYP3A4 and CYP2C9. Particular caution should be taken with concomitant administration with CYP450 inhibitors (for example, ketoconazole and clarithromycin) which may increase the availability of THC and CBD[4,27]. Use with relevant CYP inducers and inhibitors may require dosage adjustment and re-titration. Alcohol may also increase THC levels and therefore it is not recommended to consume alcohol while on treatment.

European guidelines advise that cannabis-based medications are not prescribed in patients along with high doses of opioids or benzodiazepines. The advice for these patients is to prescribe cannabis at a low dose, or alternatively consider tapering the opioid or benzodiazepine[4].

Guidance on safe prescribing includes a full and comprehensive biopsychosocial assessment of the patient, including screening questionnaires for anxiety and depression and substance misuse/illicit drug use (either past or present). After assessing all cautions and contraindications, and a discussion of adverse effects, shared decision making to prescribe should be followed by a signed treatment agreement with the patient[4,25]. The lowest dose for clinical effect should be prescribed and gradually titrated as needed. A trial of efficacy should extend to a maximum three months after which therapy should only be continued if there has been significant functional improvement with minimal adverse effects.

Perioperative management

A recent survey noted that more that 80% of preoperative patients in the US believed that cannabinoid products would be effective for the management of postoperative pain[28]. In a study assessing perioperative cannabinoid use in orthopaedic surgery, patients who took cannabinoids preoperatively were more likely to be younger, male and be on opioids preoperatively. There was a significant difference in pain scores at rest and movement, with notably higher pain scores rated in the cannabinoid use group. The cannabinoid group also had higher incidence of sleep impairment. Cannabinoid users undergoing hip or knee surgery had higher requirements for opioids in the early postoperative period[29]. Cannabis users may thus require higher doses of analgesics for the post-surgery period[4].

Much of the available guidance refers to perioperative recreational marijuana inhalation and its respiratory side effects. Preoperative marijuana smoking, not surprisingly, is associated with increased sputum production. Laryngospasm is commonly encountered in patients that smoke cannabis and increased doses of propofol may be required for induction of anaesthesia and to overcome laryngospasm.

A recent retrospective audit found that regular users of cannabis undergoing procedural sedation for endoscopic gastrointestinal procedures required much higher doses of sedation. Cannabis users required 14% more fentanyl and 19.6% more midazolam compared to non-users. Consistent with previous studies high doses of propofol were required; with greater than three times more propofol required for the duration of their procedure[30].

Clinical implications

There are high rates of active illicit substance use within pain management programs with 7.4% of samples testing positive for heroin, cocaine or amphetamines and 15.7% positive for marijuana in a six-month sample from the United States[31]. An Australian study looking at patients prescribed opioids for chronic non-cancer pain, had similar rates with 16% of patients having used cannabis for pain relief. Of note, 12% met criteria for an ICD-10 cannabis use disorder[32]. Similarly within the general population, of the 6.8% who use illicit marijuana recreationally, 1.9% reported using it self-prescribed for medical reasons[33]. This raises concerns about medical marijuana prescription in patients with chronic non-cancer pain.

In US states with provisions for medical marijuana, there was an increase in marijuana use following passage of laws, which may reflect legitimate medical use or recreational use. Surprisingly, there was no increase in cannabis use disorder in states that medicalised marijuana[34]. Among adolescents in substance use treatment programs, almost 50% had obtained marijuana from someone with a medical marijuana licence[35], thus demonstrating its potential for diversion to vulnerable patients.

While its potential opioid-sparing effects may be beneficial, it is outweighed by its own adverse effects which may be significant enough to lead to treatment withdrawal. Driving restrictions further limit its utility, or if chosen to be ignored by patients may contribute to increased safety risk to the public.

Medical marijuana treatments are expensive. Nabiximols is not listed on the Pharmaceutical Benefits Scheme, and it is an off-label use for chronic pain in Australia. Each packet costs $A750 and lasts approximately 4-6 weeks. In comparison, assuming 3% THC content with current Australian street prices of marijuana, nabiximols is six times the price based on THC content alone (sources unnamed).

The focus of managing chronic non-cancer pain is patient education and maximising non-pharmacological methods. Coupled with the paucity of evidence, it is difficult to justify the use of medical marijuana preparations for use for chronic non-cancer pain. The Faculty of Pain Medicine states “at the present time, the scientific evidence for the efficacy of cannabinoids in the management of people with chronic non-cancer pain is insufficient to justify endorsement of the clinical use”[10].

Currently the recommended role for cannabis is as adjuvant therapy in treatment-refractory palliative care patients for cancer pain, nausea and vomiting and other symptom control.

The future of medical cannabis in Australia

Despite these clinical implications and the current evidence-base, more than 6400 applications to the TGA for the Special Access Scheme (until April 2019) have been made, not including nabiximols[36]. It is being prescribed more widely and patient accessibility is being improved. The federal government has declared there is “now no real government barriers at all to accessing medical cannabis”[37].

Greater quality trials with strong evidence is essential to further characterise the role for medical marijuana in clinical practice. In NSW, the government has made a $A21 million commitment to improve understanding of safe and appropriate use of medical cannabis products. It has established a “Cannabis Medicines Advisory Service” to provide guidance to clinicians considering prescribing cannabis medicine products. It is estimated

that Australia’s current legal medicinal market is valued at $A17.7 million annually. With rapidly widening use and relaxation of barriers to prescription, it is projected that this will boom to $A3 billion by 2028[37,38].

In NSW alone, $A9 million has been committed towards clinical trials to evaluate safety and efficacy of cannabis products. Current trials are evaluating the treatment for severe treatment-resistant paediatric epilepsy, chemotherapy induced nausea and vomiting and palliative care with a focus on quality of life outcomes.

Outcomes from this research may be able to further identify potential uses for this ancient remedy in modern medical practice.

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Anaesthetic implications of restless legs syndrome: A review

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INTRODUCTION

Restless legs syndrome (RLS) is a common neurological sensorimotor disorder characterised by the urge to move one's legs (and less commonly trunk and arms). It is associated with unpleasant paraesthesias deep within the legs during periods of rest or inactivity which are relieved by movement[1,2]. The overall prevalence of RLS is 10.6% [1,3]. It affects both children and adults and may present at any age but is most often seen in older populations, with prevalence peaking at 65 years[2,4]. It has a profound effect on the quality of life of those with the disease[5,6]. RLS symptoms may be triggered or exacerbated in the perioperative period[7]. Large scale studies are lacking, however there is no evidence to date that anaesthesia, in itself, has any negative impact on the RLS symptoms.

DEFINITION AND DIAGNOSTIC CRITERIA

RLS was first described in the literature by Sir Thomas Willis in 1685[8] and further by Karl Axel Ekbom in 1945 and 1960, in which he described the first diagnostic criteria[9,10]. In 1995, The International Restless Legs Syndrome Study Group (IRLSSG) was formed. The IRLSSG created four essential criteria for diagnosis.

These involved an urge to move the legs[11]:

1. Usually accompanied by unpleasant sensations in the legs.
2. That begins or worsens with rest or inactivity.
3. That is improved by movement as are the unpleasant sensations.
4. That is worse in the evening or night.

The diagnostic criteria for RLS have been revised and most recently released in 2013. These are described in Table 1.

Table 1. International Restless Legs Syndrome Study Group (IRLSSG) consensus diagnostic criteria for restless legs syndrome/Willis-Ekbom disease (RLS/WED). Adapted with permission[1].

RLS/WED, a neurological sensorimotor disease often profoundly disturbing sleep and quality of life, has variable expression influenced by genetic, environment and medical factors. The symptoms vary considerably in frequency from less than once a month or year to daily, and severity from mildly annoying to disabling. Symptoms may also remit for various periods of time. RLS/WED is diagnosed by ascertaining symptom patterns that meet the following five essential criteria, adding clinical specifiers where appropriate.
Essential criteria (all must be met): 1. An urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs. 2. The urge to move the legs and accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting. 3. The urge to move the legs and accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues. 4. The urge to move the legs and accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day. 5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or behavioral condition.
Specifiers for clinical course of RLS/WED: A. Chronic-persistent RLS/WED: symptoms when not treated would occur on average at least twice weekly for the past year. B. Intermittent RLS/WED: symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events.
Specifier for the clinical significance of RLS/WED: The symptoms of RLS/WED cause significant distress or impairment in social, occupational, educational or other important areas of functioning by their impact on sleep, energy/vitality, daily activities, behavior, cognition or mood.

EPIDEMIOLOGY

The prevalence of RLS (using the IRLSSG diagnostic criteria) is 10.6%[1,3]. The prevalence is doubled in women and increases with age[1]. 5% of people affected have symptoms at least once a week[5]. Further, 2.7% have moderate to severely distressing symptoms[5]. RLS symptoms are associated with: chronic sleeplessness, depression, despondency, higher lifetime rate of suicidal ideation or suicidal behavior (27.1% compared with 7.0%) and depression history (65.6% compared with 22.8%)[6]. Increasing syndrome severity is associated with increased likelihood of suicidal activities[6]. People with RLS symptoms occurring more than 16 times per month also have a higher incidence of cardiovascular disease[12].

In pregnancy, RLS is a common movement disorder with a prevalence of up to 26%[13-15]. It typically appears in the third trimester and disappears within a month following delivery[14,15]. For most of these women (62.7%), it is their first experience of RLS[15]. Pregnancy-related RLS is associated with a higher risk of chronic RLS (four-fold) and a higher risk of developing RLS in a later pregnancy (58% compared with 3%)[16].

Children are also affected by RLS (prevalence of 2-4%)[17-19]. Symptoms are usually mild and do not require drug therapy. Unlike adults, boys and girls are equally affected[17]. There is a higher incidence of RLS in children with the following diseases: anxiety, depression, attention-deficit/hyperactivity disorder, chronic kidney disease and sickle cell disease[20]. Children may be unable to communicate their symptoms clearly, making diagnosis challenging. Symptoms may present as disrupted sleep, daytime sleepiness, behavioural or education issues, sleep-talking, night terrors and/or bruxism[20]. Children may mistakenly be identified as having “growing pains”, but a proportion of them may actually be experiencing RLS[21].

PATHOPHYSIOLOGY

Two subsets of RLS have been identified, primary (idiopathic) and secondary RLS. Patients with secondary RLS develop their symptoms secondary to another disease process or drug. Causes of secondary RLS include: iron deficiency, pregnancy, kidney disease, rheumatic disease and medications[2].

The pathophysiology of primary RLS is partially known and includes a genetic component along with theories of dopamine and brain iron dysregulation[22]. Genetic transmission appears to be autosomal dominant, with variable expression. More than 50% of patients with the disorder have a positive family history and 83% of monozygotic twins are concordant[7,23].

Dopamine dysfunction

It is clear from clinical observation that dopamine dysfunction plays a role in the pathophysiology of RLS. Dopamine agonists relieve symptoms, while dopamine antagonists may trigger and intensify symptoms. Evidence of up-regulated dopamine transmission is seen in Single Photon Emission Commuted Topography (SPECT) and Positron Emission Topography (PET) neuroimaging studies. These modalities demonstrate decreased dopamine sensitisation as evidenced by decreased D2 receptors and increased tyrosine hydroxylase activity. Tyrosine hydroxylase is the rate limiting enzyme in the dopamine synthesis pathway[2,24,25].

Iron

Iron deficiency within the brain has been implicated in the pathophysiology of RLS. In people with iron deficiency anaemia, there is a 30% incidence of RLS[26]. Brain imaging shows reduced iron stores in the brains of those with RLS[2]. Iron is a necessary cofactor for the brain’s synthesis of dopamine and regulation of dopamine receptors[2]. IRLSSG guidelines advise for the assessment of peripheral of iron status and iron replacement when deficiency is diagnosed[26]. Lower ferritin levels are associated with increased RLS severity[27] and symptoms may be improved with iron supplementation[26].

TREATMENT

In 2016, a task force commissioned by the IRLSSG published guidelines for the treatment of RLS[28]. These guidelines are used to guide management and to prevent the augmentation of symptoms which can occur after starting treatment. Augmentation may present with increased severity of symptoms, shorter latency at rest, earlier symptom onset during the day, and symptoms extending to other body parts including the trunk and arms[29].

Treatment of Primary RLS

If symptoms are not pervasive, simple non-pharmacological measures may be implemented alone and include[22,29]:

- Good sleep hygiene (with regular sleep patterns).
- Avoidance of daytime naps.
- Avoidance of alcohol and caffeine.
- Exercise.
- Massage.

Daily pharmacotherapy should only be used when symptoms have a significant impact on quality of life. Intermittent drug treatment should be considered for less frequent symptoms[29].

Antiepileptics

Alpha2 delta ligands (gabapentin and pregabalin) are the initial drug therapy as they are effective and carry a low risk of augmentation[28-30]. Gabapentin is usually started at 300 mg nocte and may be increased to 2400 mg/day. A mean dose of pregabalin of 123.9 mg of pregabalin showed 90% efficacy in reducing symptoms of RLS. Allen et al (2014) demonstrated that 300 mg/day of pregabalin provided a greater reduction in severity scoring compared with placebo and pramipexole 0.25 milligram. Pregabalin (300 mg/day) has similar efficacy to pramipexole (0.5 milligram/day) and is associated with lower rates of augmentation. Higher doses of pregabalin (300-450 milligram/day) resulted in more significant improvements in symptoms but with more frequent adverse effects (somnolence, dizziness, depression and weight gain)[29,30].

Dopamine agonists

Dopamine agonists should be given at the lowest effective dose and should not exceed the recommended treatment dose for RLS (due to the risk of augmentation)[28]. Dopamine agonists have a positive impact on RLS rating and quality of life scales[31]. Non-ergoline agonists (pramipexole, rotigotine) are first line medications. These have a lower incidence of augmentation than ergoline agonists[2], satisfactory efficacy and a wider safety margin[31]. A Cochrane review in 2011 reported higher efficacy with ergoline derivatives (cabergoline, pergolide and levodopa). However, these medications not used in RLS due to their association with cardiac valve, retroperitoneal, pericardial and pleuropulmonary fibrosis[31]. Table 2 outlines the pharmacology of dopamine agonists and alpha2 delta ligands relevant to RLS[32].

Table 2. Use of dopamine agonists and alpha2 delta ligands for the treatment of RLS. Adapted with permission[32,33].

	Pramipexole	Ropinirole	Rotigotine	Gabapentin	Pregabalin
Time to maximum concentration (h)	2	1-2	15-18	1	3-4
Half-life (h)	8	6	5-7	5-7	6
Initial dose (mg)	0.125	0.25	1	300	100
Usual total daily dose (mg)	0.125-0.5	0.5-2.0	1.0-3.0	300-1800	100-300
Maximum dose (mg)	0.75-1.0	4.0	3.0	3600	450
Metabolism	Renal	Hepatic	Hepatic	Renal	Renal
Common side effects	Nausea, vomiting, fatigue, somnolence, augmentation, application site reaction (rotigotine)			Somnolence, unsteadiness, dizziness, weight gain, dry mouth	

Opioids

Low quality evidence supports the use of opioids as a second line agent to treat severe RLS symptoms that are resistant to conventional treatment. The mechanisms of their effect are unknown[34]. Adverse effects of somnolence, nausea, constipation, dependence, tolerance, and potential for abuse diminish their usefulness[35]. Trenkwalder et al found sustained release oxycodone-naloxone (mean dosage 10/5 mg twice a day) is efficacious for short-term treatment of patients with severe RLS symptoms[36]. This is the only opioid licensed for use for the treatment of RLS[34]. Methadone may also be beneficial. Ondo et al showed methadone provided up to a 75% reduction in refractory RLS symptoms, but this study was limited by its high attrition rate[37]. Silver et al found methadone had a lower per year discontinuation rate (0%) compared with pergolide (8%) and pramipexole (9%)[38].

Benzodiazepines

Benzodiazepines have been used for the treatment of RLS due to their effect on sleep initiation and maintenance, however there is little data to support their use[39]. A study comparing pramipexole with clonazepam showed that pramipexole reduces periodic limb movements without effecting the electroencephalogram (EEG), while clonazepam suppresses sleep EEG instability but does not reduce the motor effects of RLS[40].

Treatment of Secondary RLS

After diagnosis, secondary causes must be considered and treated when present. Patients with uraemic end-stage renal failure have a 30% incidence of RLS[41]. Nocturnal haemodialysis may improve symptoms[42]. Renal transplantation has been shown to improve symptoms within days[43]. Pregnancy-related RLS usually goes into remission within a month of delivery[14,15]. If possible, causative drugs should be ceased and an alternative agent initiated[29]. Causative medications include: antihistamines, dopamine antagonists, neuroleptics, mirtazapine, tricyclic antidepressants, selective serotonin reuptake inhibitors, beta blockers, thyroxine and lithium[2,29].

Iron

A 2016 Cochrane review demonstrated iron is better than a placebo for reducing the severity of RLS symptoms[44] and it should be replaced when deficient[26]. IRLSSG Guidelines (2017) advise iron supplementation when the serum ferritin is below 300 micrograms/L or transferrin above 45%[27]. When serum ferritin is below 75 micrograms/L, oral iron ferrous sulfate 325 mg once or twice a day and 100 mg vitamin C twice a day should be administered. Serum ferritin levels between 75 micrograms/L and 300 micrograms/L show a variable absorption of oral iron and should be treated with intravenous iron (ferric carboxymaltose 1000 mg). Less than 2% of oral iron is absorbed when the serum ferritin level is greater than 75 micrograms/L, due to the action of hepcidin. Intravenous iron may also be used when oral iron is poorly tolerated due to gastrointestinal side effects[28].

In children, iron replacement is indicated if the serum ferritin level is less than 50 micrograms/litre. Oral ferrous sulfate may be used at a dose of 3 mg/kilogram/day (maximum of 130 mg/day). If there is poor oral absorption or no resolution of symptoms at 3 months with oral therapy, intravenous replacement may be considered. Iron sucrose is the only formulation studied for use in RLS. A dose of 3-6 mg/kilogram (maximum of 120 mg) can be used, aiming for a serum ferritin of greater than 50 micrograms/litre[27].

ANAESTHETIC IMPLICATIONS

Perioperatively, RLS may worsen, recur or present for the first time. Common perioperative triggers include sleep deprivation and immobilisation. Patients who are pregnant or have iron deficiency, kidney failure or are using a potential triggering medication are at increased risk of RLS perioperatively[7].

Recommendations for perioperative management

Drug therapy for RLS should be continued perioperatively where possible. RLS drug therapy is usually taken at night. If interruption is required, it should be for the shortest time possible to prevent rebound symptoms. If a patient is immobilised for a prolonged period, dopamine agonists may be required three times a day (due to their short half-life)[23]. Therapy with a rotigotine patch may be continued in most patients. Premedication with benzodiazepines or pregabalin may be useful as both are used therapeutically in RLS[7].

Patients with RLS have difficulty remaining motionless. Prolonged medical imaging procedures or procedures performed under local anaesthetic alone may not be possible[7]. Postoperative agitation due to akathisia may be misinterpreted as delirium. This may be mistakenly treated with haloperidol (a dopamine antagonist), exacerbating the akathisia and agitation[45]. Benzodiazepines should be used as treatment for akathisia instead[7].

Pharmacotherapy

Medications may be a trigger of symptoms. As outlined above, dopamine antagonists, serotonergic agents or opioid antagonists should be avoided[7]. The following tables (3 and 4) summarise the potential drug effects on RLS.

Table 3. Drugs that may possibly exacerbate RLS symptoms. Adapted with permission[7].

Classic neuroleptics: Pronounced blockade of dopamine D2 receptor
Butyrophenones: haloperidol, droperidol
Phenothiazines: prochlorperazine, chlorpromazine, promethazine
Thioxanthenes: flupentixol, zuclopenthixol
Atypical antipsychotics: Less pronounced blockade of dopamine D2 receptor
Clozapine, olanzapine, risperidone, quetiapine, amisulpride
Antidepressants: Alter dopamine and serotonin metabolism
Tricyclic and tetracyclic: amitriptyline, nortriptyline, imipramine, doxepin, mirtazapine
Selective serotonin reuptake inhibitors: citalopram, escitalopram, fluoxetine, sertraline
Venlafaxine
Lithium
Antihistamines: Cross blood brain barrier, can induce RLS symptoms
Sedating: diphenhydramine, cyproheptadine, dexchlorpheniramine, pheniramine, promethazine
Dopamine antagonist antiemetics: Blockade of dopamine D2 receptor
Metoclopramide, droperidol
Opioids
Tramadol: Serotonergic effects
Antagonists: naloxone, naltrexone

Table 4. Drugs with no effect on RLS symptoms. Adapted with permission[7].

Inhalation anaesthetics: No effect
Sevoflurane, desflurane
Intravenous anaesthetics: No effect
Propofol, ketamine, thiopentone, benzodiazepines, etomidate
Opioids: Beneficial effect
Oxycodone, morphine, hydromorphone, fentanyl, sufentanil
Muscle relaxants: No effect
Local anaesthetics: No effect
Non-opioid analgesics: No effect
Nonsteroidal anti-inflammatories, paracetamol
Antiemetics: No effect
Glucocorticoids
5-hydroxytryptamine 3 receptor antagonists: ondansetron, granisetron, tropisetron

Regional neuraxial techniques

A prospective study by Hogl et al followed 202 consecutive patients undergoing spinal anaesthesia. They showed an 8.7% incidence of new onset RLS following spinal anaesthesia (mepivacaine heavy or bupivacaine plain ± fentanyl 15 micrograms was used for spinal anaesthesia). Patients were evaluated for the presence and severity of RLS symptoms at 48 to 72 hours post-surgery and then again at 1 week, 1 month and 6 months. Of the 161 patients who had no prior history of RLS, 8.7% developed first onset RLS after spinal anaesthesia. The mean duration was 33+/- 30 days. Low red cell volume and low mean haemoglobin concentration were associated with the onset of RLS. This study lacked a preoperative assessment to identify any preexisting undiagnosed RLS and there was no control group of patients[46]. It remains unclear whether regional neuraxial techniques have any role in triggering a new onset of RLS. No studies have indicated the effect of neuraxial anaesthesia on preexisting RLS.

There have been no large-scale studies investigating the influence of general anaesthesia on RLS. A prospective study involving 359 patients who underwent general or spinal anaesthesia were surveyed on admission and again at 1 and 4 weeks postoperatively. No patients from either group had worsening of pre-existing or new onset of RLS[47]. It appears that there may only be a temporal relationship between anaesthesia and worsening of RLS symptoms, but no causal effect[47].

Perioperative treatment of symptoms

If RLS symptoms occur perioperatively, patients should be allowed to walk or move their legs in bed as soon as possible. If prolonged bed rest is required, the frequency of RLS medications may be increased to three times a day. If oral intake is feasible, a patient's usual oral medication may be given. Levodopa (a dopamine agonist) may be administered by nasogastric tube. Alternatively, parenteral apomorphine or a rotigotine patch may be used. Apomorphine (1 milligram) may be injected subcutaneously on an hourly basis. Nausea is a common side effect so it may need to be given with an antiemetic. Rotigotine patches may be used every 24 hours[23,48]. Opioids, benzodiazepines and pregabalin may also be used to alleviate symptoms[7]. Patients should be proactively investigated and treated for iron deficiency, targeting ferritin level greater than 300 micrograms/litre in adults, and 50 micrograms/litre in children[27]. Table 5 summarises the perioperative goals.

Table 5. Anaesthetic implications of RLS. Adapted with permission[23].

Prevent RLS exacerbation
Neuroleptics and phenothiazine antihistamines are contraindicated
Domperidone and ondansetron can be used to prevent nausea and vomiting
Benzodiazepines can be used to achieve sedation
Continue RLS treatment, and reintroduce oral agents as soon as possible
When oral route is not available, apomorphine (subcutaneously) or transdermal rotigotine patches can be used
Alleviate postoperative RLS exacerbation
Use parenteral opiates
Apomorphine
Authorise the patients to move and walk as early as possible (under supervision) or to move their legs passively if bedridden
Alleviate long-term exacerbation of RLS after surgery
Monitor serum ferritin, especially if acute blood loss during surgery
If ferritin <75 mcg/mL, provide oral or intravenous iron (or <50 mcg/L in children)
Transiently increase the daily dose of dopamine agonist and administer 3 to 4 doses per day if the patient is bedridden

CONCLUSION

RLS is a prevalent disease that causes significant morbidity. Patients may experience an exacerbation of their symptoms in the perioperative period. Many factors relating to their hospital stay may contribute to this. These factors may be pathophysiological (for example iron deficiency), non-pharmacological (for example immobility) or pharmacological (for example the use of dopamine antagonists). To date, no large studies have been performed to examine if there is an interaction between RLS and anaesthetic agents or technique. Given the high prevalence, and significant morbidity of disease, it is important for anaesthetists to understand this syndrome to optimise the care of patients with RLS perioperatively.

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Liver/ Metabolic/ Immune System

Obesity and anaesthesia

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INTRODUCTION

"Obesus – to fatten by excess eating"

Obesity, an excess of fat, is a complex chronic condition with multiple causes and treatment options. It has a lifelong time course with relapses and consequences including multiple associated diseases, long-term costs and decreased quality of life and reduced life expectancy. Obesity can be prevented and managed. Sustained weight loss and improvement in complications can be achieved.

An epidemic of obesity is present in the world today with more than half of adults in many countries with a BMI above the healthy weight range (>25) and many millions living with morbid obesity. This results in a huge burden on the individual suffering from the condition and also healthcare-related costs of managing the associated diseases, especially diabetes, hypertension, sleep apnoea, and cancers. Estimates predict the healthcare cost associated with obesity to the Australian economy will be $A21 billion by 2025 unless drastic changes to trends are seen.

Despite extensive efforts by individuals, the medical community and health experts around the world, obesity rates continue to rise[1]. As countries become wealthier and adopt western lifestyles, the population starts to gain weight. Within an economy, however, data are suggesting that the worst obesity rates are seen in the lower-income areas[2]. This fact makes the provision of government-supported initiatives even more important for tackling the problem. Alarmingly, population forecasters have been reporting that the current generation of obese will have reduced life expectancies, a reversal of trends not seen in a century[3]. Governments have implemented various strategies including policies to improve food labellings, such as the healthy star rating system, education of adults and children about healthy eating and exercise, advertising of better lifestyle choices, sugar taxes and weight loss programs. "LiveLighter" is one such initiative in Western Australia[4,5].

Intuitively, it is only possible to lose weight with a negative energy balance. Human physiology is biased towards weight gain and very resistant to weight loss. Large and difficult lifestyle changes are required to lose and maintain lower weight while much smaller sustained changes in energy balance will provide stable energy and thus weight balance[6]. It is thus imperative that preventative measures are promoted to prevent weight gain and also help individuals maintain healthy weight balance throughout their lives.

Many still believe that if obese people could simply eat less and exercise more, they would not be obese or suffer the consequences of obesity[7]. The obese will often state that they are discriminated against within the medical system and society in general and this contributes to depression and anxiety, both being major risk factors for worsening obesity[8,9].

The evidence about what constitutes a healthy diet is well known and widely publicised. It includes high levels of vegetable and fruits, whole grains and high-quality proteins. There should be a low intake of added sugars, refined grains and highly processed foods[10]. Portion sizes must be appropriate. Calorie counting is important but difficult to follow long-term. People who maintain weight loss have several behaviours that are associated with success including weighing themselves at least weekly, exercising regularly (usually walking daily) and limiting their intake of unhealthy foods such as high calorie, fat-laden fast foods, and alcohol[11].

To date, bariatric surgery has provided individuals with the best sustained weight loss albeit at a price[12]. The cost includes a large initial financial outlay, side effect, and complications of surgery and rarely the possibility of great difficulty with eating a healthy diet, malnutrition, especially micronutrient deficiency and high rates of re-operation. Of the three common bariatric procedures, the gastric band (LGB) has the lowest early complication rate but results in lower weight loss, with the gastric sleeve (LSG) and Roux-Y bypass (RYB) having roughly equal weight loss results at one year. Complications with LSG and RYB are higher however with reflux, ulceration, bleeding and anastomotic breakdown being serious risks[12]. Re-operations including removal of devices, skin surgery, revision bariatric surgery, and cholecystectomy are common[13]. On a population level, however, there is a low uptake of bariatric surgery with around 10% of those eligible for surgery having it done. While obesity rates are highest in the lower socioeconomic groups, the surgical interventions are mostly seen in the higher income groups[14]. The reasons for this are complex and include high out-of-pocket costs, lack of public funding, unacceptable risks and lack of support for bariatric surgery within society. Indeed many people still believe that obesity is the fault of the individual and using public services and funding is not justified.

Eating is an essential part of life and forms a foundation in culture and family life. The relationship that each individual has with food is complex. Modern society has trended to overeat high-calorie food with poor nutritional values coupled with reduced energy expenditure in daily life and recreationally. Fresh healthy food has incorrectly been seen as more expensive than calorie-laden, fast and processed meals. The reasons why lower-income families spend more on unhealthy choices is due to good marketing, convenience, and preferences[15]. Portion control is out of control with a high content of saturated fats, sugars, and salt. This coupled with lack of exercise has contributed to an epidemic of obesity, diabetes, hypertension and heart disease. Alcohol consumption contributes to obesity however this complex topic will not be covered further in this article, save to say that individuals on a weight loss journey should reduce alcohol consumption to a minimum.

The obese individual has a failure of satiety and indeed the obese will often complain of feeling hungry all the time even though they are consuming well over normal daily calorific requirements[16]. The person may be addicted to food, receives short-term enjoyment from eating sugar and fat-laden foods, followed by feelings of guilt and shame. With the acceptance by the medical profession and society of obesity as a chronic condition, and better publicity and acceptance of the treatment options, hopefully, it can become destigmatised and people will come forward for treatment. General practitioners are well placed to educate patients and co-ordinate the necessary lifestyle changes and treatment options.

As the body becomes bigger it starts to suffer from the pathology associated with excessive fat including elevated blood pressure, heart disease, sleep apnoea, and diabetes. Every system in the body is affected by what is thought to be a low-grade inflammation possibly driven by hypoxic fat tissue that has outgrown its blood supply. Higher cancer rates are associated with obesity. Daily life becomes more difficult and enjoyment of normal activity declines. Depression is incredibly common in the obese and losing weight becomes increasingly difficult the longer a person has been overweight. The good news, however, is that with weight loss many of these conditions can be reversed.

One of the most poorly understood parts of the human energy experience is the subject of metabolism[17]. To begin with, this is a field of science that is difficult to work out and many unanswered questions regarding the effects of food types and phenotypes remain. Many myths abound in the popular arena about being able to alter one's metabolism such as through exercising or low carbohydrate diets. It has been proposed that certain additives can increase energy expenditure and thus fat burning. The fact remains that none of these interventions can predict or change metabolism. We don't know why many metabolic processes happen, for example after rapid weight loss; the metabolic rate slows down in an adaptation that persists for years[18]. The largest contributor and most important metabolic rate is the resting one and very few things will alter it in the long term. A subgroup of humans, roughly 20% of the population, is stubbornly lean no matter how many calories they consume. Others can become obese without any of the ill effects on blood pressure, diabetes, and heart disease. Much of this is poorly understood. Exercise will burn more calories but leads to an immediate increase in food intake. Only about 15% of people can diet to lose and maintain weight loss, and this is only achieved at the expense of hard work. Extremely strenuous exercise will burn calories and result in improvements in muscle mass and metabolic rate will increase by up to 40% but very few people can afford to spend this much time and effort on regular extreme exercise.

Studying people who have successfully maintained lost weight leads us to see that they have certain traits and behaviours in common: They weigh themselves at least weekly, they exercise regularly (mostly walking), they restrict calorie intake and avoid high-fat foods, and they moderate portion size. There is no consistency in the type of food they eat but they do count their calories[19]. The factors that influence the resting metabolic rate include how much lean muscle and fat is in the body, age, genetics, and gender. It is worthwhile for individuals to know roughly what their metabolic rate is so that they can moderate their fuel intake, and there are online calculators for this.

The idea that obesity is a chronic condition or disease process that will be with the person for life is an opportunity to educate the individual – if one can live a healthy lifestyle as discussed, weight loss can be maintained, excess fat kept off and the diseases related to obesity can be improved and avoided.

We know from US data in the National Weight Loss Register that lifestyle changes of reduction in calorie intake and increased expenditure of energy through exercise can result in weight loss and impressive results can be achieved by individuals. Unfortunately, this method is not sustained over the long-term and on a large scale does not work. Indeed, fewer than 20% of successful dieting weight loss people will maintain their goal weights after three years[11]. The measure of successful weight reduction is placed at 10% excess weight loss which is very low compared to the numbers published for surgical interventions. There is value in losing 10% excess weight both for the functional and pathological state of the patient. The physiological adaptations to weight loss and personality traits have a large influence on the ability to maintain a healthy weight while living in an "obesogenic" environment[20].

MEDICAL THERAPY

Medications for weight loss produce some benefits in the order of 10% excess weight loss which can result in improvement in blood pressure, cholesterol profile, sleep apnoea, and diabetes control. However, this modest success is not sustained once medication ceases[21]. The medications currently available have side effects and costs which have been unable to make a meaningful impact on obesity rates on a large scale. Many weight loss medications are not covered by Medicare in Australia. The use of lifelong medication in conjunction with bariatric surgery may become more accepted following the paradigm shift that obesity is a chronic disease that needs ongoing medical management.

SURGERY

Bariatric surgery has been shown to produce the most reliable weight loss (excess weight loss at three and five years of 50-70%), sustained for several years and has also been shown to improve diabetes rates and the need for diabetes treatment[12]. Successful weight loss results in great improvements in patient's quality of life and functional ability; especially if the starting weights are very high. As surgical skills, training and knowledge increase, there is a trend to fewer complications and very low mortality rates, comparable with many routine operations.

In a review by Pedroso et al looking at bariatric surgical weight loss results in US adolescents, weight loss was safe, effective and sustained at three years[22]. It may become more accepted as a way to prevent the long-term consequences of obesity.

In rare cases, bariatric surgery patients suffer from catastrophic complications that leave them hospitalised for months or even result in death. In Australia, these cases end up being cared for in the public hospital system. Some are left as "gastric cripples" with such scarred upper GI tracts that they cannot eat and further surgery is too dangerous and ineffective. It is necessary to include this rare but serious consequence into the consent process and also be mindful that these cases will occur. As bariatric procedures and surgical techniques and knowledge have increased, better outcomes are seen with fewer serious complications.

It is worthwhile looking at the features of the perfect bariatric operation (Table 1) as well as listing the known complications (Table 2) from bariatric surgery to concentrate efforts to maximise benefit, safety, and efficiency for the individual and society while avoiding complications and mortality.

Table 1. Features of the perfect bariatric surgery.

Safe with low morbidity and mortality.
Effective with long-term sustained weight loss.
Controls or eliminates obesity complications.
Low side effect profile (nausea, reflux).
Easy to perform and reproduce.
Cheap.
Short hospital stay/day case.
Minimally invasive with minimal blood loss.
No need for HDU/ICU.
Good patient satisfaction.
Easy to live with.
Allows patients to mobilise early and eat normal food.
No need for ongoing intervention, cost or resources.
Low re-operation rates.

Table 2. Complications following bariatric surgery.

Early:
▪ Bleeding.
▪ Nausea and vomiting.
▪ Pain.
▪ Leak.
▪ Infection.
Late:
▪ Ulceration.
▪ Leak.
▪ Internal hernia.
▪ Oesophageal dilation.
▪ Regurgitation.
▪ Aspiration.
▪ Band erosion.
▪ Failed weight loss.
▪ Malabsorption.
▪ Dumping syndrome.
▪ Loss to follow up.
▪ Relationship breakdown.
▪ Stenosis.
▪ Re-operation.
▪ Cholecystectomy.
▪ Endoscopy.
▪ Skin surgery.
▪ Possibly cancer.

There has been an evolution of various operations for weight loss with some procedures now far less popular due to failed weight loss or unacceptable effects and complications[23]. Many options do not have long-term data available. Currently in Australia, the LSG is the most common procedure, while the use of the LGB is declining. Far more removals of gastric band are being done and this author believes that this will continue until almost all of them have been removed[24].

Types of surgery

While the ideal bariatric operation has not been developed it seems wise to have a range of surgical options as no one procedure will work in all cases. Surgical options are broadly divided into restrictive and mal-absorptive operations. Some procedures have an element of both. See Table 3 for an outline of surgical procedures. New operations are being developed but long-term data are lacking. Improvements in skill and equipment for laparoscopic surgery has made the routine bariatric operations incredibly safe and hospital stays of 1-2 days are now common. Mortality rates of less than 1/1000 are quoted[13].

Table 3. A list of surgical procedures available for weight loss surgery.

Laparoscopic adjustable gastric band	Adjustable restrictive device with a port. Placed around the top of the stomach. Simple surgery, day case, very safe, high failure and re-operation rates. First used in 1980s.
Laparoscopic sleeve gastrectomy	Restrictive procedure reduces stomach to a tube of less than 50ml. Safe, effective and easy to eat normal food. Most popular procedure worldwide. Evolved in the 1980s.
Roux-Y gastric bypass	Mal-absorptive procedure first proposed in 1977 to reduce severe bile reflux. Highly effective for diabetes and weight loss. Higher complication and mortality rates although much improved complication rates over time.
Omega loop bypass (Mini loop)	Mal-absorptive procedure first done in 1997, single loop of bowel is anastomosed to the gastric pouch. Quick, effective and safe however high bile reflux rates and possibly cancer risk.
Stomach intestinal pyloric sparing surgery (SIPS)	Modification of the duodenal switch. Proposed to be best balance of risks, effectiveness and complications, especially malabsorption, reflux and dumping.

The SIPS, (Stomach Intestinal Pyloric Sparing Surgery) is also known as the SADI (Single anastomosis duodenal-ileostomy) is being promoted as the best option currently available. It is a modification of the well-known duodenal switch (BPDS) that is 20+ years old[25]. The duodenal switch has a proven long-term record for sustained weight loss and resolution of diabetes and hypertension[26].

The SIPS operation begins with sleeve gastrectomy and the duodenum is divided, leaving the pylorus intact to reduce bile reflux, with a lower risk of glucose surges and dumping. A longer than usual common channel (300cm) is brought up from the distal ileum and single anastomosed onto the duodenum – one anastomosis will reduce leak and stenosis risks. The longer common channel reduces nutritional deficiencies. Data to date show SIPS mean excess weight loss at two years of close to 80% with lower long-term severe diarrhoea and malnutrition rates than the BPDS. Surgical revision rates at five years are under 7%[25].

Bariatric Surgical Register

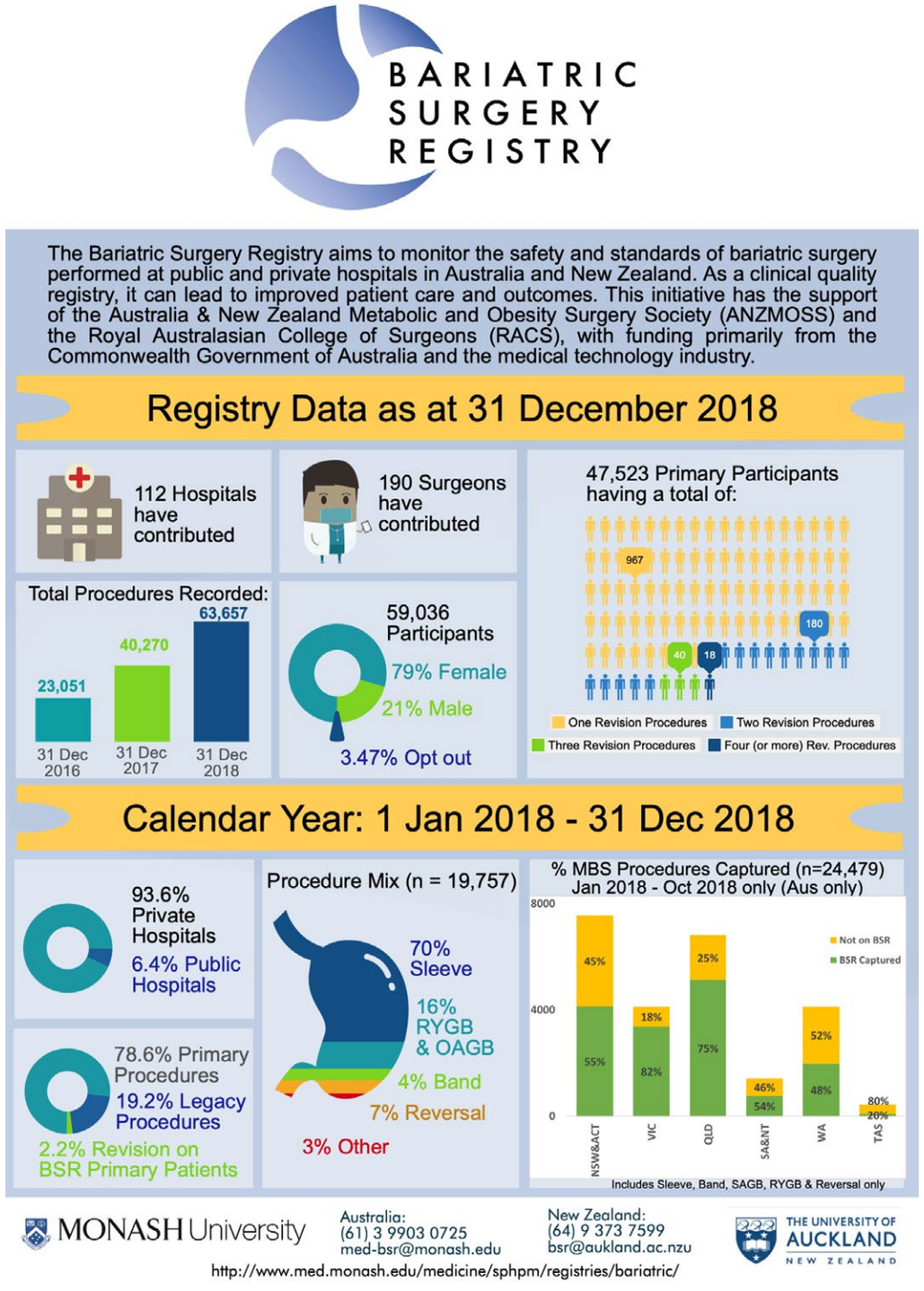
The Bariatric Surgical Register (Figure 1) is an Australia-wide, independent ongoing clinic quality audit run out of Monash University in Melbourne[24]. It is designed to monitor the number and type of bariatric operations performed, the surgical equipment used, weight loss results, complications and diabetes changes over time. It was established following a two-year pilot period and was rolled out nationally in 2014. Funding is partly provided by the Commonwealth Government and partly through the industry. The aim is to follow patients for 10 years. While all bariatric surgeons and hospital sites in Australia are encouraged to participate, roughly half have taken up the challenge. Data can be compared with MBS data and reports are published annually. One major advantage of joining the registry is that alerts will be sent to surgeons and sites if complication rates greater than expected are noted.

So what has the register shown us about bariatric surgery in Australia to December 2018?:

- Initial participants have reached 3 years (n=2433).
- Excess weight loss for all procedures at 12 months is 68.3% (n=18,789).
- Total weight loss at 12 months is 27.1%(n=19,057).
- By 3 years the weight loss reduced to around 50% EWL and 20% TWL.

Of the 3277 diabetics that make up 14.5% of the total, by 12 months post-any bariatric surgery over half (54%) is off medication for diabetes. Of the remaining patients, oral medications and insulin use dropped significantly. Of note, there was a dropout rate of 25% on the diabetic data which will impact the robustness of conclusions. Nonetheless, these are impressive results showing that bariatric surgery is highly effective in curing or improving established diabetes. The results for specific surgeries such as the RYGB procedures may show even better results in the future.

Figure 1. The Bariatric Surgery Registry. From: www.med.monash.edu/medicine/sphpm/registries/bariatric/



Funding for bariatric surgery: public and private

The current financial landscape in Australia is one dominated by high levels of government and personal debt and guarded outlooks for both individual families and health providers. The private health industry is facing challenges as the cost of providing medical services increases and the numbers of private insurance policyholders are dropping, especially among younger Australians. Many very cheap policies taken to avoid the Medicare levy are virtually useless when claims are made. Despite these difficulties, the health insurance industry posted $A1.8 billion pre-tax profit[27].

The provision of bariatric surgery in Australia is 90% in the private sector[24]. As an example in Western Australia, public bariatric surgery is limited to certain sites and annual numbers of operations. Almost 1000 patients are currently waiting two years to be seen by a surgeon and roughly half of these will qualify for a gastric sleeve procedure. These patients will wait another two years for their surgery (personal communication).

The public numbers are inadequate and the head of the BSR has called for a large increase in funding for bariatric medicine and surgery in Australia to try to address the problem of those already obese[28]. Provision of surgery and management of the waiting lists is under regular review by state health providers.

As patients struggle to get public access to bariatric surgery and health funds try to reduce payments, people are frequently turning to alternative ways to pay for their bariatric procedures. The cost of a sleeve gastrectomy is currently about $A25,000 in Australia. The bulk of that is covered by the health fund and Medicare however even the best cover will still leave out of pocket costs of $A5000-7000.

To self-fund, a person will need to pay the full amount upfront. The occurrence of complications and requirement for high acuity care could blow the costs out. Medicare will reimburse a portion of the costs. Medical payment schemes are available and also the use of superannuation on compassionate grounds is increasingly being seen.

The use of superannuation is a controversial area under review. The government is concerned that the money used by people in their 30s and 40s will never be replaced. The amounts being drawn are in the order of $A14,000 and will result in final fund reductions of more than $A40,000. The group most frequently accesses their superannuation are women who traditionally have lower lifetime balances. To access superannuation there is a fairly strict process and qualification criteria. More information can be found on the ATO website (www.ato.gov.au). Patients, however, do have a compelling argument that their obesity will impact on their life expectancy to the extent that early mortality will make a large superannuation balance irrelevant. The paradox is that to reach retirement they need to access the funds early and will have less money, placing more burden on the state. This solution of using superannuation is blatantly unfair and provision of public bariatric surgery would be far more just and cost-effective in the long run for the individual and society.

ENDOSCOPIC BARIATRIC MEDICAL THERAPY (EBMT)

An alternative weight loss approach is the use of endoscopic bariatric medical therapy[29]. The first gastric balloons were placed in the 1980s. However, it took until around 2015 for the FDA to approve some of the current devices for use in the US. EBMT consists of the placement of a variety of devices into the GI tract and there is a multitude of devices and novel ideas available worldwide. Several are in development or already being used in Australia. The proposed benefits over conventional bariatric surgery are lower cost, lower complication rates and the perception that they are safe and easily reversible. Long-term safety and efficacy data are lacking and many of the devices are only licensed for six months use. Early rates of nausea and vomiting are high while weight loss failure can leave patients feeling cheated as the therapy is not covered by Medicare. As with all weight loss procedures, the intervention is part of a lifestyle and diet modification and weight loss cannot be guaranteed. Without a reversal of the energy balance, there can be no weight loss. Indeed if any bariatric intervention is not accompanied by lifestyle and dietary changes it will fail.

EBMT has been proposed as a cheaper alternative to bariatric surgery, in fact, many of the devices currently fall outside Medicare and thus private health will not pay for them. Table 4 summarises the devices and technologies in EBMT. The place of EBMT in obesity management is still evolving and it could become mainstream as an alternative for those that are in the lower weight ranges or as a staging or holding therapy. It has opened up weight management medicine to a whole cohort of gastroenterologists and if it can be shown to be cheaper and safer than surgical methods it could help make an impact on the obesity epidemic. Another concern at this stage is that complications of new technologies will only become evident as the number of cases and long-term follow up data is published. Of note, the FDA has issued device alerts for gastric balloon devices after 12 deaths were reported[30]. Morbidity information for some technologies is high and early failure rates of 30% in some series will lead to patient dissatisfaction, especially if patients have to self-fund. The good news about new techniques is that after initial learning curves for practitioners, procedures tend to become safer and more effective[31].

Table 4. A list of endoscopic bariatric medical therapies.

OBALON (R) Intragastric balloon – gas filled up to 250ml	2X effective as diet and exercise Swallowed in clinic – no anaesthesia Up to 3 can be used – 2 weeks apart (new advice) Safe	Cost $US6000-10,000 Only used for 6 months, removed at endoscopy Modest weight loss Early failure Ulceration Mortality reported
ORBERA (R) **Silicone spherical intragastric balloon – saline filled up to 700ml**	Single device 10% TBWL at 6 months More than 5000 devices placed worldwide	Cost $A5000-7000 Requires anaesthesia to place and remove Mortality rate 0.06% Early failure
RESHAPE DUO (R) Seperate saline filled, linked balloons	Migration hindering device, if one balloon bursts, methylene blue is released 6-7% TBWL at 6 months	Cost $A9000-13,000 Requires anaesthesia Mortality reported Early failure Remove at 6 months
SPATZ (R) **Adjustable saline filled balloon, now in Version 3. Fill between 400ml and 800ml saline**	Inflation tube allows for personalised filling depending on weight loss and tolerability Up to 12 months 20% TBWL	Cost $A7000 Requires anaesthesia for insertion and adjustments Earlier models had design issues
TRANSPYLORIC SHUTTLE (R) **Smaller silicon end advances under peristalsis to ball valve pylorus.**	Intermittent seal delays emptying, increases satiety 40% EBWL loss at 6 months	Cost unknown Fixed size, silicone balloon Not available in Australia Minimal longterm data
FULL SENSE (R) **Gastro-oesophageal stent applies pressure on the gastric cardia**	Easy to insert and remove 70% EBWL at 6 months initial data	Cost unknown Not licensed for use Minimal risk of displacement or obstruction No data on risks or longterm results
Self assembling magnet compression. Reciprocal magnets click together, 4cm anastomosis takes 4 days to form and magnet passes after 9 days.	No incision Complex procedure Good results in animal and human cases Multiple anatomical options	Cost unknown 2 endoscopists and X-ray guidance Longterm data and risks unknown
ASPIRE (R) or A Tube, PEG tube that allows removal of up to 30% of a meal	Safe and easy insertion option to aspirate or not Discrete Ability to lavage tube 15% TBWL 12 months	Cost $A8000 Need to aspirate 20 minutes after meal Need to chew food well Risks: granulation, infection, peritonitis (1%), ulceration (1%)
Endoscopic Sleeve Gastroplasty – full thickness gastric sutures. Endoscopic suturing device used.	No surgical incisions TBWL 18% at 12 and 18 months Improved metabolic effects shown	Cost $A16,000 Risks: Full thickness suture – pneumothorax, collections, splenic injury Possibility of longterm failure
POSE (R): primary obesity surgery endoluminal: plication of the gastric body using special tissue anchors to reduce size	Sutures targeted in cardia and fundus Metabolic effects, restrictive, slow gastric emptying, satiation TBWL 7% at 12 months	Cost $A18,000 Special scope with 4 channels, 2 operators Risks: nausea, vomiting, pain, bleeding and liver abscess No data on longterm safety or effectiveness
Endoluminal barrier: A sleeve placed in duodenal bulb, extending 65cm to bypass absorption and enzymatic secretions.	Placed and removed easily and safely EWL 35% at 12 months Improves diabetic control Improved anchoring under development	Cost $A7000 Hepatic abscess 3.5% halted trial early. 11% early withdrawal due to side effects. Deaths have occurred Migration, bleeding ulceration, pancreatitis can occur. Not in use
Gastrodoudenojejenal bypass sleeve. 120cm sleeve, excludes stomach and duodenum.	Endoscopic placement mimics the RYGB with possibility of similar results Currently in development	Cost unknown Not in clinical use Pilot study had high incidence of losing anchors
Duodenal resurfacing uses thermal ablation of mucosa after lifting with saline. Hot water is used to ablate about 10cm.	Safe, easy Duodenal surface fully healed by 6 months Indication is T2DM and NASH, some metabolic improvements noted.	Cost unknown Very few cases Results unknown Temporary effect Minimal weight loss in published cases

SGLT2 INHIBITORS AND BARIATRIC SURGERY

Diabetic patients have started taking SGLT2 inhibitors that result in an impressive reduction in blood glucose readings. When these patients present for surgery, especially if they are on a ketotic low-calorie diet, they run the risk of euglycaemic ketoacidosis. This is a risk that continues to be poorly understood and managed[32]. [Please see the chapter "Euglycaemic diabetic ketoacidosis associated with sodium-glucose cotransporter-2 inhibitors: New drugs bring new problems" in this edition of *Australasian Anaesthesia* for additional material].

SGLT2 inhibitors work by the inhibition of filtered glucose reabsorption in the renal tubules. As sugar is lost into the urine, blood glucose levels fall and there is a mild diuresis, blood pressure falls and weight reduces slightly. These medications are proving very popular and are being used as second-line oral agents and also to supplement type 1 diabetic treatment. The main complication is urinary infections. Patients on SGLT2 inhibitors can develop acidosis and this has been recognised in the endocrine literature. The exact mechanisms and risks from the ketoacidosis are complicated and debated.

It is being increasingly recognised that a relative insulin deficiency leads the patients on this medication to have lipolysis and ketogenesis thus leading to ketoacidosis in the face of normoglycemia. This risk is increased when the person is under physiological stress such as exercising, fasting or suffering from infections. When a bariatric patient is put onto a preoperative ketotic 2-week low-calorie diet for liver shrinkage, there is a high risk of normoglycemic ketoacidosis that has been increasingly recognised.

Numerous cases have been reported leading to alerts from ANZCA and others[33]. The presence of ketosis may be missed if only the blood glucose is measured. It is now recommended to test for ketones in the blood, easily done with a bedside finger prick test. Urine ketone testing does not always pick up the problem. If ketones are high, check for acidosis with a blood gas analysis.

The management is to start glucose and insulin to switch off the ketogenesis. Fluid status needs attention and the patients are best cared for in a high acuity area. Withhold the SGLT2 until the patient is well and has reasonable calorie intake. Resolution can take several days as the drug effect seems to last longer than the drug half-life. Clinically cases have been picked up when post-operative patients seem unexpectedly sleepy or lethargic, tachycardic, hypotensive and tachypnoeic. The advice perioperatively is to stop the medication for at least two days but preferably longer if on the low-calorie diet. As the medication can come in a combination

preparation, expert advice about alternative medication should be sought before stopping the SGLT2. Close monitoring of glucose levels is prudent. Get diabetic teams and specialists involved early[33]. The dangers of the SGLT2 medications in the perioperative period is not well publicised among surgeons and GPs.

CONCLUSION

In brief, it looks like we are making little headway in the prevention and management of obesity. If our society is serious about managing the obesity epidemic, much more funding and effort needs to be placed on prevention of obesity through government initiatives such as a sugar tax, sound and sensible nutrition information, exercise and lifestyle training for adults and children, access to bariatric medicine and surgery for those who are overweight and diabetic. Development of new medications and technologies such as the EBMT must continue. The evidence for interventions that are safer, cheaper and have a lasting effect will be where more resources can be directed. Targeting high-risk patients such as diabetics will yield the most cost-effective long-term benefits. Bariatric medicine and surgery will continue to play a major part in healthcare for the foreseeable future. There is great scope for service, research, and education in nutrition, obesity medicine and surgery.

Almost all people are at risk of suffering from the chronic disease of excess fat in the body known as obesity. Risk increases if one is older and female. Most people will not be able to lose and maintain weight loss if they have reached morbid obesity (BMI >40). Dieting and medications can play a small role in weight loss but at this stage, nothing has shown a sustained and worthwhile effect comparable to surgery. Bariatric surgery can play a major part in weight loss for individuals but until access to much more is afforded to the population, little large-scale impact on obesity rates will be realised. The perfect bariatric operation has not been confirmed however the SIPS looks like a contender with a good balance between safety, acceptable side effects, sustained weight loss, and most importantly resolution of diabetes and hypertension. For the foreseeable future, the gastric sleeve will be the most popular procedure while the gastric band will continue to decline. Newer technologies of endoscopic procedures hold some promise however they are relatively expensive, have unproven long-term weight outcomes and also hold significant morbidity and mortality risk. The use of SGLT2 inhibitors for diabetic management has increased however these patients present a specific risk of keto-acidosis when coming for bariatric surgery.

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Euglycaemic diabetic ketoacidosis associated with sodium-glucose cotransporter-2 inhibitors: New drugs bring new problems

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INTRODUCTION

Diabetes is a chronic condition affecting approximately 1.2 million Australians (6%) and it is projected that 3.3 million Australians will have diabetes by 2031[1,2]. Type 2 Diabetes (T2D) accounts for nearly 90% of all cases[3]. The prevalence of diabetes among hospital in-patients is even greater (15-35% in Victoria)[4], and it is estimated that 15% of all surgical patients have diabetes[5]. Metformin is the first-line choice for the pharmacological treatment of T2D, but in time with progressive beta cell destruction and insulin resistance many patients require a second- and third-line medication[6,7].

Sodium-glucose cotransporter-2 inhibitors (SGLT2i, Gliflozins) are a new category of oral non-insulin glucose-lowering agents approved for T2D. They improve glycaemic control by facilitating urinary excretion of glucose along with sodium. Their mechanism of action is independent of beta-cell function and they have low risk of hypoglycaemia.

Dapagliflozin, empagliflozin and Ertugliflozin are currently available within Australia. Canagliflozin is widely used in other markets[8]. Empagliflozin and canagliflozin have been shown to decrease cardiovascular mortality and morbidity in high risk cardiovascular patients with T2D[9,10]. Empagliflozin, Dapagliflozin and Canagliflozin have all been shown to reduce hospital admission rates for heart failure when used in patients with T2D with known or potential atherosclerotic cardiovascular disease[11]. Other extra-glycaemic benefits for these drugs include

renal-protection[9,12], weight loss and reduction in blood pressure[13]. These agents are used as second-and third-line oral therapy, with or without the addition of insulin. If metformin is not tolerated in patients and there is co-existing cardiovascular disease, gliflozins can be used as a first-line therapy[14], thus making them commonly prescribed, and they are increasingly encountered in the perioperative period.

Diabetic ketoacidosis (DKA) associated with gliflozins is a recognized adverse event in the perioperative and the non-perioperative setting[15-17]. Patients can either present with elevated blood glucose levels or with near normal blood glucose levels (BGL <14 mmol/L) which is termed euglycaemic diabetic ketoacidosis (EDKA)[16]. This is rare in the non-surgical population, and it is estimated that 1000 patients need to be treated for one year with a SGLT2i to detect one DKA episode[18]. Incidence, however, may be more common in the perioperative setting due to the presence of precipitating factors; dietary modifications, fasting, surgical stress, intercurrent illnesses, inappropriate handling of these agents perioperatively, and reductions in insulin[16]. This review provides an overview of the pharmacology of the commonly used gliflozins (SGLT2i), the pathophysiology of EDKA and proposes a considered and balanced approach in the perioperative management of patients on SGLT2i therapy.

DEVELOPMENT OF SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS

Dapagliflozin, was the first SGLT2i to be registered in Australia in October 2012 and was listed on the Pharmaceutical Benefits Scheme (PBS) in December 2013. Empagliflozin was PBS listed from January 2015. Canagliflozin was only available in Australia for a short time before being withdrawn from the PBS in August 2015, a decision made by the sponsor[19,20]. We may, however, see a re-emergence of canagliflozin on the Australian market due to the recent reno-protective benefits seen from the recent CREDENCE trial (refer to Table 2). Ertugliflozin is the latest of the drug class to be available, listed on the PBS in December 2018.

The genes SLC5A1 and SLC5A2 encode for SGLT1 (Sodium-glucose cotransporter-1) and SGLT2 (Sodium-glucose cotransporter-2) respectively[21]. Both SGLT1 and SGLT2 are important mediators of epithelial glucose transport throughout the body, particularly within the small intestine and the nephron. SGLT1 is the cotransporter responsible for the majority of glucose absorption in the intestine, while SGLT2 accounts for the majority (roughly 90%) of glucose *reuptake* in the proximal tubule. It follows that SLC5A1 mutation affected individuals suffer intestinal malabsorption, while SLC5A2 mutations result in urinary glucose losses. Interestingly, familial glucosuria is a relatively benign condition without any major risk of ascending urinary tract infections.

Phlorizin is a naturally occurring competitive inhibitor of both SGLT1 and SGLT2, found in the roots, bark, leaves and fruit of the apple tree. Discovered over 150 years ago it was shown to increase urinary excretion of glucose in healthy individuals[21]. Since the cloning of SGLT1 some 30 years ago, drug development in this area has been much enhanced and formulation of soluble forms of phlorizin derivatives, ideal for oral consumption, have culminated in the drug class available today.

Differences within SGLT2i drug class include respective selectivity profiles for SGLT2 and SGLT1 inhibition (Table 1). Of those available within Australia, empagliflozin has the strongest selectivity for SGLT2 and dapagliflozin the least. Sotagliflozin, while not currently available in Australia, has a 20 times higher potency for SGLT2 over SGLT1 and is considered a dual inhibitor of SGLT1/SGLT2.

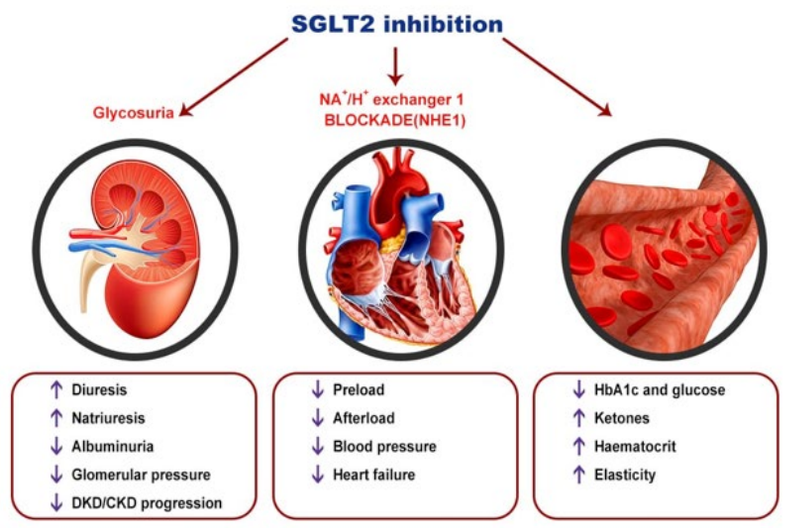
Table 1. Respective selectivity profiles for SGLT2 over SGLT1. IC_{50} – the concentration of an inhibitor where the response (or binding) is reduced by half.

Drug	SGLT2 IC_{50} (nmol/L)	SGLT1 IC_{50} (nmol/L)	SGLT2/SGLT1 selectivity
Dapagliflozin	1.2	1400	1200
Empagliflozin	3.1	8300	2700
Ertugliflozin	0.9	1960	2200
Canagliflozin	4.2	663	160
Ipragliflozin	5.3	3000	570
Luseoglifl ozin	2.3	3990	1770
Tofogliflozin	6.4	12,000	1875
Sotagliflozin	1.8	36	20

ADDITIONAL BENEFITS BEYOND GLUCOSE LOWERING

The beneficial glycaemic effects of SGLT2 inhibitors include HbA1c reductions of up to 1.98%, and improvements in glucose variability and insulin sensitivity. There is a relatively low hypoglycaemic risk[22]. (The 10% of glucose absorption attributable to SGLT1 in the later parts of the proximal tubule still offers some homeostatic control when blood glucose is low). Other beneficial metabolic effects include weight loss, reductions in visceral adiposity and natriuresis with a reduction in blood pressure. Twenty-four-hour ambulatory systolic pressures are reduced by roughly 4 mmHg with both dapagliflozin[23] and empagliflozin[24]. Effects on blood pressure may be greater in patients with uncontrolled blood pressure at baseline[23,24].

Figure 1. Organ protective effects of sodium-glucose cotransporter-2 inhibitors: kidney, heart and vessels. Adapted and modified from Giugliano[25]. DKD-Diabetic kidney disease; CKD-chronic kidney disease.



Major interest around this drug class has been due to their cardiovascular and reno-protective properties (Figure 1). These positive results on clinically important outcomes have stimulated recent enthusiasm for their clinical use.

To date there have been three cardiovascular and one renal disease outcome trials which have evaluated the cardiovascular (CV) safety of SGLT2i in more than 38,700 participants with T2D (Table 2), with further large outcome trials awaited. EMPA-REG OUTCOME study was a double-blind trial to assess the effect of empagliflozin versus placebo on CV events in 7021 patients with T2D and established cardiovascular disease (CVD). This demonstrated a 38% reduction in cardiovascular death and a 35% reduction in hospitalisation for heart failure in patients with T2D and established CVD with use of empagliflozin over 48 months[9]. Empagliflozin has also been shown to slow the progression of diabetic kidney disease in T2D[12].

DECLARE-TIMI 58 was a double-blind trial of dapagliflozin in 17,160 T2D patients with established or multiple risk factors for atherosclerotic CVD. It looked at both CVD and renal endpoints followed for a median of 4.2 years. Dapagliflozin was noninferior to placebo with respect to a composite outcome of CV death, myocardial infarction or ischaemic stroke. Dapagliflozin however, resulted in lower rates of hospitalisation for heart failure and reduced progression of renal disease[26].

CANVAS Program consisted of two trials comparing canagliflozin to placebo in 10,142 participants with T2D and high CV risk followed over a mean period of 188 weeks. While there was a lower CV event rate, there was a greater risk of amputation, primarily of the toe or metatarsal in the canagliflozin group[10]. While this new drug class offers considerable promise, non-inferiority studies comparing to placebo groups must be interpreted correctly and viewed with caution, and further research is required.

CREDENCE is the first SGLT2i trial in patients with renal disease. Canagliflozin versus placebo was compared in 4400 T2D patients with diabetic nephropathy, who were on either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The primary composite outcome of end-stage renal disease, sustained doubling of serum creatinine level or death from renal or CVD was reduced by 30% in the canagliflozin group over a median follow up of 2.6 years[27].

Table 2. Summary of major cardiovascular and renal outcome trials. T2D, type 2 diabetes; 3-point MACE, major adverse cardiac event defined by cardiovascular death, nonfatal myocardial infarction, nonfatal stroke; CV, cardiovascular; HF, heart failure; CVD, cardiovascular disease; ACEi, ace inhibitor; ARB, renin-angiotensin receptor blocker; ↓ – decrease.

Trial and size	Intervention	Follow up (years)	Inclusion criteria	Outcomes
EMPA-REG (n=7021)	Empagliflozin versus placebo	3.1	T2D with CVD eGFR >30 ml min 1.73 m2	↓ 3-point MACE ↓ CV death ↓ HF hospitalisations ↓ progression of diabetic kidney disease
DECLARE-TIMI 58 (n=17,160)	Dapagliflozin versus placebo	4.2	T2D with CVD and/or multiple CV risk factors eGFR >60 ml min 1.73 m2	Noninferior 3-point MACE ↓ HF hospitalisations ↓ progression of diabetic kidney disease
CANVAS (n=10,142)	Canagliflozin versus placebo	2.4	T2D with CVD or >2 CV risk factors eGFR >30 ml min 1.73 m2	Noninferior 3-point MACE ↓ CV event rate ↓ HF hospitalisations ↓ progression of diabetic kidney disease ↑ lower limb amputation
CREDENCE (n=4401)	Canagliflozin versus placebo	2.6	T2D, eGFR 30 – 90 ml min 1.73 m2, Diabetic nephropathy receiving ACEi or ARB	↓ progression of diabetic kidney disease ↓ progression to end-stage renal disease ↓ CVD

While these findings appear to be a class effect, there are multiple large cardiovascular, heart failure and chronic kidney disease outcome trials under way. Depending on the outcomes of these awaited trials we may see the indication for these medications widen to be used in patients with cardiovascular disease and heart failure without a history of diabetes.

PHARMACOLOGY OF SGLT2I

Empagliflozin, dapagliflozin and ertugliflozin are the available SGLT2i in Australia. There were over one million prescriptions of empagliflozin and dapagliflozin in 2016-2017 within Australia[28] and prescription rates are on the rise. The various formulations available in the market are detailed in Table 3.

Table 3. List of SGLT2i medication available within Australia.

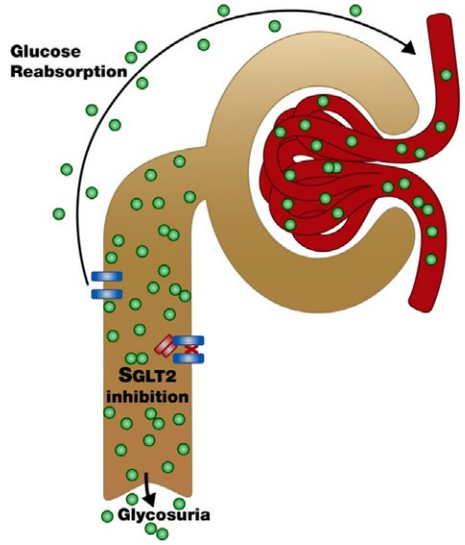
Commercial name	SGLT2i and combinations
Forxiga	Dapagliflozin (PBS July 2013)
Xigduo	Dapagliflozin and metformin XR
Jardiance	Empagliflozin (PBS January 2013)
Jardiamet	Empagliflozin and metformin
Qtern	Dapagliflozin/Saxagliptin
Glyxambi	Empagliflozin/Linagliptin
Steglatro	Ertugliflozin
Stegluromet	Ertugliflozin/metformin
Steglujan	Ertugliflozin/Sitagliptin

Mechanism of action

SGLT2 is expressed in the proximal convoluted tubules of the kidneys and promote the transport of glucose along with sodium from the tubular lumen into the cells[29,30].

Under normal physiological conditions 180 g of glucose is filtered by the glomerulus per day, and all 180 g is reabsorbed. The absorption requires Na^+/K^+ ATPase to generate the driving forces for glucose uptake into the cells. The glucose subsequently exits the cells into the circulation along a concentration gradient. Sodium is co-transported in the same direction ("symported"), from the renal tubules into the cells. Most of the filtered glucose is reabsorbed within the proximal tubule by SGLT2 channels (90%) and a smaller proportion by SGLT1 channels (10%). With overt hyperglycaemia, (normally a value greater than 11.1mmol/L) the reabsorption of glucose by SGLT2 and SGLT1 within the proximal tubule becomes saturated and glycosuria develops. (This reabsorption of glucose is mildly increased in patients with diabetes). SGLT2 inhibitors have a structural similarity to glucose and competitively inhibit the reabsorption of 30-50% of filtered glucose thus promoting glycosuria and natriuresis at a lower blood glucose "threshold"[30,31] (Figure 2). This results in urinary glucose losses of 50-100 g/day[31], equating to around 300 kcal (1255 kJ) and this is often accompanied by a 2.2 to 4.5 kg weight loss within the first 12 months of initiation[32]. Plasma volume and blood pressure are reduced as a result of osmotic diuresis and natriuresis[7]. The HbA1c reduction ranges between 0.5-2% with SGLT2i therapy, and differs with severity of the disease, dosage, baseline glycaemic control and other patient specific factors[6].

Figure 2: Primary mechanism of SGLT2i induced glycosuria. Depicted on the left is SGLT2 mediated glucose reabsorption in the proximal tubule. On the right of the image is SGLT2 inhibition (X) and resultant glycosuria.



These drugs have a rapid onset of action and a prolonged half-life of 12-16 hours. They undergo hepatic glucuronidation and are eliminated through urine and faeces (Table 4). Dose reduction is necessary in mild renal impairment, and they are contraindicated in severe renal impairment (eGFR <30 ml min^{-1} 1.73 m^{-2} for canagliflozin; eGFR <45 ml min^{-1} 1.73 m^{-2} for empagliflozin and ertugliflozin; and eGFR <45 ml min^{-1} 1.73 m^{-2} for dapagliflozin). Drug efficacy is proportional to renal function, with glucosuria decreasing with the progression of renal impairment. Regular renal function monitoring during SGLT2i therapy is recommended[7,33].

Table 4: Pharmacokinetic properties of the commonly used gliflozins[7].

SGLT2i	Dosage range (mg)	Oral bio-availability (%)	Time to peak effect (h)	Half-life (h)	Metabolism	Elimination	Precautions
Dapagliflozin	5-10	78	2	13	Primarily glucuronidation	Urine, faeces	Not recommended with eGFR < 45 ml min^{-1} 1.73 m^{-2}
Empagliflozin	10-25	60	1.5	12.5	Primarily glucuronidation	Urine, faeces	Not recommended with eGFR < 45 ml min^{-1} 1.73 m^{-2}
Ertugliflozin	5-15	70-90	1-2	16.6	Primarily glucuronidation	Urine, faeces	Not recommended with eGFR < 45 ml min^{-1} 1.73 m^{-2}

EUGLYCAEMIC KETOACIDOSIS: AN EMERGING CONCERN

Recently there have been multiple warnings from pharmacovigilance agencies including the Australian Therapeutic Goods Administration (TGA), European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) regarding the potential complication of DKA, especially EDKA associated with SGLT2i therapy[34-37]. Surgical patients are at an increased risk of DKA due to preoperative fasting, surgical stress, intercurrent illness and inadequate management of diabetes medications perioperatively. Numerous reports have emerged describing DKA as a potential complication in the perioperative period. The understanding of DKA in this setting is based on published reports from the primary literature[15-17] and from pharmacovigilance analysis such as evaluation of the FDA Adverse Event Reporting System (FAERS)[38,39], and the pathophysiology has not been entirely elucidated.

For consistency we have designated EDKA as BGL ≤ 14 mmol/L and HDKA (hyperglycaemic DKA) as BGL > 14 mmol/L. The reality is that DKA associated with SGLT2i can occur with a wide range of glucose values (discussed below). A recent systematic review (the largest of its kind) reported 47 cases of SGLT2i linked DKA in the perioperative period[16]. Of these, 42 cases were of the EDKA type and 5 were HDKA. Analysis of The Australian Therapeutic Goods Administration (TGA) database of adverse event notifications on SGLT2i associated DKA (until October 2018) in surgical patients identified 53 reported cases (unpublished data). Twenty-nine of these notifications were of the EDKA type, whereas 20 were HDKA.

Pathophysiology of SGLT2i induced DKA

The pathophysiology of SGLT2 inhibitor associated DKA is complex and it appears the drugs affect multiple effector sites which shift metabolic pathways towards ketogenesis, predisposing to DKA[40].

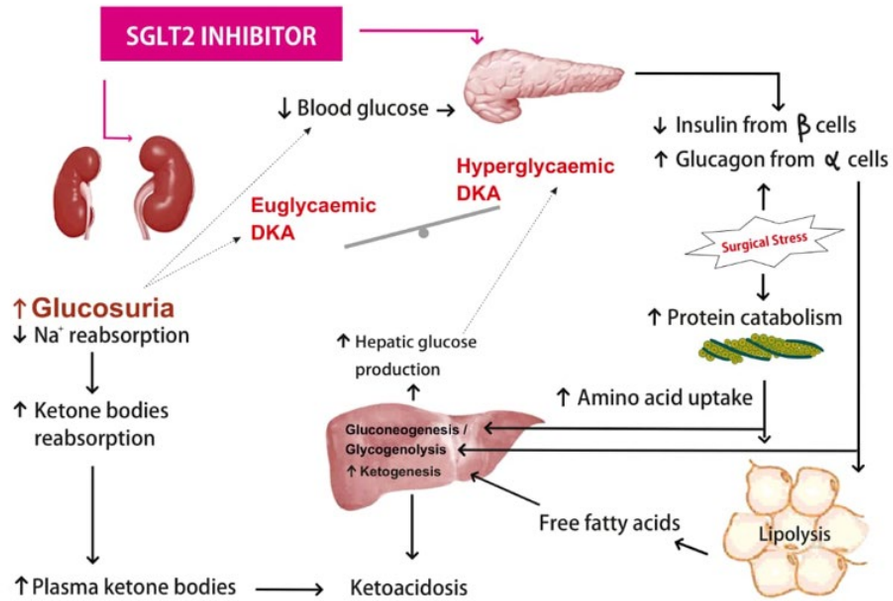
Ketone bodies, namely acetoacetate and ß-hydroxybutyrate as well as acetone, are produced in the liver. They can be thought of as water soluble products of fat breakdown which are easily transportable in the blood, and easily metabolised. Constant production of ketone bodies occurs as does their utilisation by extrahepatic tissues. The normal concentration is the blood is low, but during times of starvation, or in individuals undergoing a low carbohydrate weight reduction diet, ketones become the main mitochondrial energy source. ß-hydroxybutyrate levels in nutritional ketosis induced by very low-calorie diets are typically less than 3 mmol/l. If ketosis is present, further evaluation of the acid base profile to exclude ketoacidosis is required for diagnosis[41]. Note that ketonaemia due to prolonged fasting or very low carbohydrate diets, occurs over a longer duration than in DKA, sometimes over two to three weeks, and is an adaptive process due to a total lack in calories consumed. *In these cases the pH will be norm*al and this *situation should not be confused with DKA*.

The substrate for ketones bodies is Acetyl CoA. In times of high circulating glucagon there is a dramatic amplification of the process of breakdown of fat and the oxidation of fatty acids to Acetyl CoA and thus to increased production of ketone bodies. Such a change in the metabolic profile, from glucose to lipid oxidation and an increase in glucagon-to-insulin ratios has been demonstrated with SGLT2i[42]. SGLT2i has been shown to independently stimulate alpha cells and increase plasma glucagon levels, stimulating lipolysis, hepatic fatty acid oxidation and increased ketogenesis in the liver[15]. This glucagon-to-insulin ratio shift also stimulates glycogenolysis and gluconeogenesis, thus increasing hepatic glucose output[8]. Surgical stress elevates the counter-regulatory hormones adrenaline and cortisol, resulting in insulin resistance and stimulates protein catabolism. This effect enhances the hepatic amino acid uptake and facilitates gluconeogenesis, further increasing hepatic glucose production[43] as well as promoting glucagon secretion and ketosis. Adrenaline, like glucagon, also stimulates hormone sensitive lipase, bringing yet more fatty acids to the party. Lower blood

glucose due to urinary glucose losses exerted by the drug, along with consequent reductions in endogenous insulin may fail to suppress glucagon[17]. There is often a decrease in exogenous insulin administered near the time of surgery.

The plasma glucose level (and thus the DKA presentation as euglycaemic or hyperglycaemic) is determined by a multitude of factors including endogenous hepatic glucose production, dietary carbohydrate, β-cell functional reserve and endogenous insulin secretion, exogenous insulin administration, the degree of insulin resistance and renal glucose clearance due to the SGLT2i mechanism of action[8]. In the kidney, SGLT2i promotes ketone body reabsorption through the reduction of renal sodium re-absorption[15]. This indirectly expands the ketone reservoir, resulting in significant ketoacidosis occurring in the absence of ketonuria[15]. Therefore, urine ketones are not a reliable marker for identifying DKA associated with SGLT2i. Thus, in summary, renal glucose clearance along with elevated ketone bodies, manifests as ketosis with near normal blood sugar levels (Figure 3).

Figure 3: Pathophysiology of perioperative diabetic ketoacidosis associated with sodium-glucose cotransporter-2 inhibitors. Published with permission from the *British Journal of Anaesthesia*.



CLINICAL PRESENTATION OF DKA IN THE PERIOPERATIVE SETTING

DKA can present, preoperatively, during surgery (unpublished observation analysed from TGA adverse events database) or postoperatively, either within hours or up to 5-6 weeks in certain bariatric procedures[16]. Patients present with nausea, vomiting, abdominal pain, tachycardia, altered mental status and dehydration. Bariatric surgery is associated with a higher risk of DKA as a result of the very low-calorie diet modifications imposed before and after the procedure. Intercurrent illnesses, surgical stress, reduced carbohydrate intake, volume depletion, inappropriate handling of SGLT2i including inadequate cessation preoperatively and commencing the medication postoperatively without establishing adequate calorie intake, improper handling of insulin and misdiagnosing type 1 diabetes (T1D) as T2D are some of the known precipitating factors in the perioperative period[16].

Magnitude of the problem

Both EDKA and HDKA have similar clinical and biochemical profile except for BGL values[16]. The mean BGL values noted among perioperative EDKA presentation across 47 cases was 9.5 mmol/L whereas it was 19.0 mmol/L among the HDKA presentations[16]. Non-specific abdominal and surgical site pain together with nausea, vomiting, tachypnoea and a mild acidosis can mimic an otherwise uncomplicated postoperative state. In the

absence of elevated blood glucose levels, EDKA can be easily overlooked. There have been reports where patients with EDKA presentations in the immediate postoperative period were subjected to unnecessary advanced radiological imaging and exploratory laparotomy in an attempt to rule out other differentials such as pulmonary embolism and anastomotic leaks where the diagnosis of DKA was initially missed[44-49].

PERIOPERATIVE MANAGEMENT CONSIDERATIONS OF SGLT2I THERAPY

Measure the blood ketones

Our understanding of the risk of (euglycaemic) DKA with SGLT2i is still evolving. Currently, there are no uniform guidelines for the perioperative management of SGLT2i. The American College of Endocrinology recommends a 24-hour cessation prior to elective procedures, and immediate interruption for emergency procedures[50]. Conversely, recent editorials suggested 48 hours or even longer interruption based on the terminal half-life of 12-16 hours[28]. Some sources recommend withholding for 5-7 days before major surgery[51] and up to 2 weeks for bariatric surgical patients who are on a very low-calorie diet 1-2 weeks preoperatively[15]. In each case, the risk of DKA must be assessed depending on the clinical presentation and balanced against the practical considerations of cancelling surgery if SGLT2i are not deemed to have been held for long enough and the risk of perioperative hyperglycaemia if these agents are held and appropriate alternative therapies are not prescribed. This is a greater risk where these agents are part of a combination tablet.

The DKA risk is lower in healthy patients who are likely to resume oral intake within hours after the intervention, for example a short stay procedure. Minor day surgery procedures may not need any temporary interruption of SGLT2i medication or withheld only on the day of the procedure. A much longer duration of cessation may be needed in surgical patients likely to have delayed oral intake such as cardiac or abdominal surgery or who are taking a low calorie diet such as with bariatric surgery as discussed above. Ceasing SGLT2i for 72 hours or more is appropriate here, but this has logistic implications and requires coordination among anaesthetist, surgeon and endocrinologist. Additionally, when an SGLT2i is prescribed in combination with other agents such as metformin and DPP-IV inhibitors, appropriate strategies should be in place when the combinations are held. The agent in conjunction may have to be re-prescribed separately. Until the postoperative catabolic state is overcome by adequate oral intake, gliflozins should not be commenced[52]. SGLT2i should not be recommenced in the presence of ongoing nausea and vomiting and adequate renal function should be ensured, especially after major procedures that are associated with renal impairment perioperatively. Capillary ketones and glucose should be carefully monitored during the post-operative period and continue to be monitored even after these agents are reintroduced. In patients co-prescribed insulin, dose adjustments should be made with input from the endocrine management team. Sudden perioperative alterations in insulin doses may also precipitate DKA.

Capillary/plasma ketone measurement (such as the Abbott FreeStyle system) is the key factor in identifying DKA during the perioperative period. Other biochemical indices such as blood glucose, plasma bicarbonate, pH and anion gap should also guide management. In the absence of plasma/capillary ketone measurement, it is possible to overlook EDKA or HDKA whilst checking alternate differential diagnoses such as an anastomotic leak or an acute abdomen post bariatric or abdominal surgery, and other medical conditions such as pulmonary embolism. Plasma ketone concentrations (ß-hydroxybutyrate) up to 0.25 mmol/L are common after an overnight fast, and concentrations above 0.3 mmol/L have been considered as significant elevations. Values above 3.0 mmol/l are generally used as a cut-off for diagnosing DKA in any setting[53]. In patients prescribed SGLT2i, perioperative values > 0.6 mmol/L are considered at risk of developing DKA, and >1.5 mmol/l are considered significant for other unwell non-surgical patients. ANZCA has released an alert in this regard[54]. It is worth reiterating that urine ketones are an inferior marker of DKA associated with SGLT2i. The conventional urine testing is based on nitroprusside and measure acetoacetate instead of the more relevant ß-hydroxybutyrate[7]. In addition, increased sodium reabsorption with SGLT2 inhibition results in increased absorption of ketone bodies, thus ketones are more represented in the blood rather than in urine. Standard DKA management with insulin and dextrose applies to both EDKA and HDKA presentations.

In high risk individuals, it may be worth monitoring capillary ketones 4 hourly in the perioperative period until adequate calorie intake is established. Devices with the ability to simultaneously test capillary blood glucose and ketones are now widely available[55].

Awareness of DKA, especially EDKA with ongoing education regarding perioperative ketone monitoring and following institutionalised protocols may improve the perioperative outcome of these patients. In our institution, patients coming for every intervention including colonoscopy are routinely screened for pre-procedure capillary ketones and the further management is rationalised. (Refer to the guidelines at the end of this manuscript).

Maintain the blood volume

In elderly patients prescribed with loop diuretics with known renal impairment, it is imperative to maintain euvolaemia in the perioperative phase as SGLT2i treatment may precipitate volume depletion as a result of its

natriuretic and osmotic effects[56]. Similarly, in older patients on angiotensin-converting inhibitors and angiotensin receptor blockers, SGLT2is may result in hypotension[56]. “Sick day management rules” should be employed both preoperatively and postoperatively when patients are on SGLT2i. Appeals have been made globally to subsidise concurrent glucose-ketone testing meters and testing strips in this patient population[55].

TREATMENT OF SGLT2I ASSOCIATED DKA

Glucose insulin and potassium ± volume

In the event that SGLT2i associated DKA occurs, the medication should be ceased and the patient managed with IV dextrose and an insulin infusion. Treatment duration and dextrose requirement may be greater than that typically required for the management of T1D associated DKA due to the ongoing urinary losses of glucose which occur until the drug is metabolized and eliminated. Hospital and intensive care unit (ICU) stays however have not been shown to be longer than that occurring in cases of DKA unrelated to SGLT2i use[58].

ICU admission may be required depending on DKA severity and involvement of an endocrinologist is strongly recommended. Fluid management and electrolyte corrections should be continued until oral intake is adequately established. Precipitating factors should be investigated and it is recommended that patients undergo T1D antibody testing as a proportion of cases have been identified retrospectively as latent autoimmune diabetes in adults (LADA) or T1D[16,59].

OTHER RELEVANT PERIOPERATIVE ADVERSE EFFECTS OF SGLT2I

Urosepsis

Genitourinary infections are perhaps the most common complication arising out of SGLT2i therapy as a result of increased glycosuria[60]. It is unclear whether there is an increased risk of perioperative infections[28]. Patients undergoing gynaecologic or urological procedures and who are likely to have urinary catheters postoperatively may be at further risk[19]. Some sources even recommend withholding SGLT2i 24-48 hours prior to major surgery in patients at risk of genitourinary infections[7].

Bone fractures and peripheral ischaemia

Other concerns are bone fractures from a possible osteoporotic mechanism or increased falls risk due to blood pressure lowering effects, and an increased rate of lower limb amputations[61,62].

CONCLUSION

SGLT2i therapy is now commonly prescribed for the management of T2D not only for its antiglycaemic effects, but also because of the potential cardiovascular and reno-protective benefits, reductions in heart failure admission, blood pressure lowering effects and associated weight loss. As a result of the increased prescription rates, we increasingly encounter these medications in the perioperative period.

SGLT2i associated DKA is a significant adverse event in surgical patients, with EDKA being the predominant presentation in the perioperative setting. As there is symptom overlap between DKA and the postoperative state, there is the risk that EDKA be overlooked in the absence of elevated blood glucose levels. Known precipitating factors include diet modifications, fasting, surgical stress, intercurrent illness and the improper handling of SGLT2i which are common in the perioperative setting.

A multidisciplinary approach linking anaesthetists, endocrine specialists, the treating surgical team, general practitioners and dietitians should improve successful management. A complete understanding of the precipitating factors, presentation and treatment of DKA is vital in good perioperative management. Bariatric surgical patients may be at an increased risk of DKA attributed to very low-calorie regimens before and after surgery. Institutional guidelines and regular perioperative auditing of the perioperative journey of these patients will mitigate the DKA risk and improve surgical outcomes.

ADDENDUM: GUIDELINES FOR THE PERIOPERATIVE MANAGEMENT OF SGLT2I THERAPY AT THE AUTHORS’ INSTITUTION

“2 days plus day of surgery or match the fast”

It is acknowledged that our understanding in this area is still evolving and that ultimately, management will depend on the clinical discretion of the treating clinicians.

Prolonged withholding of SGLT2i risks loss of diabetic control especially where combination tablets are being held without suitable alterative therapy being instituted. Additionally, cancelling surgery on every occasion when

SGLT2i have not been held would be a significant issue given the high frequency of diabetes amongst surgical patients. However, peri-operative DKA with this class of drug is increasing and whilst more common with the major surgeries listed above, it has been reported even with colonoscopy and angiography. The following guidelines are used at our institution to guide the treatment plan.

General

- SGLT2i to be ceased 2 days prior to surgery and held the day of surgery and through the postoperative period until the patient is eating and drinking normally – this may require an increase in other glucose-lowering drugs during this time.
- Patients who have uncomplicated day surgery/procedures should only recommence SGLT2i when on full oral intake.
- Blood glucose and blood ketones should be checked in the perioperative patient and the medical officer informed if the blood ketone level is > 0.6 mmol/L.
- Strongly consider postponing non-urgent surgery if SGLT2i have not been ceased prior to elective surgery and either blood ketones are > 0.6 mmol/L, or HbA1c > 9.0% as these may be indicators of insulin insufficiency in the perioperative period. A pH value from a simple venous blood sample may assist in deciding whether or not to proceed.

Low risk surgery

For patients on SGLT2i agents or combination therapy who are for low risk surgery, where there is a danger of hyperglycaemia if these agents are held for 48 hours preoperatively, the anaesthetist may use their discretion and withhold the agent for a shorter duration pre-operatively. This would require blood ketone monitoring preoperatively and postoperatively until the patient was eating and clinically stable. Results should be recorded for future auditing.

Patients who are for minor surgery and expected to return to preoperative state early

- To withhold SGLT2i on day of surgery.
- BGL and blood ketone (point of care) to be performed in day of surgical admission or holding bay on arrival.
- Medical officer or anaesthetist to be notified if Ketones >0.6 or BGL>10 mmol/L. If yes, please consider management using insulin dextrose infusion.
- Postoperative:
  - Repeat Ketone testing in recovery (point of care).
  - Consider restarting SGLT2i as soon as commencing oral intake if the patient is physiologically stable.

Patients who are for major surgery (including major abdominal, hepatobiliary, colorectal and cardiothoracic procedures)

- Involve Endocrine team at pre-admission clinic.
- Only other difference in management from above may be as follows;
  - Hold SGLT2i for at least 2 days prior to surgery and day of surgery.
  - Consider withholding SGLT2i until physiologically stable and close to discharge and if there has been no elevation in plasma ketones. Manage with insulin and dextrose in the postoperative period.
- As these patients are at higher risk of Euglycaemic Diabetic ketoacidosis, need higher index of suspicion and regular monitoring (4 hourly BGL and ketones).
- Early institution of dextrose insulin infusion helps immensely.

Colonoscopy and surgical procedures that require bowel preparation

The bowel preparation for colonoscopy usually include 4 phases: phase 1: low fibre diet for 2-3 days; phase 2: clear fluids the day before the procedure; phase 3: commencing bowel emptying with a cathartic the evening before; phase 4: fasting for 2-10 hours depending on the time slot for the procedure.

Cease SGLT2i the day when low fibre diet starts. Recommence at regular oral intake. Educate the patient regarding sick day management to check for capillary ketones/seek medical help if they feel unwell.

For complex bowel preparation and diet/fasting regimes, and bariatric procedures

A “match the fast” approach may be applicable matching the time of diet restriction with gliflozin withdrawal with inputs from endocrinologists. At our institution, a very low calorie diet is started 4 weeks before surgery and SGLT2i should be stopped prior to the diet starting. In this situation, no compensatory increase in other diabetes medication may be needed as glycaemic control should improve on the very low calorie diet.

Managing combined preparations of SGLT2i (for example, SGLT2i and metformin or SGLT2i and gliptins)

The appropriate approach will depend on the patients’ baseline glycaemic control. In patients with good or fair control, stopping the SGLT2i or combination tablet combined with a healthy diet without excessive carbohydrates prior to surgery may be adequate. In patients with poorer control, consideration should be given to prescribing the non-SGLT2i medication in the combination tablet separately or even prescribing or increasing the dose of other diabetes medications including insulin. This approach may be sufficient to maintain adequate blood sugars preadmission.

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Anaesthesia and immune modulation

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INTRODUCTION

The effect of perioperative medication (local and general anaesthetic agents, steroids and antibiotics) on white blood cell populations, and specifically to monocyte and dendritic cell immune profile and apoptosis is of particular interest. The impact of these other external modulators of the immune system is important when considering changes to immune cell numbers and function during intraoperative cell salvage (ICS) and allogeneic blood transfusion (ABT). To generate a more complete measure of the immune response it is important to evaluate both monocyte and dendritic cell numbers and function[1,2].

It is essential to consider that associations with increased nosocomial infections and organ impairment during surgery and anaesthesia may be the consequence of overall immunological changes (immune modulation) rather than the activation of a specific pathway[3]. The degree of this immune modulation correlates with the extent of the surgical trauma and other factors, such as comorbidities[4], the type of surgery and disease process (for example, cancer surgery), coexisting infection, impaired nutritional status[5] and transfusion related immune modulation (TRIM)[6-13].

During the perioperative journey, changes to various types of white blood cells (neutrophils, monocytes, T lymphocytes and B lymphocytes), as a result of immune modulators (surgery, anaesthetics, comorbidities,

ICS, ABT), are potentially associated with adverse outcomes. Furthermore, the prognostic value of markers for example Lymphocyte-to-Neutrophil ratio (LNR), Platelet-to-Lymphocyte ratio (PLR) and Lymphocyte-to-Monocyte ratio (LMR), have been well established during assessment of cancer outcomes[14,15]. Original research identified an association between TRIM and adverse outcomes related to infection and cancer recurrence[16]. The question now remains if immune cell ratios (for example, LNR and LMR), currently used as prognostic indicators during cancer surgery, may also be used to predict infection risk after surgery, anaesthesia, ABT and ICS transfusion.

The purpose of this chapter is to summarise the evidence associated with changes to the immune response during surgery, anaesthesia and transfusion.

THE IMMUNE RESPONSE DURING SURGERY AND TRAUMA

The human immune response against infection involves cellular and humoral responses, both innate as well as acquired. Many studies assessed either functional or cellular immune response and often very particular individual end points within this spectrum[3].

Worldwide surgical infection risk, when increased through immune modulation, has major implications. Data from a prospectively collected trauma registry (January 1996 to December 1997, n=30,303) demonstrated that sepsis occurred in 2% of patients[17]. A significant increase in mortality (23.1% versus 7.6%) was seen in septic patients compared with non-septic patients as well as increased length of stay in hospital (34.1 versus 7.0 days) and ICU (21.8 versus 4.7 days). Pneumonia was the leading cause and Injury Severity Score an independent predictor, of sepsis in trauma[17].

Invasion of a body by a pathogen triggers an inflammatory response. Bone marrow is stimulated to produce neutrophils. These are attracted to the site of infection, followed by the release of cytokines and the recruitment of lymphocytes, mast cells and basophils. Subsequent phagocytosis of bacteria by neutrophils is part of the early (6-12 hours after initial injury) inflammatory response of innate immunity. The average half-life of a neutrophil in circulation is 6 hours[18].

Monocytes are part of the later immune response, activated in response to chemotactic factors released by neutrophils. Increased numbers of monocytes are seen as early as 24 hours after an initial insult, but most significantly 3 to 7 days thereafter[19]. A low monocyte count can be caused by acute infections, stress or treatment with glucocorticoids[20].

Classical dendritic cells (DCs) are bone marrow-derived leukocytes that develop from a common myeloid progenitor as granulocytes and macrophages, even though the exact mechanism is still unclear[21]. DCs play a unique and specialised role positioned between the innate and adaptive immune responses[21-23]. They are potent antigen-presenting cells that initiate and regulate the adaptive immune response. DCs phagocytose pathogens and process antigens for presentation to the adaptive immune system. Maturation of DCs is associated with upregulation of CD80 and CD86 expression and secretion of pro-inflammatory cytokines (for example TNF-α and IL-12)[22].

Natural killer (NK) cells are lymphocytes that originate from the same line of cells as T lymphocytes and B lymphocytes. NK cells respond mainly to eliminate cells infected with viruses and tumor cells[24]. In addition, NK cells secrete cytokines such as IFN-γ and IFN-α and enhance the immunological function of macrophages and dendritic cells[24].

Tumor-associated macrophages (TAMS) participate in the activation and maintenance of the chronic inflammatory process of several tumors[1]. The importance of TAMS in cancer has been well documented[1]. In 1992 Mantovani et al commented that tumor progression may be associated with 1) the number of monocytes, 2) their state of activation and 3) the properties of the neoplastic cell[1].

One of the first responses of the innate immune system to a foreign pathogen is phagocytosis. Foreign proteins derived through phagocytosis are processed and presented onto major histocompatibility complex class II molecules (human leukocyte antigen-DR or HLA-DR) on the surface of dendritic cells. Upregulation of HLA-DR and increased antigen presentation supports the clearance of pathogens[25] and the induction of a T-cell response[26]. HLA-DR expression on monocytes consistently correlates with infection and clinical outcomes. Patients who develop sepsis after trauma have lower HLA-DR plasma levels (between days 2 and 14 from admission)[27]. HLA-DR monocyte expression is altered for 2 weeks following severe injury[28] and a reduction is associated with increased mortality[29].

Adaptive immune responses are both humoral (mainly B-cell) and cell (mainly T-cell) mediated. The recognition of select antigens activate these immune responses[19]. The primary human immune response provides protection against lipopolysaccharide (LPS), an endotoxin contained in cell walls of gram-negative bacteria[19]. To complicate matters further, cytokines released by host cells act in both pro-inflammatory and anti-inflammatory ways. In addition, the activation of T helper 1 cells lead to activation of macrophages and cytotoxic T cells and T helper 2 cells to the activation of B cells and plasma cells and a humoral immune response, including the production of IgM, IgA, IgE and IgG[19].

POTENTIAL CAUSES OF IMMUNE SUPPRESSION DURING SURGERY

Anaesthetic drugs

Many surgical and anaesthetic factors influence humoral and cellular immune responses during the perioperative period[30]. It is known that anaesthetic drugs may affect the cellular immune response[31,32] in addition to other potential modulators of the immune system including pain, psychological stress[33], surgical inflammation, hypotension and hypothermia[34]. Various authors have investigated the suppression of immune responses related to commonly used anaesthetic drugs. Studies specifically assessing monocyte numbers are rare and those found were mostly related to cancer outcomes and not infection risk[14,35]. Few studies identified the effect of general anaesthesia on lymphocyte numbers. A reduction in immune cell populations (lymphocyte cells and T-helper cell numbers) may result from an attenuation of the stress response to surgery through induction of general anaesthesia and the type of analgesia may be an important factor (that is, opioid or neuraxial anaesthesia)[36].

The immunological consequences of the surgical stress response when comparing opioid and neuraxial analgesia during general anaesthetic remains controversial[36,37]. When neuraxial analgesia was added to general anaesthesia, beneficial functional profiles (NK cell activity, IL-2, IL-6, IL-8, IL-10, IL-1β and IFN-γ[38,39]), reduced systemic infection rates[40] and improved prognosis was seen[41,42]. The debate between total intravenous anaesthesia (propofol TCI), volatile anaesthesia and regional anaesthesia, and cancer related immunological consequences, is ongoing and a thorough report of this topic is beyond the aim of this review. However, various anaesthetic drugs may play a role in immune related adverse outcome.

Data from ex vivo human studies suggest that sevoflurane and isoflurane[43] induce lymphocyte apoptosis. When studying 3 groups of patients during inguinal hernia surgery (epidural, sevoflurane and propofol anaesthesia), increased apoptosis of monocytes were seen 6 hours after surgery in the sevoflurane and epidural compared to the propofol groups[35]. Jia et al (2015) compared 3 groups (sevoflurane, propofol and sevoflurane plus propofol anaesthesia) and confirmed the most significant lymphocyte apoptosis occurred in the sevoflurane only group[44]. Neutrophil numbers return to normal levels after extubation, even though a significant reduction in neutrophil, monocyte and lymphocyte counts are seen after induction of general anaesthesia[45]. Peripheral lymphocyte apoptosis during total knee replacement surgery lasts up to 7 days independent of the type of anaesthetic (general, spinal or spinal-epidural)[46]. Propofol may be less detrimental to the phagocytotic ability of human polymorphonuclear immune cells than isoflurane anaesthetic[47], cause less lymphocyte apoptosis[48] and may protect against neutrophil apoptosis[49]. Woo et al found both propofol and desflurane favourable when considering CD4+/CD8+ T cell ratio in the perioperative period during breast cancer surgery[50]. Ketamine reduces the differentiation of monocytes into immature dendritic cells[51] and induces apoptosis in human lymphocytes[52], while both morphine and ketamine may affect the CD4+/CD8+ ratio in vitro[53].

More studies identified the effect of general anaesthesia on lymphocyte and monocyte function. When Matsota et al (2018) studied 3 groups of patients who received either epidural, sevoflurane or propofol anaesthesia, IL-6 was increased in the propofol group at the end of surgery and TNF-α reduced 6 hours after surgery in the sevoflurane and epidural groups[35]. Ketamine suppressed the production of IL-2 and IFN-δ by activated T lymphocytes in patients with refractory cancer pain in vitro[54]. Lignocaine and bupivacaine both attenuated macrophage TNF-α secretion[55], while lignocaine may affect in vitro secretion and gene expression of proinflammatory cytokines (for example, IL-8)[56]. Propofol-remifentanil anaesthesia preserved NK cell cytotoxicity better compared to sevoflurane-remifentanil anaesthesia in patients undergoing breast cancer surgery[57]. The activation of pro-inflammatory cytokines, including TNF-α, IL-6 and IL-8 by neutrophils induced by lipopolysaccharide (LPS) is attenuated by remifentanil[58]. Opioid-induced or opioid-withdrawal-induced immunosuppression during remifentanil based anaesthesia was associated with an increased incidence of surgical site infection[59].

Anaesthetic drugs have been implicated in studies assessing prognosis after cancer surgery. Xu et al found improved cellular immunity and prognosis in patients with non-small cell lung cancer when epidural analgesia was added to standard general anaesthesia during an assessment of the differentiation of T lymphocyte subsets: CD3+, CD4+, CD4+/CD8+ and natural killer cells CD56+[60]. On the other hand, the opioid sparing effect of spinal anaesthesia (during radical cystectomy for bladder cancer) compared to general anaesthesia did not provide a significant change in mortality in a retrospective cohort (n=195 study group, n=195 control group) study by Weingarten et al (2016). These authors did however report an association between blood

transfusion and increased mortality[61]. In a retrospective assessment of associations with survival in patients who had resection of pancreatic adenocarcinoma (n=144) in 2015 Call et al (2015) identified a survival benefit in those who received dexamethasone and epidural analgesia as part of their anaesthetic care[62].

Steroids

Dexamethasone as a corticosteroid drug holds immune suppressive properties. Dexamethasone is currently often used as a prophylactic antiemetic agent during general anaesthesia. The exact impact of dexamethasone on outcome, specifically related to the subsequent incidence of surgical infection, is however still unclear[40,63]. Corticosteroids decreased both monocyte and T-cell function[64]. The activation of monocytes plays a major role in graft rejection[65,66]. In order to avoid rejection and graft loss after liver transplant long term immunosuppression is required. The use of steroids is still common for this purpose[65].

Antibiotics

The immune suppressive implications of antimicrobial drugs is a large and growing field of study[67]. Macrolides, tetracyclines, polymyxins, sulfones, antifungal, antiviral and antiparasitic drugs are among those with known immune modulatory effects[67].

Surgery

Immunoparalysis after a surgical insult was identified by studying TNF-α, low monocyte surface mCD14 and HLA-DR expression ("a hallmark of altered immune status in patients with a systemic inflammatory response syndrome")[68], impaired lymphocyte function and high IL-10 levels in response to endotoxin (LPS)[69,70,64,71]. After severe trauma, significant changes to IL-6, TNF-α, monocyte IL-12 production and monocyte HLA-DR expression correlated with risks of postoperative infection, sepsis and death[72,73]. Early in the post-operative period an increase in NK cells, neutrophils (at 1h), $CD14^+$ (at 24h) and monocytes (at 72h) are seen, followed by a reduction in $CD4^+$ and $CD8^+$ T cells over the following 24h. All values returned to normal after 6 weeks[74].

Comorbidities

Patients may already have other comorbidities that present an immune compromised state (for example, HIV infection, additional opportunistic infection, neoplasm and taking regular medications) when presenting for surgery[75]. The severity of the disease state in patients with HIV/AIDS is classified according to $CD4^+$ lymphocyte counts and organ involvement and may predispose these patients to opportunistic infection or neoplasm. Blood transfusion in patients with advanced HIV infection increases the HIV viral load[76,77,4]. Patients awaiting liver transplant may be immune compromised as a result of liver disease or DM as identified through neutrophil impairment[78]. Patients with renal failure experience significant immune cell changes. Monocyte, neutrophil, and dendritic cell abnormalities are directly linked with infection risk in this patient population[79]. Corticosteroids, antibodies, antiproliferative/antimetabolic drugs, and calcineurin inhibitors are 4 groups of immune suppressant drugs used to prevent rejection of a transplanted organ[4]. These drugs mainly inhibit lymphocyte and macrophage function and may result in increased risk of infections[80]. Immune compromise in cancer patients, resulting from the primary cancer or secondary effects on nutrition, catabolism and related medication, may result in a susceptibility for opportunistic infection[4].

TRIM

TRIM is defined as a delayed (>24 hours), immune (suppressive) response after allogeneic blood transfusion. The associated effects attributable to TRIM include cancer recurrence, postoperative infection and virus activation[6-13]. The association between allogeneic blood transfusion, altered immune function and risks of nosocomial infection has been studied widely[6,11,12]. Allogeneic transfusion followed by LPS stimulation reduces TNF-α induction capacity and increases IL-10 production[81].

Blood transfusion is an independent risk factor for ventilator associated pneumonia in ICU[82] and associated with subsequent ICU acquired blood stream infection[83]. Nosocomial infection rates are higher in transfused compared to non-transfused ICU patients[84], even when corrected for illness severity scores[85,86]. In a retrospective comparison between autologous and allogeneic blood transfusion Duffy et al found a statistically significant higher odds ratio towards post-operative infection rate in the allogeneic group of 2.37 (95% confidence interval (CI) 1-6-3.6, $P < 0.0001$)[87].

Muszynski et al (2012), considered the implications of both blood storage time and method on monocyte function and immunity during allogeneic blood transfusion. During critical illness, a period of hyperinflammation was followed by subsequent reduced innate immune responsiveness (reduced TNF-α and increased IL-10) and increased risk of nosocomial infection[88]. A similar modulation of monocyte and overall inflammatory response was confirmed after stored ABT[88]. An in vitro study by Biedler et al (2002), confirmed that stored allogeneic whole blood resulted in significant TNF-α depression and IL-10 induction compared to fresh allogeneic blood[89].

THE PERIOPERATIVE CONSEQUENCES OF IMMUNE SUPPRESSION

Infection

Alterations of the immune system after trauma and surgery result in activation of antigen-presenting cells such as monocytes and dendritic cells[90] as well as HLA-DR expression rate and the subsequent susceptibility to postoperative infection[91].

Suppression of both acquired and innate immunity, noted in trauma patients, results in nosocomial and other infection risks[92]. The inability to produce TNF-α after ex vivo stimulation with LPS was studied to assess the innate immune responsiveness during critical illness[88]. This reduction of TNF-α and increase in IL-10 was associated with immune suppression and increased risk of nosocomial infections[69,88,93]. In this context the term "immunoparalysis" describes the reduced ability to produce TNF-α and monocyte surface expression of HLA-DR in response to LPS and is associated with life-threatening infectious complications[69]. This "hyporesponsiveness" occurs during surgery, peak at the time of ICU admission after surgery and trend back to normal within 24 hours after surgery[69]. Monocytes, T lymphocytes, activated B lymphocytes and macrophages in liver, lung, kidney and myocardium, secrete IL-10[69]. IL-10, detectable 7 hours after monocyte activation by LPS, reached a maximum at 24-48h and subsequently inhibit the monocyte secretion of IL-6, IL-8 and TNF-α[94]. A decrease in cytokine production by monocytes was seen during severe infection in response to LPS stimulation[95]. The risk of late nosocomial infection and a shorter more uncomplicated ICU stay is linked to the in-ability to produce TNF-α, IL-6, IL-8 and IL-10[69] and impaired monocyte IL-12 production to the severity of postoperative sepsis[96]. The consequences related to nosocomial infection risk as a result of immune suppression are frequent and serious[31,97,98].

Both cellular (numbers of lymphocyte sub-populations) and functional immune cell responses are important during surgery to protect against nosocomial infection. If the adaptive immune response is impaired through a reduction in proinflammatory lymphocytes this may result in a higher incidence of infection and postoperative complications[36,92,99,100]. An increase in leukocyte and a reduction in lymphocyte numbers occur within a perioperative period until 5 days after surgery[99,101,102]. TAMS participate in the activation and maintenance of the chronic inflammatory process of several tumors[1], and neutrophils as the first line of defence against microbial pathogens[103].

Munford et al (2001) suggested that the normal protective immune response may sometimes act in a suppressive way that allow bacterial, viral and fungal infection to progress. This system relies on a balance between pro-inflammatory and anti-inflammatory processes. Pro-inflammatory mechanisms include activation of leukocytes, vascular endothelium transudation of fluid into tissue spaces and transfer of leukocytes to the site of injury. These mechanisms promote the human defense against infection. Pro-inflammatory mediators include TNF-α, IL-1β, interferon, chemokines and bioactive lipids (leukotrienes, thromboxane and platelet-activating factor)[92]. The anti-inflammatory process, on the other hand, inhibits the production of these mediators and impair phagocyte activation. Anti-inflammatory mediators include IL-4, IL-6, IL-10, IL-11, IL-13, transforming growth factor, catecholamines, prostaglandin E2, glucocorticoids, α-MSH, IL-1 receptor antagonist (IL-1R α) and soluble TNF receptors[92].

Inflammation during surgery reduces the capacity of monocytes to produce TNF-α, IL-1α and IL-1β[104]. Serious injury results in increased IL-12 production and a shift towards increased Th-2 cells as well as an increase in IL-4 and IL-10 that inhibit Th-1 function[100]. Patients who developed sepsis often produced less TNF-α, IL-1β and IL-6[105,106]. A reduced resistance to infection and/or response to LPS stimulation was shown when major injury and surgery led to increased Th-2 lymphocyte production and reduced IL-12[100], changes to monocyte/macrophage proinflammatory (for example, TNF-α release) and antigen presenting functions (for example, IL-10) and apoptosis of immune cells[2]. An inability to produce TNF-α during acute illness in response to LPS exposure is an early predictor of increased risk for nosocomial infection and mortality in critically ill patients[107].

MEASURING IMMUNE SUPPRESSION

A large volume of evidence exists where various different individual functional mediators and cytokines were studied to describe the mechanism of action associated with immune suppression during surgery and anaesthesia, including monocyte, macrophage and T lymphocyte function, monocytic cytokine secretion, monocytic HLA-DR and CD86 expression (through quantitative flow cytometry), T lymphocyte cytokine profiling and many more[2].

Changes to monocyte proinflammatory (for example, TNF-α release) and antigen presenting functions (for example, IL-10), lymphocyte apoptosis and the response to lipopolysaccharide (LPS) may represent the downregulation of the immune system after stressors for example trauma, injury and blood loss[2]. Changes to monocyte function rather than numbers, specific to the release of tumor necrosis factor TNF-α, HLA-DR

expression and Il-10 release has been noted in association with surgical infection risk[92]. Changes to monocyte numbers**,** specifically LMR were studied in association with long term surgical outcome and cancer recurrence[5].

MEASURING IMMUNE CELL NUMBERS: LMR AS PROGNOSTIC INDICATOR TO PREDICT IMMUNE RELATED ADVERSE OUTCOMES

Studies assessing the numbers of neutrophil and monocyte populations in the perioperative period are surprisingly rare, especially considering the enormous volume of studies that have focused on immune cell function. A decrease in immune cell numbers occurs when the infectious process exhaust the supply of these cells, in other words when cells are transferred from the circulation into infected tissues faster than they can be replaced[19]. Even though the importance of functional studies cannot be denied, these may be of less value if essential subpopulations of immune cells, responsible to produce this functional response, are significantly reduced.

During a literature search to study the normal changes to monocyte numbers within the perioperative period, few applicable studies could be found. The association between anaesthetic drugs and cell apoptosis in vivo and/or the relationship between apoptosis and postoperative infection risk are both topics where knowledge gaps exist.

Recently, investigations have focused on basic cell number ratios, that is, LNR, Neutrophil-to-Lymphocyte ratio (NLR) and LMR ratios, and their association with cancer recurrence and survival after cancer surgery[14]. Literature to assess basic cell number ratios and changes during the immediate surgical time, particularly in association with infection related adverse outcome, could not be found. When considering the importance of an adequate monocyte response during surgical stress and the potential for subsequent infection, it seems likely that these ratios may be useful prognostic indicators.

A differential full blood count (which includes a monocyte and neutrophil count) is routinely undertaken during the standard preoperative anaesthetic assessment for major surgery[18,19]. It is a relatively simple, fast and economical test compared to detailed functional humoral and cytokine testing that require specialised and expensive equipment. LMR, LNR and NLR can be determined from the differential full blood count[108].

Many authors have studied various ratios of immune cells in association with outcome measures. NLR represents a validated independent risk factor when assessing overall survival in patients with non-metastatic renal cell carcinoma[109]. Hutterer et al reported LMR as an independent prognostic indicator for poor outcomes when cancer-specific survival was studied as the primary outcome measure in nonmetastatic renal cell carcinoma (n=678 over 10 years)[110].

Leukocyte cell number changes are apparent after thoracotomy and lung cancer surgery. As early as 1977 Roberts et al found lymphopenia to be associated with metastatic disease in bronchial cancer[111]. In 2017 Yuan et al confirmed an association between Neutrophil-to-White blood cell Ratio (NWR), Lymphocyte-to-White blood cell Ratio (LWR), Monocyte-to-White blood cell Ratio (MWR), NLR, Monocyte-to-Lymphocyte Ratio (MLR) and Platelet-to-White blood cell Ratio (PWR) and poor overall survival in patients with curatively resected non-small cell lung cancer[15]. In patients with lung cancer a lower pre-treatment lymphocyte count was associated with poorer prognosis[112] and lymphocyte count decreased in the early postoperative period[99].This is hypothesised to be due to the consumption of leukocytes and proliferation of lymphocytes as a subsequence of the adaptive immune response[99,101]. Abnormalities in lymphocyte count (reduced T-helper and B-lymphocyte numbers) were previously identified in patients with lung cancer[101]. These changes in lymphocyte subsets were also associated with disease progression and the risk of opportunistic infection[113]. Hai et al studied 433 patients after lobectomy for lung cancer and found postoperative elevated monocyte count was an independent poor prognostic indicator[114].

Li et al in 2012 did the first study using LMR as a prognostic marker in patients with diffuse large B-cell lymphoma undergoing chemotherapy. They confirmed baseline LMR, as surrogate biomarker of the immune microenvironment and as a prognostic factor[115]. Porrata et al in 2012 similarly found LMR at the time of diagnosis, was an independent prognostic indicator for survival in patients with Hodgkin's lymphoma[116]. In 2014 Temraz et al published a retrospective analysis where, a small group (n=68) with transitional cell carcinoma of the bladder were included. This group found that an elevated preoperative LMR was associated with a longer time to treatment for recurrence and overall survival compared to those with a lower preoperative LMR[117]. Preoperative LMR predicts clinical outcome in patients with stage III colon cancer undergoing curative resection[118]. In a landmark study by Chan et al in 2017 a low LMR (<2.85 cut off point) was a significant predictor of poorer outcome in a combined series of prognostic indicators associated with older age, higher tumor and lymph node grading and reduced overall survival[14]. Furthermore, these authors found LMR was a superior prognostic marker compared to previously studied NLR and PLR to predict overall survival after curative colorectal tumor surgery[14]. LMR also has prognostic significance for soft tissue sarcomas[119]. Sierzega et al (2017), showed a high NLR and low LMR were associated with an unfavourale prognosis in resectable pancreatic cancer[120].

A significant reduction in lymphocyte numbers are seen during total knee replacement surgery, in particular $CD3^+/8^+$ T lymphocytes and to a lesser extent $CD3^+/4^+$ and $CD19^+$ cells, that lasts for up to 7 days after surgery[46]. This reduction was not evident for NK cells ($CD16^+/56^+$). In addition, a significant increase in lymphocyte apoptotic changes, independent of the type of anaesthetic was identified[46]. Wang et al found no significant difference comparing propofol and etomidate in patients with septic shock, specific to CD8+ levels and CD4+/CD8+ ratios[121]. Naess et al studied NLR and MLR in patients admitted to hospital with fever. NLR and MLR were higher in patients who developed bacterial infections and NLR significantly higher in those who developed septicaemia[122]. No studies were found where the normal LMR ratio was studied, before or after surgery (and ABT and ICS), to assess the implications of immune suppression and subsequent risk of nosocomial infection.

CONCLUSION

A healthy lymphocyte response (cellular and humoral) is essential to ensure adequate protection against infection after surgery. When other known immune modulators, including transfusion, anaesthesia, surgery and medications impair this immune response the risk of developing nosocomial infection increases. To date, there has been a focus on functional immune modulation, but a knowledge gap exists regarding the role of perioperative lymphocyte ratios (for example, NLR and LMR) and their association with surgical infection risk.

The perioperative changes to various types of lymphocytes as a result of immune modulators, the associated adverse outcomes, and the value of LMR as an indicator for immune health and subsequently as prognostic indicator to predict postoperative infection risk should be considered in future research. Anaesthetists have an important role to play in future research regarding the impact of anaesthesia and transfusion on the perioperative immune response and related adverse outcomes.

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Ob/Gyn

Role of simulation in obstetric anaesthesia training

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Role of simulation in obstetric anaesthesia training

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INTRODUCTION

Medical education has traditionally used the teaching approach of the Halstead "apprenticeship model". This 1921 model of "see one, do one, teach one" was primarily focussed on transfer of skills, aimed at individual groups of providers such that nurses only learned with nurses and doctors only learned with doctors. Apprenticeship relies on the relationship of the trainee and supervisor as well as an adequate number of cases and hours of training. Present-day issues around hours, reduced number of particular cases as well as evolving modern best practice evidence-based teaching methods have led to healthcare and clinical educators moving away from solely relying on this "apprenticeship model".

Clinical education experts recognise that training is not purely about individual staff knowledge and skills. Best practice encompasses communication and multidisciplinary team training to foster a culture of teamwork and excellence resulting in safe, high-quality care. Education globally is now challenging the traditional apprenticeship model with simulation emerging as a safer and more effective methodology for training of healthcare professionals in skills, communication and teamwork. This article provides an overview of current best practice simulation-based education (SBE) and the arguments for incorporating SBE into obstetric anaesthesia training and supervision.

What is clinical simulation?

Simulation is defined as the most accurate possible representation of a situation and is "a technique to replace or amplify real experiences with guided experiences that evoke or replicate substantial aspects of the real world in a fully interactive manner[1]". Simulation has long been used in high-risk industries like the airline industry, space exploration, defence forces and the nuclear industry. Would you get on an airplane if you knew the pilot, crew and staff had not spent time in dealing with high-risk situations in a simulated setting? Simulation in healthcare, which is both complex and complicated, is much the same.

In a simulation, real patients are not involved so that practice and learning take place without any risk to patients. SBE is any educational activity that utilises simulation to replicate clinical scenarios to achieve educational goals through experiential learning[1,2]. SBE is one educational method or tool among many and while highly useful it should be part of a broader educational "toolbox".

SBE can take many forms and can be categorised according to the degree of clinical realism or fidelity.

High-fidelity simulation (HFS) uses "full scale computerised patient simulators, virtual reality or standardised patients that are extremely realistic and provide a high level of interactivity and realism for the learner"[3-5].

Medium-fidelity simulation (MFS) uses "manikins or task trainers that offer breath sounds, heart sounds, bowel sound or simulated blood with less of a degree of realism and interactivity"[3-6].

Low-fidelity simulation (LFS) is defined as "experiences such as case studies, role-playing, using partial task trainers or static mannequins to immerse students or professionals in a clinical situation or practice of a specific skill"[3-5].

These traditional categories are also closely linked to the cost of the simulation (high, medium and low-cost simulation) and the assumption that high-cost simulation equates with high-fidelity simulation. The view that high cost, high technology models are superior is being challenging by academics in the field who are questioning whether fidelity is fundamentally linked to the model or to the ability of participants to suspend reality and immerse themselves in the simulation. This later situation can be done with fairly simple, low-cost (traditionally low-fidelity) simulation[7].

In simulation, there is a clear focus on communication within a team and an individual's and team's thinking and clinical reasoning – "learning why someone did or did not do something". Simulation can be confronting to participants as it can uncover both knowledge and performance gaps. This challenges practitioners but the focus is improving performance and incrementing knowledge, often something that can be challenging in a busy clinical environment. The key to reduce risks to participants and guarantee participants can securely immerse themselves in a simulation is to ensure psychological safety at the time. This maximises learning and engagement.

The healthcare workforce often does not have time, and it may not be appropriate, to discuss at the bedside with each other or explicitly learn. Simulation aims to provide a safe space to both *do* and reflect or *debrief* and teaches participants *how* to reflect, debrief and talk with each other. Learning from debriefing has significant impact on culture and communication with the focus often being on patient quality of care and safety as well as training. It provides a way to learn in a safe environment away from a real patient and to then reflect on what has been learned to gain an understanding of systems and human actions and be able to safely manage a similar situation should it arise in the future. This is particularly useful for training for rare and uncommon critical incidents such as difficult tracheal intubation in a pregnant woman or profound hypotension due to a gas embolism in a patient undergoing laparoscopy.

SBE scenarios are environment dependent and can involve entire teams working together such as anaesthetists, obstetricians, midwives, surgical and anaesthetic nurses, and theatre technicians in a maternity hospital. This allows all members to learn how to work effectively together. Simulation is more than skills training. It aims to create an open culture and focuses on team-based learning. Learning as a team allows us to learn as we practice in real life and uncover the issues needed to provide the best care for patients. Simulation helps participants learn about themselves and others, not just how we do things but why we do or do not do things and how to communicate effectively within a team. All are critical to providing best practice quality safe patient care.

"In situ" simulation refers to simulation in the clinical space. This form of simulation has some clear benefits over a simulation centre or laboratory such as enabling evaluation and troubleshooting of systems in the real clinical space. The term "translational simulation" has been proposed for this type of simulation[8]. In situ simulation facilitates the development and implementation of new systems such as introduction of new equipment or an Electronic Medical Record (EMR) to see how they would perform in real life and iron out any issues before real world implementation. In situ or translational simulation is more than just a teaching tool because it can be used to test systems and improve the quality and delivery of healthcare in the actual clinical space[8].

Advantages of simulation-based education

If implemented correctly by using the right tool, right task and right teaching many potential benefits of SBE exist[9]. Broadly these include:

- Adequate exposure to key scenarios and skills despite progressive restriction on work hours. Residents and registrars within Australia now strictly only work 40 hours per week reducing exposure to clinical scenarios and procedures.A method for teaching clinical decision making and psychomotor skills in a way that promotes reflective learning, in accordance with the principles of adult educational theory, in an environment that is safe for both patient and provider.
- Exposure to high-risk, low-frequency, error-prone scenarios that may require specialised training such as anaphylaxis, eclampsia, maternal collapse, amniotic fluid embolism, trauma, trocar or Veress needle injury at laparoscopy.

- Practice of both skills and behaviours within actual care delivery teams, to eliminate silos, improve the quality of communication, and decrease errors without impact on patient safety. This can apply to multiple simultaneous emergencies which can often occur in a busy hospital.
- A unique opportunity to evaluate new devices, larger systems and processes, as well as how an individual performs within the system. Particularly useful with introduction of robotic surgical devices, EMR.

Simulation-based education has advantages over opportunistic learning, as clinical events can be scheduled, observed and repeated to consolidate learning. It also facilitates deliberate practice, enhances transfer of theoretical knowledge to the clinical context and eases transition into the workforce for more junior staff or those returning from extended leave[10]. Healthcare requires a safe functional multidisciplinary team, but inadequate communication can cause errors and inefficiencies in care. Structured information exchanges can improve communication, and SBE provides an ideal environment for learning clinical and teamwork skills[10,11]. Additionally, in situ SBE may reveal system issues under safe circumstances[12].

Communication and teamwork deficiencies have been identified as major contributors to poor clinical outcomes in birthing units. In response to these findings, multidisciplinary SBE has been used to focus specifically on skills training for teams[11].The evidence demonstrates that multidisciplinary and multi-professional SBE team training minimises poor outcomes by focusing on the elusive teamwork skills that cannot be taught in a didactic setting or to individuals alone. This may also detect latent system errors in existing or new units, to rehearse complicated procedures (*surgical dress rehearsal*), and to identify knowledge gaps of maternity teams[13].

SIMULATION IN ANAESTHESIA

Australian anaesthesia training has established links with simulation over more than two decades. The first facilities in Australia and New Zealand opened in opened in the mid-1990s. World's best practice at the time was replicated by local Australian faculty due to collaboration with the pioneers of SBE in the United States of America at Stanford University and Harvard University's Center for Medical Simulation.

The affinity for SBE in anaesthesia stems from the familiar aviation analogy, drawing parallels between flying a plane and administering anaesthesia. Many of the Crisis Resource Management (CRM) skills are derived from aviation training. Development of debriefing skills for the clinical environment, use of alternative technology and incorporation of evidence-based practice means that SBE in medicine is now very different, compared to 20 years ago.

Anaesthetists regularly use SBE to educate themselves or others. Using a broad definition of simulation being "replicating real world situations in the absence of patients", discussions of alternative management in a morbidity and mortality meeting might be considered simulation.

Psychomotor tasks

The specialty of anaesthesia requires the clinician to undertake a wide range of psychomotor tasks, including intravenous line insertion, front of neck access (FONA) procedures and ultrasound guided regional anaesthesia (UGRA). Many of these involve layering multiple skills, including vigilance and knowledge of physiology and pharmacology. There is evidence that SBE improves success of these procedures in patients when taught in simulation (for example, UGRA in novices[14]) and reduces patient harm (for example, infections in central lines performed by residents[15]). For less commonly performed procedures, such as emergency FONA, these skills may only ever be performed in simulation, and the purpose of training is to achieve proficiency and aid performance of the task in the real world setting as required[16]. This is clearly different to performance on a manikin, and therefore training must incorporate factors other than simple skill performance – the stress and pressure of a clinical environment and strategies to manage this must be practiced. Incorporation of virtual reality to add additional complexity to these skills is an alternative to the immersive simulation experience, in comparison to practicing skills on a part task training without the performance stress or cognitive load, or the environment in which we practice.

Crisis management ("non-technical") skills

Clear communication and sound clinical decision making in high stakes environments are hallmarks of anaesthesia. Principles governing the management of crisis situations including leadership and followership, strategies to reduce cognitive load and enhance teamwork were developed and propagated through bespoke courses[17] prior to integration into the Effective Management of Anaesthetic Crises (EMAC) course, attendance at which is a requirement of training. 70% of anaesthetists felt that crisis management was improved by attendance at the course, and nearly 90% would attend a similar course again, demonstrating a need for skills training[18]. These essential skills are measurable and translatable to critical situations, with increasing evidence of a positive effect on patient outcomes[19,20]. Essential in SBE is the role of the educators and guidelines are published by ANZCA in relation to this. Fundamentally educators need to have context expertise and be able to

provide high quality feedback and debriefing, while holding the basic assumption: that everyone participating is well-trained, intelligent and wants to improve[21,22].

Cognitive aids, checklists and teamwork

Strategies to help anaesthetists manage the rare emergencies, when working with an unfamiliar team, include checklists, protocols and memory aids[23], are ideally designed to produce good patient outcomes and promote teamwork. Simulation provides a testing ground for these aids, as well as identifying common problems that can be addressed with these strategies. Well-designed cognitive aids promote teamwork[24] and timely patient care[25].

Systems testing and patient safety

Simulation will continue to influence medical systems and practice. Features of the work environment which affect patient safety may be detected and evaluated with simulation, not only clinician skill and behavior but the effects of fatigue, technology, work flow, job sizing and complex systems[26]. Failure to test systems may have catastrophic consequences, including avoidable patient harm due to latent safety threats, such as malfunctioning equipment or poor communication between clinical sites.

Transmission of debriefing skills to clinical environment

It is easy to believe that the learning and practice change in SBE takes place in the "doing", in the scenario itself. However, there is clear evidence that the debriefing or feedback on performance has the most significant impact on learning[27]. The use of simulation in anaesthesia has proven benefits to the professional group as well as their interaction with other team members including obstetricians, midwives, neonatologists and nurses. There is evidence for integration at all levels, from novice to expert, in developing and improving both technical and management skills, practicing emergency management, finding flaws in our systems and improving our abilities as educators. Given this, and the value of debriefing for formative assessment in the clinical environment[28], all clinicians should seek to develop debriefing skills to provide excellent supervision and education. Thus, debriefing skills apply in the many situations where SBE is used in anaesthesia as well as for debriefing after critical events.

OBSTETRIC ANAESTHESIA

Obstetric anaesthesia is a subspecialised area of practice based around a unique patient demographic, surgical requirements and physiological conditions. Like other areas of anaesthesia, it requires significant teamwork skills however specific to obstetric anaesthesia it involve working with people in both the operating theatre and birthing units. It is also unique in that it involves consideration of the pregnant woman and also fetal/neonatal issues. In addition, surgery frequently occurs in an awake patient undergoing regional anaesthesia with no sedation.

There is potential for significant mortality and morbidity during pregnancy, and with emergencies in obstetric anaesthesia, with high rates of maternal mortality seen worldwide. Fortunately, currently in Australia and New Zealand overall pregnancy morbidity is low and mortality in the pregnant population is rare[29]. The maternal mortality rate in Australia in 2016 was 8.5 deaths per 100,000 women giving birth with the commonest reasons for death being non-obstetric haemorrhage and suicide[29]. In the same time period, the maternal mortality rate in New Zealand was 9.8 deaths per 100,000 women giving birth from similar causes[30]. The critical events that occur in obstetric anaesthesia however are often life threatening and require immediate emergency management. When these events occur the morbidity and mortality is considerable[31].

Preeclampsia and eclampsia, amniotic fluid embolism (AFE), the difficult obstetric airway, post-partum haemorrhage (PPH) and maternal collapse and the pregnant trauma patient, are all conditions unique to the pregnant patient. Preeclampsia and PPH are common whereas the other conditions are thankfully rare in Australia and New Zealand. These are all conditions that anaesthetists may encounter at varying frequencies. These emergency situations are complicated by significant anatomical and physiological changes of pregnancy with the added considerations of the gravid uterus and fetus.

Preeclampsia is a hypertensive disorder of pregnancy. The condition is a leading cause of maternal morbidity and mortality and complicates 5-8% of pregnancies[32]. Eclampsia, while uncommon in Australia and New Zealand, is a serious and fatal complication of pregnancy. With specific and timely treatment most deaths from preeclampsia and eclampsia are preventable[33]. Appropriate management requires knowledge and familiarity with resuscitation and administration of correct medications, for example, magnesium sulphate is the first line medication for an eclamptic seizure.

In addition, pregnancy results in significant systemic and organ-specific changes to accommodate the developing fetus, the increased metabolic demand and in preparation for blood loss during childbirth. While these physiological changes are generally well tolerated, they can contribute to maternal morbidity and mortality and complicate anaesthetic management[34].

Training requirements

Training hospitals aim to have a volume of practice completed in obstetrics throughout the four years of training. However critical events, as with all emergencies, cannot be planned and often result in infrequently encountered scenarios for trainees.

The completion of the obstetric specialised study unit (SSU) aims for trainees to be able to provide safe general and regional anaesthesia and labour analgesia for pregnant women[35]. In addition, the trainees are expected to be able to work as part of a multi-disciplinary team to care for pregnant women and participate in neonatal resuscitation. The work-based assessments (WBAs) that are required for the completion of the SSU assist with achieving these goals. However, there is only one requirement for discussion on an "obstetric emergency or complication". As there are more than one emergency situation in obstetric anaesthesia the use of simulation for training provides wider exposure to these vital clinical scenarios.

The fellowship examination curriculum requires preparation and knowledge acquisition of emergency obstetric scenarios. However, direct hands-on clinical exposure, particularly for rare cases such as eclampsia and AFE, cannot be guaranteed throughout training. For instance, examples of curriculum learning points that could be reinforced and taught with a hands-on approach with the use of simulation is; "Explain the difference in basic and advanced life support in the pregnant patient; discuss the management of severe pre-eclampsia and eclampsia; discuss the management of post-partum haemorrhage and amniotic fluid embolism."

Simulation of these scenarios not only facilitates clinical experience but also the opportunity to be exposed to new team dynamics and locations of critical events. When caring for pregnant women anaesthetist often undertake complex anaesthesia procedures in the birthing suite as well as the operating theatre. Care of a woman on the birthing unit as well as care of an unsedated and anxious pregnant woman in the operating theatre undergoing caesarean section surgery may be two new scenarios for ANZCA trainees. These are two ideal situations suited to simulation as part of trainee orientation prior to or as part of commencement of obstetric anaesthesia terms.

Role of simulation in obstetric anaesthesia training

Regular practical training, using SBE, is a requirement for common emergency scenarios in anaesthesia throughout both ANZCA anaesthetic training and fellowship. These emergency courses include Advanced Life Support (ALS), Can't Intubate Can't Oxygenate (CICO) and training for massive haemorrhage and anaphylaxis. While these emergencies do occur in the pregnant woman, the provision of training in these scenarios is often generic (a non-pregnant adult person). This limits the application to the unique and more complex situations and physiology encountered in obstetric anaesthesia. SBE has shown that repeated exposure to a situation improves memory of management as well as mastering non-technical skills[37]. The integration of formal obstetric anaesthesia SBE programs for ANZCA trainees and fellows particularly in hospitals that provide care for pregnant women may augment these current programs and ensure they are also applicable to the population receiving obstetric anaesthesia and analgesia.

PRactical Obstetric Multi-Professional Training (PROMPT) program is an example of a maternity safety SBE program delivered by and to a multi-professional team. In Australia and New Zealand this is currently licenced to Royal Australia and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and they provide the training and oversight of PROMPT. PROMPT is a hospital-based SBE program originally developed in the United Kingdom. PROMPT uses simulated common emergency obstetric scenarios to teach multidisciplinary teamwork with the aim of improving clinical management of the deteriorating and at-risk pregnant woman and neonate.

A study evaluating PROMPT implementation in Australian hospitals found a positive change in the early recognition and management of postpartum haemorrhage. Participants also reported an increased confidence and awareness of obstetric emergency situations[38]. This corresponds to the outlined benefits of SBE programs for both clinical and non-technical skills.

Simulation of emergency scenarios not only allows clinical experience but also the opportunity to be exposed to new team dynamics with effective communication and locations of critical events. Teamwork is essential for maternal and neonatal care and simulation is a crucial part in training for obstetric and neonatal emergencies. There are therefore a number of new challenges for ANZCA trainees including new clinical environments, clinicians with varied professional groups as well as new procedures. In addition, the awake patient undergoing a caesarean section surgery in the operating theatre with a support person present is frequently a new clinical encounter for ANZCA trainees requiring a heightened level of situational awareness and communication skills training.

A recent survey of obstetrics and gynaecology trainees and fellows in Australia and New Zealand found access to simulators was higher for trainees at tertiary hospitals compared with other hospitals. While simulation techniques are varied and dependent on a number of factors, most trainees had access to at least one type of simulation[39]. To assist with implementing SBE for ANZCA trainees in obstetric anaesthesia a survey of ANZCA

trainees' exposure to obstetric anaesthesia simulation may be informative to understand the current landscape across Australia and New Zealand.

CONCLUSION

Simulation-based education in anaesthesia, particularly in obstetric anaesthesia, is an important component of training and quality improvement in the delivery of routine and emergency care. Simulation of both common and uncommon scenarios involving the pregnant patient, particularly emergencies, allows for training of the unique rare, critical and life-threatening cases that occur in this population to be practiced as well as familiarising trainees to new environments. This should ideally be a core part of anaesthesia training and integrated into the ANZCA training program. This would ensure that ANZCA trainees and fellows have high-quality evidence-based training, optimise performance in multidisciplinary teams with obstetric, midwifery and neonatal colleagues and that the benefits of SBE are translated to ongoing best practice and improved clinical outcomes for women and neonates.

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Assessment

Prehabilitation
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Reifying race in medicine
Alan McLintic

Prehabilitation

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INTRODUCTION

Despite advances in surgical and anaesthetic practice, morbidity after major surgery remains a major public health issue. Elderly, frail, medically complex patients increasingly present for major surgery. Patients that could be identified as “high risk” at the time of surgery have been shown to account for 80% of deaths following elective surgery[1]. Morbidity is far more common, and complications in the early postoperative period have been shown to influence long-term survival[2]. Preoperative assessment traditionally places emphasis on detection and optimisation of existing organ pathology, ischaemic heart disease and chronic obstructive pulmonary disease, for example. There is evidence that major surgery can be associated with detrimental physiological changes that impact quality of life as long as 5 years after initial surgery[3]. Even in the absence of any complications, major surgery alone is associated with a 40% reduction in physiological and functional capacity[4]. Reducing both morbidity and functional impairment associated with surgery is therefore of paramount importance in improving longer term outcomes and reducing health care costs.

There has long been a focus on interventions in the intraoperative and postoperative period to improve outcomes following surgery. Such interventions may come too late in some patients once the surgical insult has occurred, and can be affected by barriers such as pain, fatigue and emotional responses to surgery. The preoperative period presents an appropriate time for physiological optimisation. Actively engaging the patient early in the preparation process not only allows for better education and understanding of the issues in the surgical journey, but it also gives the patient greater control in altering their physical and psychological status to improve overall wellbeing. There is a growing body of work showing promise in the impact of “prehabilitation” on postoperative function and clinical outcomes.

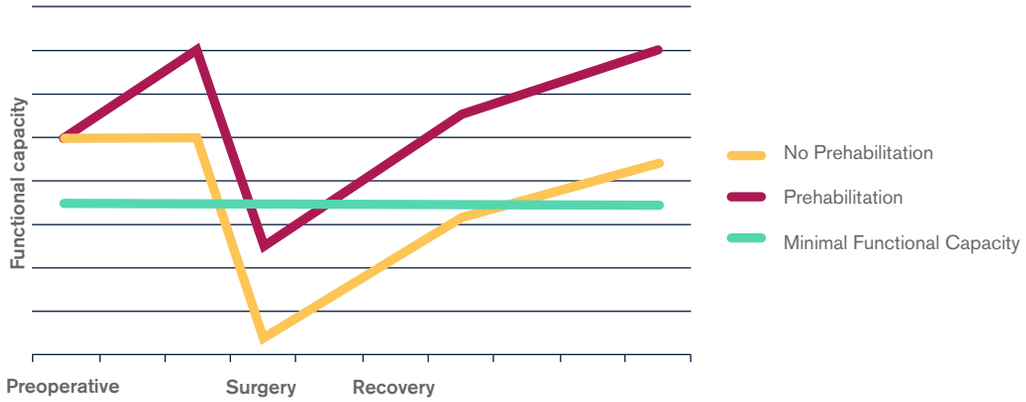
THE BASIS FOR PREHABILITATION

Prehabilitation is the practice of enhancing a patient’s functional and physiological capacity before surgery. The aim is to improve tolerance to the anticipated physiological stress, thereby improving postsurgical outcomes.

Surgery and hospitalisation are major physiological stressors that can cause significant deconditioning. The stress response is a neuroendocrine, metabolic and immune response leading to increased oxygen consumption and a catabolic state characterised by protein breakdown and negative nitrogen balance[5]. Tissue injury results in the release of inflammatory markers and the acute phase response. The magnitude and duration of this response is proportional to the extent of the surgical injury and the development of complications. Bed rest and inactivity lead to muscle atrophy and weakness, changes in pulmonary function and decline in aerobic capacity[5,6]. Cardiac deconditioning further compounds this by producing a reduction in $\dot{V}O_2$ max, stroke volume and cardiac output[4].

All these effects are more pronounced in the frail, elderly and multi-morbid patients, who are therefore predisposed to postoperative complications and may be candidates for prehabilitation. Physical training aims to increase cardiac output, arteriovenous oxygen difference and $\dot{V}O_2$ max[7]. Skeletal muscle exercise leads to increased mitochondrial content and oxygen uptake capacity. The result is an overall improved functional reserve capacity and the ability to meet increased metabolic demands. This would theoretically result in a quicker return to an acceptable minimal level of functional independence after surgery as evidenced by Figure 1[7].

Figure 1. Both prehabilitated and non-prehabilitated groups experience a functional decline postoperatively, but it takes longer for the non-prehabilitated group to reach an independent minimal functional capacity threshold compared to the prehabilitation group.



The concept of prehabilitation moves away from reactive organ-based assessment and optimisation, towards a proactive, comprehensive and holistic process. A multimodal approach in the prehabilitation program is proposed[6], the core components being medical optimisation, behavioural and lifestyle interventions, exercise, nutrition and psychological intervention.

The "marginal gains theory" has been used to describe prehabilitation, with analogies often drawn from the preparation of elite sports teams[8]. The principle is that of multiplicity – what might seem to be insignificant improvements and interventions can collectively achieve a far superior output than the individual parts. In the perioperative field, enhanced recovery has been cited as a process where evidence for individual components is debated but the whole package appears to have had a clear beneficial impact on clinical outcomes and costs[9,10]. It would seem reasonable to apply this to the preparation phase for surgery by breaking down every step or component in the process and identifying improvements or interventions to be made.

The optimal time frame is uncertain. Programs range from 2-8 weeks with some extending to 12 weeks. A short program may be ineffective, while a longer program makes recruitment and compliance challenging. Longer delays in cancer surgery may also negatively impact prognosis[11-13].

Medical optimisation

Along with optimisation of existing co-morbidities, particular attention in prehabilitation is paid to anaemia and cognitive dysfunction.

Reduced haemoglobin levels lead to reduced oxygen carrying capacity and thus reduced tissue oxygen delivery. Coupled with a higher metabolic demand in the surgical period, this increased mismatch leads to higher postoperative cardiorespiratory morbidity and wound infections. Management should be based on investigating and treating the underlying cause. Enteral or parenteral iron and multivitamin supplementation may be beneficial, with blood transfusion used judiciously as a last resort when the above therapies fail or are not feasible, and the benefits of transfusion outweigh risks. Reticulocytosis is usually not seen until 7-10 days after commencing oral iron supplements, and normalisation of values may take weeks. Furthermore absorption may be limited in chronic disease states[14]. Intravenous iron infusion at doses of 1000 mg of elemental iron is a faster option and overcomes issues of patient compliance and bioavailability. Improved efficacy is offset by cost and concerns over anaphylaxis. Ideally a locally agreed protocol should be in place for preoperative anaemia investigation and treatment.

Pre-existing cognitive impairment is the strongest predictor of postoperative delirium among those who are frail or have multiple co-morbidities. This leads to prolonged hospitalisation, increased need for institutionalised care, persistent cognitive decline and increased all-cause mortality[14]. Assessing a patient's cognitive function early with screening tools such as the Mini-Mental State Examination[15] or Mini-Cog[16] is essential for those at risk. A coordinated multidisciplinary effort that includes the expertise of geriatricians and general practitioners is essential. With identification of at-risk patients, steps can be taken during anaesthesia and the postoperative period to prevent, recognise and promptly treat delirium.

Behavioural and lifestyle interventions

Major surgery can be a significant life event and may therefore be a trigger for behavioural change. The preoperative period may therefore represent a "teachable moment" comprising of a motivated patient amenable to change and active engagement with healthcare professionals, encouraging healthy behaviours that may have an effect well beyond surgery. Intervention during this period may have a marked impact on public health and associated health care expenditure, and is an area for future research.

A wide range of co-morbidities is associated with obesity. Metabolic syndrome is often seen, where insulin resistance is associated with low glucose tolerance, dyslipidaemia, hypertension and central obesity. The effects of poor glycaemic control on postoperative outcomes are well known. Obstructive sleep apnoea is common and increases the risk of postoperative respiratory complications. As such, weight reduction strategies should ideally be implemented. This includes dietary modification and exercise programs. The use of pharmacological appetite suppressants, lipid absorption modifiers and bariatric surgery is as yet inconclusive and unproven[14].

Smoking is a well-known independent risk factor of postoperative surgical complications[17,18]. Multiple pathophysiological mechanisms result in an increased risk of pulmonary complications such as unplanned intubation, postoperative mechanical ventilation and pneumonia; cardiovascular morbidity such as myocardial infarction, cardiac arrest and stroke; as well as impaired wound healing and sepsis[14]. This is mainly attributed to the direct cellular injury, disordered coagulation and free radical release in response to toxins such as nicotine and carbon monoxide. Smoking cessation programs are thus important and should be initiated at any stage in the perioperative process, though the benefits increase proportionally with the length of cessation[19]. A Cochrane review suggests that behavioural management in combination with nicotine replacement therapy 4-8 weeks prior to surgery has proven to be the most effective in reducing postoperative complications and ensuring long-term smoking cessation[20]. The Gold Standard Programme is a highly effective tool and has been shown to halve postoperative complication rates when commenced 4-8 weeks prior to surgery[21,22]. It is an intensive, comprehensive, effective outpatient-led program[23] and in Denmark, it is the standard intervention as it has a higher abstinence rate compared to other smoking cessation tools[24]. Table 1 summarises this smoking intervention[24].

Table 1. The Gold Standard Programme[24].

Gold Standard Programme
▪ Introduction via motivational conversation.
▪ 5 meetings in 6-8 weeks depending on date of operation.
▪ Structured education on health and financial benefits, training in dealing with risk situations and relapse prevention, withdrawal support and future planning.
▪ Group or individual sessions.
▪ Nicotine replacement therapy tailored to habits, Fagerstrom score and patient preference.
▪ Hotline availability.
▪ 3 months after the quit date, a meeting covering relapse prevention is recommended.

Alcohol misuse is a significant public health issue, with a clear dose-response relationship with postoperative morbidity, even at lower levels of consumption[14]. Alcohol excess not only causes disorders of the liver, pancreas and nervous system, but is also associated with increased postoperative complications such as infections, cardiopulmonary morbidity and bleeding[25]. The risk of alcohol withdrawal should be considered. Behavioural therapy and alcohol cessation 4-8 weeks prior to surgery is shown to reduce complication rates[25].

Exercise

An assessment of physical fitness is essential in the work up to major surgery. Tools such as the Eastern Cooperative Oncology Group (ECOG) Performance Status and Karnofsky Performance Status are used by physicians to track changes in level of functioning as a result of treatment[26]. More objective measures for perioperative purposes include the 6-minute walk test (6MWT), and cardiopulmonary exercise testing (CPET). CPET has been studied extensively and offers the most objective tool for measuring aerobic capacity. Lack of adequate fitness, as determined by CPET, has an adverse effect on outcomes after high-risk surgery[27,28]. The objectivity of CPET testing allows it to be repeated later to assess the progress of the patient's prehabilitation.

Regular exercise has been shown to increase functional capacity in patients across ages and conditions, including cancer. It may also have a broader impact by increasing treatment options for patients. For example, it has been suggested that a structured preoperative exercise program could increase the numbers of candidates eligible for curative-intent pulmonary resection[29].

Patients should ideally be enrolled into a physical exercise program. The aim is to incorporate aerobic, musculoskeletal strength and flexibility training. High intensity interval training (HIIT), cycling and walking are examples of aerobic training that have been utilised in multiple studies. Strength training using weights or resistance may either target all major muscle groups or focus on specific muscle groups to achieve a desired outcome (that is, inspiratory muscle training in lung resection surgery). Moderate intensity exercise for a minimum of 4 weeks represents an achievable, and likely beneficial intervention, ideally with three to five 30-minute sessions a week, in line with global and national recommendations[30].

The intensity of exercise can be measured with a rate of perceived exertion (RPE) scale or through heart rate monitoring devices. RPE tools are the method of choice, especially for those on beta-blockers and those using water based activities where heart rate monitoring is not as effective[31,32]. The most common RPE tool is the Borg scale. The Borg scale[6] is a psychophysical category, 15-grade scale that subjectively estimates how strenuous the training is based on how the exercise feels. It has been shown to be reliable and valid in adult populations and correlates well with exercise physiology markers such as heart rate and blood lactate concentration[33]. It is thus a more cost effective and practical tool compared to heart rate monitors. A scale of 12-16 is thought to be adequate for prehabilitation[6]. The scale is summarised in Table 2.

Table 2. Borg's RPE 6-20 scale.

BORG RPE	Level of exertion
6	No exertion
8	
9	
10	
11	Light
12	
13	
14	
15	Hard
16	
17	
18	
19	
20	Maximal exertion

Barriers such as pain, motivation and financial cost should be minimised as much as possible to create a positive environment to encourage this change. Home-based programs are cheaper and more convenient as patients do not need to travel nor comply with a timed session. However, hospital-based programs with supervised group sessions do increase adherence to the program and provide far better outcomes[6,14]. Exercise prescription could follow the "FITT" principle: frequency; intensity; time; and type[34], but ultimately it needs to be tailored to the individual. Even in sedentary patients or those who cannot or do not want to partake in a structured program, benefits can be achieved by short sessions of increased activity through light walks, gardening or housework.

Nutrition

Malnutrition is a significant risk factor for poor postoperative outcomes including increased infection rates, hospital length of stay, critical care utilisation, long-term morbidity and delayed wound healing[14]. The abnormally low BMI patient is at greater surgical risk than the obese patient. However both sets of patients are often found to be deficient in micronutrients and lack adequate lean muscle mass, increasing the likelihood of sarcopaenia and poor recovery[14]. Surgery leads to the catabolic breakdown of lean muscle, which further exacerbates that effect.

A nutritional screen is encouraged as part of a multi-modal prehabilitation program. There are three screening tools recommended in the literature and they are summarised on the opposite page:

1. **Nutritional Risk Index (NRI)**[35]. This is a simple equation consisting of serum albumin and amount of recent weight loss.

   NRI = (1.519 x serum albumin g/L) + 0.417 (present weight/usual weight x 100).

   An NRI > 100 is normal, 97.5-100 mild malnourishment, 83.5-97.5 moderate malnourishment and < 83.5 severe malnourishment.

2. **Malnutrition Universal Screening Tool**[36]. This has 5 steps that not only estimate the severity of malnutrition, but also provides management guidelines. The steps include calculating BMI, weight loss and acute disease effect scores, which in combination will determine the overall risk of malnutrition and its subsequent tailored management.

3. **Nutritional Risk Screening Tool**[37]. This has been validated in surgical populations. It involves two screening stages and the parameters measured include weight loss, food intake, BMI and the severity of medical disease.

Intervention should commence about 5-7 days prior and continue postoperatively. Enteral and rarely parenteral supplementation should be organised in conjunction with a dietician. Appropriate therapy can attenuate the loss of lean body mass in the postoperative period, lower infection rates, expediate return to baseline functional status and shorten length of stay[38]. The aim is to provide patients a macronutrient reserve to limit the effects of the postoperative catabolism, as well as to increase their lean body mass to fat ratio[39]. This can be achieved by:

- Ensuring patients are meeting their minimal daily protein and caloric intake.
- Giving carbohydrate loading preoperatively.
- Using protein supplementation with whey protein extract (1.5 g/kg per day).
- Adding immunologically active supplements (Omega-3 and arginine-rich formula) which counteract the hyperinflammation and immune impairment caused by the surgical stress response[40].
- Considering multivitamins and calcium supplementation in the elderly.

Psychological intervention

In the preoperative period, patients and their families can suffer significant levels of stress, depression and anxiety, particular with cancer diagnoses. This is associated with longer hospital stays, more frequent readmissions, increased demand for analgesia and decreased wound healing[41].

Strategies to consider includes counselling, support groups, breathing exercises, sessions with a psychologist and relaxation techniques such as music or art. Concentration and visualisation exercises are useful as distraction techniques. Education about the surgery and expectations during the perioperative journey as well as tours around the hospital grounds can be empowering. The aim is to gain the patient's trust and to motivate them to engage fully during the perioperative process.

The synergy of interventions may be important. In addition to specific psychosocial interventions, the physical exercise component of prehabilitation may decrease emotional distress as well as improve physical fitness.

EVIDENCE FOR PREHABILITATION

A wide variety of regimens and specialty specific outcome measures have been used. For example, in orthopaedics, numerous small studies have suggested effective functional, mental and economic outcomes for joint and spinal surgery[42-46]. A single-centre, randomised control trial (RCT) of 650 elderly patients with severe osteoarthritis presenting for knee arthroplasty found that a 4-8 week exercise regimen preoperatively improved leg strength and functional task ability after surgery[47]. A small RCT of 60 patients presenting for spinal surgery showed that an integrated prehabilitation and early-rehabilitation program led to improved functional outcome and shortened length of stay without more complications, pain or dissatisfaction[48]. An RCT of 20 patients undergoing anterior cruciate ligament reconstruction concluded that a 6-week progressive prehabilitation program improved knee function up to 12 weeks postoperatively[49].

In cardiac surgical patients, a single-centre RCT of 249 patients showed that an intensive 10-week exercise program reduced hospital length of stay by 1 day, reduced ICU length of stay and improved quality of life at 6 months[50]. A small RCT of 17 patients concluded that a rigorous twice-weekly, 4-week exercise program was not only safe for patients preoperatively, but conferred a benefit in functional activity and increased enrolment in postoperative cardiac rehabilitation programs[51]. Another small study suggested that adding a brief, cognitive-behavioural intervention therapy to standard nursing preoperative counselling alone was cost effective and could reduce depression, increase patient satisfaction and improve physical functioning preoperatively and postoperatively through increased participation in cardiac rehabilitation[52]. A larger single-centre RCT of

655 patients concluded that preoperative inspiratory muscle training reduced the incidence of pulmonary complications and length of stay in hospital after cardiac surgery[53].

There is a growing body of literature on major abdominal surgery. An early study of 112 patients undergoing colorectal surgery compared functional capacity between two interventional groups[54]. One was assigned to walking and breathing exercises, whereas the other underwent a more structured and higher intensity intervention consisting of stationary cycling and weight training. The primary outcome measure was functional walking capacity, measured with the 6-minute walk test 5-9 weeks postoperatively. Subgroup analyses showed that regardless of exercise technique, patients whose functional exercise capacity improved preoperatively recovered well in the postoperative period[55]. A third of patients interestingly had a decline in preoperative exercise capacity, and these patients were at higher risk of delayed postoperative recovery. Poor preoperative physical performance, fatigue, malnutrition, anxiety and depression were predictors of delayed recovery. This supports the notion that multi-modal prehabilitation may have more significant effects after major abdominal surgery, and colorectal cancer in particular has been an area of interest.

A large proportion of cancer patients are elderly, who already may have significant pre-existing chronic diseases. Additionally, these patients may have the combination of the underlying malignancy causing cachexia, reduced functional impairment and malnourishment[56]. Cancer prehabilitation was first established in pulmonary cancer management as early as 1997, when Weiner et al[57] conducted an RCT on 32 patients with COPD and lung cancer awaiting lung resection. They found that preoperative incentive spirometry and inspiratory muscle training used 2 weeks before and 3 months after surgery significantly improved respiratory muscle strength and lung function. Lung cancer surgery has been used as a model for improving outcomes in other types of cancers. A 5-year secondary analysis of 3 consecutive studies consisting of 185 participants at a single centre undergoing colorectal cancer resection found that a structured multimodal prehabilitation program (exercise, nutritional care and anxiety management) improved functional capacity preoperatively, at 4 and 8 weeks after surgery compared to those receiving the same therapy after surgery[58].

Cancer patients may have undergone systematic therapies that may also impair their physical and physiological reserves. These may be given either as neo-adjuvant or adjuvant therapies. A recent pilot study of 39 patients looked at objective measures of physical fitness in patients with rectal carcinoma, aiming to evaluate physical fitness changes following neoadjuvant chemoradiotherapy (NACRT) and a subsequent preoperative 6 weeks structured responsive exercise training program[59]. Baseline fitness was determined by CPET 2 weeks prior to NACRT and then repeated immediately post NACRT, then at 3, 6, 9, and 14 weeks, before surgery was performed at week 15. A 19% drop in fitness levels was measured by CPET following preoperative chemoradiotherapy. This decline was reversed in those who partook in a 6-week high intensity interval training program 3 times per week. At the time of surgery, this fitness was preserved in the intervention group but in the control group had dropped further, to 34% below initial baseline. Although underpowered to detect differences in clinical outcomes, the study demonstrates the effectiveness in exercise therapy in preserving functional capacity in this cohort of patients. With any intervention programs in oncology patients, it is imperative to bear in mind that delays in surgery may negatively affect prognosis.

Most of the single centre trials cited here have looked at functional capacity as a primary outcome, with many essentially being feasibility or pilot studies, and underpowered to detect differences in complications and morbidity. Multiple systematic reviews and meta-analyses have been conducted to further establish a role for prehabilitation. An early meta-analysis of 1245 patients recruited to 12 randomised controlled trials, concluded that preoperative exercise therapy contributed to decreased postoperative complication rates including pulmonary complications, and shortened length of stay in surgical patients undergoing cardiac and abdominal surgery[60]. Prehabilitated joint arthroplasty patients showed no such improvement. The results are in keeping with another review[61] analysing 8 RCTs in cardiac and upper abdominal surgery, which showed that preoperative inspiratory muscle training improved postoperative respiratory function and halved the risk of pulmonary complications. Improvement in length of stay in the prehabilitation group was not statistically significant.

A recent review[62] looking at 15 RCTs of major abdominal surgeries showed that overall as well as pulmonary morbidity was reduced when deep breathing exercises, inspiratory muscle training and aerobic conditioning were part of the prehabilitation program. Again length of stay was no different. A systematic review and meta-analysis of 9 studies and 914 patients undergoing colorectal surgery, found that patients receiving at least 7 days of preoperative nutrition with or without exercise, had length of stay reduced by 2 days[63].

Other systematic reviews have been less conclusive. A review of 8 studies in colorectal cancer patients, found that preoperative improvements in fitness through exercise did not translate into improved postoperative outcomes[64]. Two further systematic reviews specifically looking at elderly patients undergoing major surgery were also inconclusive[65,66]. As many authors have alluded to, performing systematic reviews and meta-analyses is difficult given the heterogeneity in the study population, study design, intervention received and outcomes

measured. The generalisability of any results therefore becomes challenging.

There is a need for larger, high quality studies powered to detect differences in patient centred outcomes. Barberan-Garcia et al recently published data on prehabilitation in elderly or multimorbid patients (ASA 3 and 4) undergoing major elective abdominal surgery[67]. The control group received counselling on lifestyle habits, nutrition, physical activity and had anaemia management, whereas the intervention group additionally entered a personalised exercise program. This consisted of simple step-based activity as well as high intensity training on a stationary bicycle. 144 patients were randomised and intervention was safe, improved aerobic capacity and reduced postoperative complications by 50%. Length of stay in ICU was also reduced in those in the intervention group who went to ICU. This study addresses some of the limitations of previous literature by targeting a cohort at risk of complications, and being adequately powered to detect differences in complications. The first multi-centre randomised trial of multi-modal prehabilitation before colorectal cancer surgery is under way and will study the efficacy of prehabilitation in an ERAS pathway[68]. Postoperative complications will be a primary outcome measure, and secondary measures will include length of stay, cost-effectiveness, and quality of life up to 1 year after surgery.

CONCLUSION

Prehabilitation is an emerging field that is built on sound physiological principles. It represents a move to a more proactive, holistic approach focusing on the assessment and optimisation of preoperative fitness integrated with management of chronic organ-based co-morbidities. There are a number of components that can be addressed from the moment the decision to proceed with surgery is made, with the end objective being a rapid, complication-free functional recovery.

While there has been encouraging data pointing towards improved objective fitness through the perioperative period, effect on postoperative morbidity, mortality and quality of life is less robust. Prehabilitation programs are not as yet standardised within current ERAS pathways. The issues surrounding the implementation of prehabilitation are captured in a recent survey regarding the state of programs in the UK[69]. Prehabilitation was routinely offered by half of respondents. There was a wide variation in the components offered, with few offering multi-modal programs. On-going audit or data collection was also rare. The most common challenges identified were lack of funding, lack of consensus within departments and insufficient time allocated to the perioperative period.

Gaps remain in the knowledge of which outcome measures should be used, which patients should be targeted, optimal timing for interventions and which “recipe” may be best. It can be assumed that frail, elderly, and multi-morbid patients, particularly those undergoing major surgery would benefit most from a comprehensive prehabilitation program. It may be the synergy of the different elements rather than the individual components that lead to telling differences. Research in perioperative medicine is becoming a priority and high-quality trials in prehabilitation should be informative. It promises to be an area where multidisciplinary collaboration and multimodal intervention can have a major impact on patient centred outcomes after major surgery.

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Reifying race in medicine

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INTRODUCTION

In 2003 the Human Genome Project released this statement:

> *"DNA studies do not indicate that separate classifiable subspecies (races) exist within modern humans. While different genes for physical traits such as skin and hair colour can be identified between individuals, no consistent patterns of genes exist to distinguish one race from another"*[1].

Despite this, medical journals continue to publish studies describing genetic differences between races as if races are discrete biological divisions of humans. There is a long precedent. In 1839 Samuel Morton measured the cranial capacity of skulls and ranked the inherent intelligence of races: Africans were at the bottom, Caucasians at the top. Morton's notion of innate racial differences in intelligence extends into the contemporary work of Murray, Rowe, Rushton and others who advance the idea that those of African ancestry may be inherently less intelligent than Europeans[2-5]. This has been thoroughly refuted, but I mention it because such claims tend to induce in us a sense of wrongness that is in contrast to other claims of inherent racial difference that pass us by without reflex scepticism[6,7]. There is far less reaction when genetic causes are proposed to account for greater sensitivity to propofol in Blacks compared with Whites[8,9]. Or that Blacks are inherently different in terms of adrenergic and mu receptors[9-11], renin-angiotensin system function[12,13], endothelial nitric oxide availability[14], intracellular calcium mechanisms[15-17], salt handling[15,18], descending inhibitory pain pathways[19,20] and the normal reference level for serum creatinine[21]. The latter ultimately being the reason we had to highlight any Black patients we recruited in the ISOS study[22]. Many more racial genomic differences are proposed and their authority is strengthened as they are assimilated into our textbooks, including the estimable *Acute Pain Medicine: Scientific Evidence* that describes racial differences in drug metabolising enzyme and mu receptor alleles[23].

Running parallel to these proposals is a vociferous commentary that much of this research is misleading, lacks scientific rigour, lacks clinical utility and reinforces a racial stereotype[24-32]. This is countered by a vigorous defence that those who reject claims that there are inherent differences between races are simply left-leaning, politically-correct, egalitarians who are inhibiting free speech in science[33-35].

The aim of this article is to unravel that argument and, in particular, to examine the validity and clinical utility of claims about genetic differences between races. I concentrate on the categorisation of patients using any version of five traditional 18th century race categories. It is increasingly common for authors to use these same categories but to refer to them as ethnicities. The semantic distinction between race and ethnicity is thus becoming blurred and usage is being governed by author preference rather than objective taxonomy. Moreover, the issues highlighted can be applied to genomic generalisations about any broad division of humanity, whatever the label. In discussing the topic, I must use the race terminology that authors use in their papers. This does not legitimise the categorisation. Lastly, I do not, in any way, denigrate the efforts and motivations of cited authors who are simply adhering to longstanding medical practice.

RACE AS A SOCIAL CONSTRUCT

Advocates of race as a clinically useful biological categorisation are often met with "Race is a social construct". This is true. There is no agreed definition of race in biology and no scientific criteria with which to assign race. Categorisation is, therefore, at the whim of individual choice and social convention.

Many people appear to readily fit a traditional race category but many do not and, in the absence of measurable criteria, must be boxed in by a best-fit approach. The result is an ambiguous, inconsistent approach to taxonomy that has no equivalent in any other field of biology. Thus, you may be classified as White in Brazil but Black in the USA[36]. Chinese are classified as Asian in most trials but may be excluded from the Asian category in British trials[37]. Indians are classified as Asian in some studies but Caucasian in others[38,39]. Caucasian has the imprimatur of science but is the fudgiest of all categories. Some authors use it interchangeably with White in their papers[9], other authors imply Northern Europeans[40], and other authors all Europeans, North Africans, Middle Eastern, South West Central Asia and the whole of the Indian subcontinent[39]. Can we really define Caucasian genetic traits when we can't agree on what a Caucasian is?

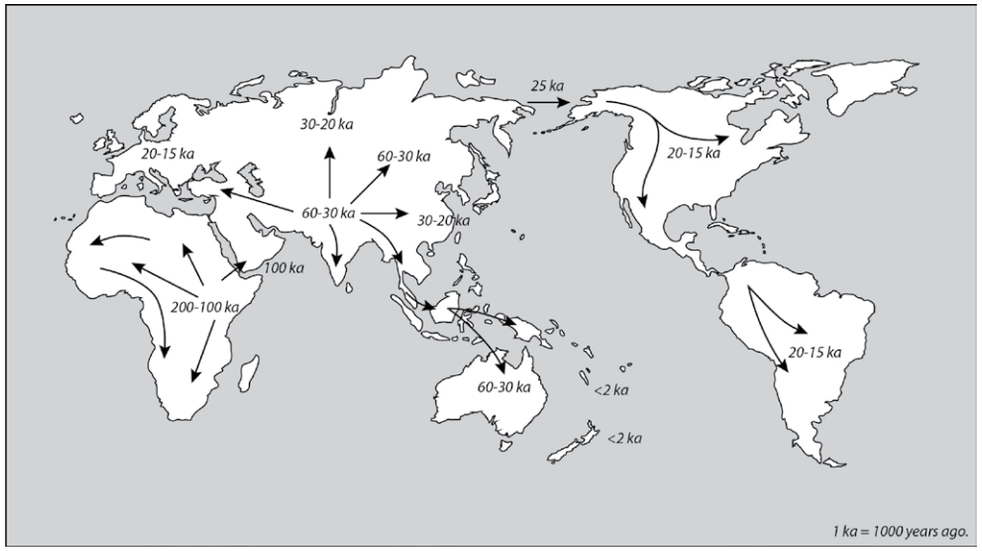
Race also changes with time. Forty-two per cent of 6000 Americans in an NHNES1 survey changed their race or ethnicity over a 10-year period[42]. One third of subjects in a US Bureau of Census survey changed race or ethnicity over a 12-month period[43]. The whole country of Puerto Rico has become more White over the last century not because of migration, but because of a reassessment of race allegiance[44]. The genome is fixed but race is not.

"Are Russians considered White?", "Are Ethiopians truly Black?", "Are Jews a race?" "If my family is Argentinian, what is my race?" These are questions posed on the internet by puzzled bloggers. It is socially ingrained in us that race is a biological categorisation so it is tacitly assumed there must be correct answers to those questions. There are no correct answers because there are no measurable criteria with which to assign race. The squeezing of seven billion people into five 18th century categories is governed by historical precedent and a varied set of social conventions.

HUMAN GENETIC VARIATION

It is still possible that socially ascribed race categories coincide with discrete genetic divisions of humans. To test this we must consider how the world was populated and the genetic processes that shaped humans during that time. The Out-of-Africa hypothesis is the most supported theory to date (see Figure 1).

Figure 1. The Out-of-Africa hypothesis of global colonisation by anatomically modern humans. Dates are approximate and based on reference 45.



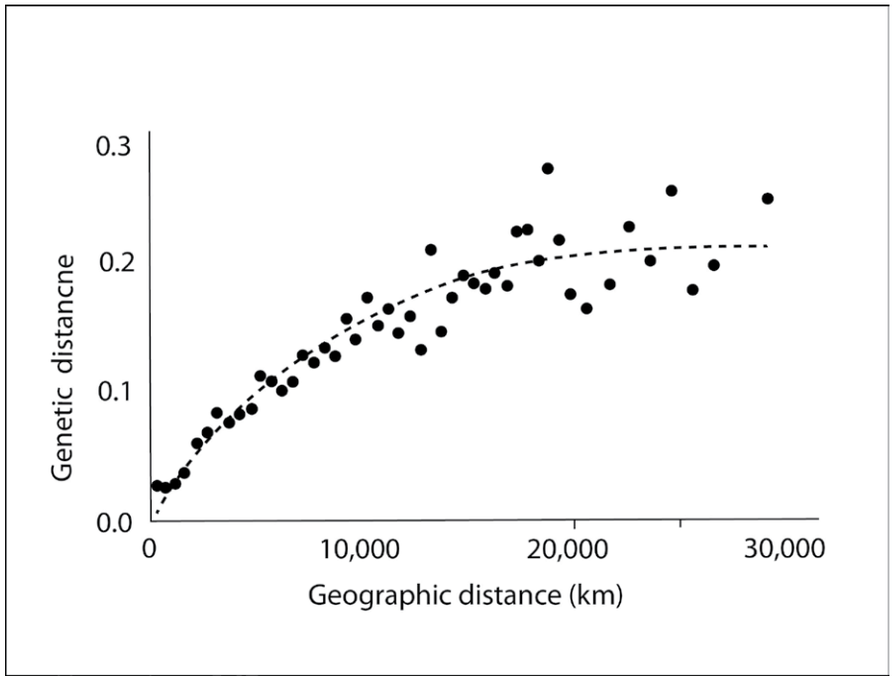
Anatomically modern humans (AMH) first appeared in East Africa at approximately 200,000 thousand years ago (200ka) and, for the next 100ka, migrated and mixed extensively within Africa[45]. At ~100ka a very small group left Africa, expanded and gradually populated the world at the eventual expense of their archaic ancestors[45]. The fact that the group was small has direct bearing on genomic patterns today. As only a small fraction of African genetic variation populated the rest of the world, today's non-African genome is a subset of a far more diverse African genome[45,46].

Throughout 200ka of AMH there has been one genetic force that has most shaped our species and that is gene flow: genetic exchange between migrating populations[47,48]. Thus, 200ka of gene flow has meant we remain completely unified as a single species with no evolutionary separation into subspecies and we share a 99.5% identical ancient African genetic code[47,49]. When the enormous number of nucleotides is considered, the 0.5% that does vary leads to considerable human genetic diversity. What form does this take?

The vast majority of genetic diversity is between individuals. This is what gives people their uniqueness and drives the need for personalised genomics. A small amount of genetic diversity correlates with geography. Gene flow and other mechanisms have diffused alleles across landmasses to form smooth gradients called clines. Human genetic variation thus changes gradually over landmasses and the clines cross continental boundaries without sharp distinctions[46,47]. A necessary consequence of clinical variation is that the genetic similarity

between populations decreases as geographical distance increases between them[50,51]. This is termed isolation by distance[47,48] (see Figure 2).

Figure 2. Isolation by distance. Each dot represents a pair of populations. The geographic distance between pairs increases from left to right. Genetic distance is a fraction based on allele frequency differences between populations and can be seen to increase as geographic distance between populations increases. Diagram adapted from reference 48.



Etched on top of the clines are other patterns of genetic variation from isolations, founder effects, migrations and adaptive pressures[52]. Pressures such as latitude temperature, subsistence and ultraviolet intensity that causes skin colour to vary with gradient distribution[53]. Such adaptive processes only affect the specific gene loci under pressure and do not cause general differences elsewhere in the genome[47,53]. It is tempting to see stark differences in external appearance, particularly skin colour, as indicating stark differences in the underlying genome. This is not the case.

ISLAND-SAMPLING, CLUSTERING AND THE RE-EMERGENCE OF RACE

The depiction of early AMH splitting into four or five genetically-discrete racial branches is unsupported in research and regarded as morally irresponsible in education[47]. However, research published in the early 2000s challenged established thinking and has been used subsequently to justify races as useful surrogates for genetic divisions. Researchers had used *Structure* software to analyse DNA from global populations and found that DNA clustered in similarity into five groups that approximated traditional race categories[54,55]. This became headline news around the world and was interpreted by some as validation of race as a biological division[56,57]. What was not publicised was that the software had grouped the data in multiple different ways. The probability of each grouping was not analysed yet the model with five divisions gained publicity because it fitted with the traditional view of race[58].

A second criticism has direct relevance to how we treat race in medicine. Rather than being a grid-like representation of global populations, sampling was dominated by populations that were geographically distant from each other[47,58,59]. This is sometimes called *island-sampling* because it creates artificial islands of genetic variation[50]. High populace, so-called "intermediate regions" of West-Central Asia and South America were markedly underrepresented and, in the case of the 1.4 billion people of India, completely absent.

Island-sampling is common in medical racial profiling because, when authors are referring to innate characteristics of Caucasians, Asians or Blacks, they are often referring to Northern Europeans or their

diaspora, East Asians or their diaspora and West Africans or their diaspora. Because these populations are geographically distant from each other in the old world, we will inevitably find differences in allele frequencies because of isolation by distance. Thus, when reading these papers, it is important to remember that these are allele frequency differences between populations isolated by distance, not differences between races. To continually couch them as such reinforces the illusion that human genetic variation is divided up into a handful of discrete chunks. Worse, it encourages extrapolation beyond the studied sample to an enormously broad and varied continental group. If we make that extrapolation, we are stereotyping.

AUTHORS' USE OF RACE

Race is a subject where facts rarely settle matters because the science is at the mercy of semantic argument about what race is in the first place.

Some authors use physical appearance as the key factor in assigning race while others see people from a handful of regions, isolated by distance, as the races. Others use ancestral continent-of-origin as the racial division, but then personalise those judgments by, for example, excluding Spanish from Europeans, Indians and Filipinos from Asians and Ethiopians from African categories. The highly varied populace of Ethiopia have notable allele patterns but does this make them outliers to be excluded or just one example of the diversity of Africans? The same is true of Asia. A prominent survey looking at racial differences in VKORC1 polymorphism removed Indian data from the Asian category after the fact because they prevented genomic cohesion60. This contrasts with other studies that exclude Chinese data from the Asian category and leave Indian data. Why should we expect the 4.5 billion people of the vast and complex continent of Asia to be usefully summarised in a single, numerical variable?

Others see races as population groups with distinctive genetic characteristics. These are better termed demes and there are many thousands across the globe[47].

Whenever we find cultural, linguistic or geographical barriers we may well find genetic distinctions. If we then suggest there are thousands of races, we are being very loose with meaning.

The way authors get around the problem is to leave us guessing. Table 1 lists surveys on authors' use of race variables[61-65]. Between 70-100% of authors do not explain what they mean by race but most still draw conclusions about race, genetics and outcome. Are authors being uncritical about race or are they relying on readers being uncritical?

Table 1. Use of race variables in genetic research.

Subject	Criticisms	Survey
34 articles on genetic differences between races: nicotine addiction.	Race categories not defined in 25. 28 had no explanation of race assignment. Only two accounted for grandparents' ancestry.	Shields 2005[63]
268 studies examining race, genotype and health outcome.	72% had no explanation of race assignment yet 67% reached conclusions about race, genotype and health outcome.	Shanawani 2006[62]
330 genetic research articles involving race/ethnicity.	No article defined race or ethnicity.	Sankar 2007[66]
30 genetics scientists in race/ethnicity research.	No agreed method for assigning race or ethnicity. Admixture assumed rare and ignored.	Hunt 2008[64]
204 studies that examined link between race and cancer.	Race seen as important but 75% studies gave no definition of race and most no criteria for assigning race.	Lee 2008[65]
36 researchers in population genetics.	No standardised criteria for assigning race. Race assignment a personal judgment of researcher. Admission that political correctness plays a part in decisions.	Bliss 2011[61]

THE CLINICAL UTILITY OF RACE

Races are clearly not biological divisions of humans but perhaps a person's "race" can still indicate important genetic characteristics that are therapeutically useful to the clinician? The following are the main obstacles to the clinical utility of race as a proxy for the genome:

Individual variability

The vast majority of genetic variation is between individuals. The utility of a racial difference in allele frequency is swamped by the uncertainty generated by the genetic variability between individuals.

Continental heterogeneity

"Continental ancestry" has become a popular descriptor in medical research but it again divides humanity simplistically into five groups as if they are genetically homogenous and discrete. Just because we can place a patient or their ancestor on a certain continent it does not mean that we can predict their genome. Africa, in particular, is the most genetically and phenotypically diverse landmass on the planet and, within it, Sub-Saharan Africa is the most genetically diverse region[48,51,59]. The notion of a general Black or other racial trait is untenable.

Admixture

In an increasingly admixed society, mixed race categories are almost never published. Racial genetic traits are usually labelled as if they are attributes of a "pure race" sample with no information on local admixture64. The result is a misleading impression of ethnic and genetic homogeneity that belies the biological reality. Many who are included in studies of apparent "pure race" have admixture that is either beyond the reach of family history questionnaire or that is unacknowledged through strong allegiance to one particular category[67]. The latter introduces a special bias because society tends to assign those of mixed race, to the category that is socially non-dominant whatever its proportionate contribution[46,48,64,68]. The degree and nature of admixture also varies markedly depending on locale and origins of the diaspora. The net effect is that the allele patterns of each "race" have considerable variation and overlap[36]. This interesting and potentially important complexity is obscured behind simplistic racial labelling.

Allele frequency differences between races do not equal utility

Common disease, common variant theory

Racial differences in common allele frequencies seldom translate to clinical utility because of the natural inter-relationship between allele frequencies, effect size and geographical distribution.

Common, complex conditions such as hypertension, Type II diabetes and obesity are linked statistically with a large number of alleles. These alleles have widespread global distribution but statistical differences in racial frequency can be demonstrated with island-sampling. Utility does not automatically follow because common disease alleles have weak effects and explain a small proportion of disease heritability[69,70]. Thus, although an individual's race might give them a higher probability of an allele than someone of a different race, that alone should not make us treat one differently from the other. Apart from the difficulties of race assignment, admixture and individual variability, the presence of the allele in any individual is still a guess, the allele effect is weak and environmental factors are usually a more ascertainable and influential trait.

Predictive value of race in rare disease

What of racial differences in the frequency of alleles with strong, Mendelian effects? Given time, natural selection eradicates alleles with strong adverse effects. Those that we see today are, therefore, of relatively recent origin. Because the variants are recent, they have not had time to be universally distributed and can be more population-specific[71,72]. If those "hot-spots" occur in one continent more than another, racial differences can be constructed. The utility "catch" is that, because of the rarity, the probability of disease, given the apparent race of the patient, remains low.

Sickle cell trait (SCT) is not nearly as rare as most Mendelian conditions because of heterozygote advantage in regions of endemic malaria. Despite common knowledge that SCT is not bounded by race, it is tacitly seen as an example where race can be useful. After all, African-Americans have 6-10 times the US national average of SCT. However, because the prevalence of SCT is still relatively low, African-American identity as a screening test in new-born babies has a predictive value of only 6.7%[31]. Because of this, the blurring of categorisation by admixture and the concern for premature diagnostic closure in other ethnicities, race is not used as a screening tool in US newborn[73].

Diaspora equivalence

The traits of a diaspora are not necessarily the same as those of their ancestral populations. Phenotypes change as people move between rural and industrialised societies and genotypes drift as new admixtures arise[74-76]. Despite this, it is common for local race data to be generalised across the globe.

The MDRD (Modification of Diet in Renal Disease) equation is used to estimate glomerular filtration rate (GFR). It was developed in the USA and contains a race adjustment that increases the calculated GFR by 20% if the patient is African-American[21]. This stems from data showing healthy African-Americans have a higher serum creatinine than other American racial groups. Whether the higher creatinine is due to greater innate muscle

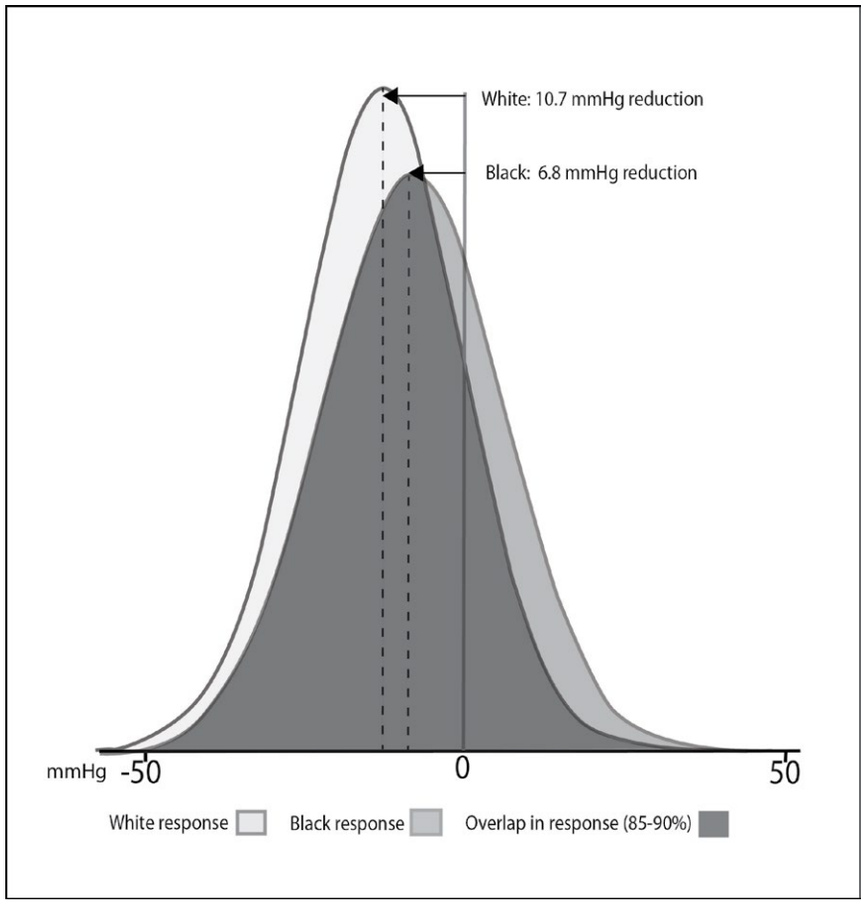
mass or whether it is an indication of greater prevalence of subclinical early kidney disease (EKD) is a point of contention[77,78].

A further concern is that the elevated norm has been recast worldwide as a general Black trait, hence the ISOS request. A stark indication of the problem is that the Black adjustment has proved inaccurate in African studies. When the equation was used in the Ashanti of Ghana and Black South Africans, the race adjustment overestimated GFR and potentially under-estimated EKD[79,80]. The reason was the African groups had markedly different body mass from the African-Americans of the original MDRD studies. Africa has the tallest and shortest people on the globe, the greatest phenotypic and genotypic diversity of any continental landmass. Data collected in African-American studies is not generalisable to all Africans and certainly not to all who might be designated Black across the world.

Overlap

Kaufman and Cooper examined the entrenched meme that Blacks do not respond well to angiotensin converting enzyme (ACE) inhibitors[31]. It is true that studies in industrialised countries regularly show Black-White differences in blood pressure (BP) response and, although genetic explanations are often given primacy, it is likely that life-long environmental differences are the biggest influence on hypertension disparities[75,81]. Kaufman and Cooper's meta-analysis of BP response to ACE inhibitors did show a small difference in systolic BP between Blacks and Whites, although it amounted to only 4 mmHg (see Figure 3). What was striking was the variability in responses and the huge overlap between the two groups. Between 85-90% of Black and White patients had similar responses. From the practical point of view this means that judging the race of a patient is of no help in predicting how that individual will respond to ACE inhibitors.

Figure 3. Systolic blood pressure reduction in patients receiving ACE inhibitors.
Adapted from reference 31.



SEEING RACE THROUGH A GENETIC LENS

A last question is whether there is any harm done in proposing there are important genomic differences between races? Disease expression and drug response are the result of complex gene-environment influences and, for individuals of different cultures, the environmental influences may be quite different. In studying racial differences in complex disease it is, therefore, very difficult to tease out the relative importance of genes versus life-long environmental influences.

A common criticism of racial health studies is that authors tend to privilege genetic explanations and give them almost Mendelian significance at the expense of the more complex socioeconomic and behavioural explanations. This was a concern raised over critical care research into Black-White mortality differences in acute lung injury where authors seemed overly focussed on postulating genetic causes at the expense of addressing the life-long health differences between the two groups[28]. Particularly life-long socioeconomic differences that are almost impossible to adequately control for in the snap-shots used in many papers[30,75].

Tidy genetic explanations deflect attention from more complex causes of health disparities but there is another concern. Far from deconstructing the notion of race, medical research appears to reinforce it by perpetuating stereotypes and entrenching a belief in innate differences between races[29]. We are reifying race through our simplistic dichotomous labels, our island-sampling and the scientific authority that goes with genetics.

Our work also influences the public perception of race. Media studies suggest the repeated exposure of the public to messages linking race to genetics cements in their minds that race is genetic and immutable and this becomes a justification for discrimination[82]. Several authors have proposed a vicious cycle. The genetic explanations we offer for racial health differences reinforce belief in inherent differences between races which, in turn, licenses the discrimination and social segregation that is at the heart of many racial health disparities[32,83,29,49,84].

CONCLUSION

Race may not be real genetically but it is very real socially and that has biological consequences in terms of health disparities. Even the most vehement critics accept that race variables are appropriate when studying the health disparities that have been caused by the racial classification itself. This is different from *a priori* sorting of patients into racial categories and expecting genetic differences to emerge with therapeutic importance. Few, if any, such moves have resulted in race-specific therapeutics that have had any impact on health disparities[25,85-87]. Again, this is because of the dominance of individual variation, the influence of social and environmental factors on phenotype, the blurring effect of admixture, the imprecision and ambiguity of the classification and because the vast majority of our genetic code is identical. For two decades Nature Genetics has asked authors to refrain from recasting population data as race data. Their requests have been largely ignored[88,89]. The sampled population must be described accurately if readers are to apply the information to their patients or replicate the study. Once the sample has been described precisely the residual information in race is redundant and, warns Nature Genetics, the legacy of discrimination[89].

The point is not that everyone across the world is the same. The point is that mapping people on to a five-category, 18th century template is misleading, encourages stereotyping and is hopelessly inadequate. Useful information is on a much finer scale. Geographic allele patterns are fascinating reflections of genetic drift, migrations, founder effects, adaptive pressures and geographic, cultural and linguistic isolations. Thus, the geographic origins of an individual may well entail a different probability of a specific allele being present. This can only be useful if their population is well defined and projects such as 1000 Genomes are revealing important genomic variation in bounded groups[90]. All this potentially important detail is completely lost in racial generalisations. Contemporary medicine is now in an era of intense, optimistic precision. The focus now is towards identifying molecular biomarkers that accurately predict personal disease risk and therapeutic response. In contrast race is a fluid, ill-defined, generalisation that cannot serve as a proxy when the genome is of real therapeutic importance.

Statistical clustering reinvigorated the notion of race as a genetic division of humans. This has been thoroughly refuted. In an era of increasing political division, there is a poignant addendum to that work. When *Structure* was given a more representative group of world populations with all their interesting complexity it came to an interesting conclusion: it best sorts us into *one* cluster[58].

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Education

Human factors in anaesthesia: Beyond non-technical skills
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Human factors in anaesthesia: Beyond non-technical skills

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INTRODUCTION

"Human factors" is a commonly misunderstood term variably describing the errors that humans make, the interpersonal skills that govern their interactions or the way that humans perform under different circumstances and organisational situations[1]. However, the professional bodies representing human factors practitioners take a more comprehensive view:

"Ergonomics (or human factors) is the scientific discipline concerned with the understanding of interactions among humans and other elements of a system, and the profession that applies theory, principles, data and methods to design in order to optimize human well-being and overall system performance[2]."

In other words, it is the science of optimising the effect of the human in the system to make the system safer and more efficient. Ensuring the physical environment is comfortable minimises the risk of injury or repetitive strain. It reduces staff sickness and creates a setting that ensures that clinicians and patients are able to function at the highest levels. Producing an environment where it is easier to communicate, make the correct, timely decisions and coordinate critical actions also reduces the rate of adverse events. This ensures that the safety of the patient is maintained, but even if something does go wrong, that the mitigation strategies are easy to implement to prevent harm.

Human factors/ergonomics (HF/E) as a discipline is not new. The Chartered Institute for Ergonomics and Human Factors (CIEHF) in the UK celebrates its 70th birthday this year. At its core the specialty is concerned with safety and has infiltrated almost every high hazard area of manufacturing, transport and power generation, yet it lags behind in health. In this article I will outline what HF/E is, what it has achieved and to what extent anaesthesia might be affected and indeed has already been affected by this area of research.

A SHORT HISTORY OF HUMAN FAILURE

Humans fail for a myriad of reasons, but despite popular opinion, failure is for the most part predictable. Anaesthesia consists of dichotomous situations that vary between high stress and boredom. Regardless of whether the setting presents new problems or demands repetitive tasks, the types of mistakes are foreseeable. With the addition of fatigue, poor lighting, distraction and the requirement to multitask, it is clear why decisions and actions may occasionally result in an outcome that was the opposite of what was intended. Anaesthesia inevitably provides all of these preconditions and more. The fabled "hours of boredom punctuated with moments of terror" that characterise our work environment both pose very different challenges[3]. During the low levels of activity, prolonged vigilance is required and this is challenging as humans we thrive on variety and finding patterns in information. When these low stress times include repetitive tasks such as drawing up medications, attention can be lacking[4]. At the opposite end of the spectrum, it is well-recognised that the information we are able to attend to during emergencies is more selective than normal ("cognitive tunnelling"). This means that crucial information that might challenge a suspected diagnosis or affect management can easily be missed in the flood of signals and data that need to be processed. Furthermore, retrieval from memory is also impaired[5], and communication may be degraded under high stress conditions, as the attention must switch between tasks which have very different cognitive and social requirements[6].

Until recently, errors have been classified into groups such as slips, lapses and mistakes[4]. By classifying errors and counting the number of times they happen, researchers had hoped to provide a broader understanding of their nature, and to determine where the solutions might lie. This method of error classification unfortunately over-simplifies the processes that lead to the issue[7]. It puts the onus on the human to take more care, rather than changing the preconditions that the error occurred in. Merely advising more vigilance or providing piecemeal solutions to complex problems has not had the lasting effect on patient safety that those collecting data on clinical events had hoped for. This is primarily because of the systemic, rather than individual nature of errors that lead to adverse events.

When mistakes happen, it is not surprising that they are commonly associated with conditions within the broader system that act as contributing factors. The common response to these mistakes is to blame ourselves rather than to recognise that all decision making processes occur as a result of the entire system rather than an internal cognitive process. Indeed, some HF/E purists believe that there is no such thing as "making an error", but that errors are a product of the system rather than the person[7]. In other words, it should be feasible to produce a system that makes erroneous decisions and actions impossible to commit.

In 1949 Alphonse Chapanis was a psychologist working for the US air force. Several aircraft had been damaged because the undercarriage knob was being activated rather than the retraction of the wing flaps after landing[8]. After some initial work, it was clear that the reason for the mistakes was the close physical proximity of the identical controls in the cockpit for the flaps and landing gear. Chapanis performed several experiments looking at how the controls could be more easily identified by shape and in the process discovered "shape coding". A round knob was placed on top of the landing gear controls (shaped like a wheel) and a flat surface on top of the wing flap control (shaped like the wing flap). There were no further reported instances of the mishap occurring thereafter.

Chapanis' story is instructive to health professionals and particularly anaesthetists in many ways. As a specialty we are perhaps more aware than other clinicians of the importance of design. There is no doubt that all of the pilots recurrently making the same mistake were well-trained, highly-motivated and keen to avoid any disciplinary action – just like clinical staff in a hospital. Consequently, it's unlikely that further education would have helped prevent this mishap from occurring. Unfortunately, the standard response to adverse events like this in hospitals is further education, or disciplinary action, for not following the protocol.

Perhaps the most perfect analogy to Chapanis' levers is the problem with medication labelling. Medication vials that can look almost identical can be stored next to each other or even spill into the adjacent receptacle and be mistaken for another medication. Rather than taking systemic steps to change the cues that prevent these mix-ups occurring, time after time the corrective measures are punitive to the individual clinician that has been set up to make the mistake. Rather than taking steps to ensure distinctive packaging, clinicians are just advised to "take more care" by reading the label more carefully[9]. A substantial failure rate will always remain when education and training solutions are used in place of redesign.

The solution that Chapanis found was not born out of aviation knowledge or education but from engineering and psychology. This is in effect a parallel situation to health, with solutions to many of our problems found in design and psychology, not in more extensive education of clinicians or greater knowledge of traditional clinical sciences.

Nevertheless, there are aspects of human factors that are amenable to educational solutions, at least in part. Improvement of teamwork and management of emergency situations can be improved by behavioural interventions, something that Australia has been at the forefront of.

THE EDUCATIONAL SOLUTION

In 2001, several simulation centres under the guidance of the Australian and New Zealand College of Anaesthetists (ANZCA) ran a course for the first time that would change the face of anaesthetic training across the region[10]. The Effective Management of Anaesthetic Crises (EMAC) course had been in development for a couple of years and had been prompted by a number of events that had occurred in a short period of time. The first commercial human patient simulator had been displayed at the World Congress of Anaesthesia in Sydney in 1996 and had generated a lot of interest. The combination of an increasing interest in simulation to improve safety (much as aviation had done decades earlier) and the availability of new technology led ANZCA to explore how simulation could address team issues in anaesthesia.

The core of the EMAC course was (and still is) the human performance module. This module examines the physical and cognitive limitations of the anaesthetist and the broader perioperative team. The initial structure of the module and the philosophy behind it was very much aligned with aviation human factors training at the time – that humans in complex systems should be aware of the cognitive and physical biases that lead to errors. Some 20 years earlier, Robert Helmreich, an aviation psychology pioneer recognised that most of the commercial aviation crashes were not due to equipment failure but to human failings[11]. Examples such as the 1977 Tenerife airport disaster, where two 747 passenger jets collided on the runway killing 583 people, were due in the main part to communication deficiencies and organisational process issues. This and other incidents led to the development of specific, mandatory training of pilots in human performance and "non-technical" or teamworking skills, termed Crew Resource Management, or "CRM". Initial CRM training consisted of education around psychological principles such as fixation, risk and management of "difficult personalities". However, as it evolved, it became clear that a more practical approach was required. The training evolved to include specific topics such as safe management of automation and speaking up (graded assertiveness) on the flight deck when mistakes or dangerous conditions were noted. Later versions of aviation CRM involved prospectively identifying

threats and errors (threat and error management) and observing the features of CRM not in simulation but in regular routine flights[12]. These real-world observations, called Line Oriented Flight Training (LOFT) ensured application of CRM principles not just in simulation but into the normal functioning of an airline.

Although the incorporation of human performance education in anaesthesia has lagged behind the aviation industry, the training in human performance and Crisis Resource Management has followed a very similar path. The Anaesthetic Crisis Resource Management course (ACRM) was developed by David Gaba and his team in Stanford in the early 1990s[13]. The purpose of ACRM was to teach the hidden curriculum of non-technical skills. The ability to plan, communicate, anticipate, make decisions and manage one's own performance-shaping factors (such as fatigue) were rarely and certainly not explicitly taught in undergraduate or anaesthetic training programs. In parallels with aviation, there was a growing recognition that in anaesthesia and perioperative care, deficiencies in care often happened because of the breakdown of effective teamwork, rather than as a result of technical flaws.

The ACRM course included reference to several "key points" of Crisis Management (outlined in Table 1). Over the years the number of key points has expanded to reflect perhaps some of the subtleties and subdivisions of these broad overarching statements[14]. The key points represent reminders to the clinician of ideal behaviours. Unfortunately, these points are often difficult to translate into observable behaviours. For example, "call for help early" might seem to be straightforward, but when variables such as the type of help required, where the help is located and the time of day are considered, "early" could equate to very different time scales. In a large tertiary centre it might be pressing the emergency bell after a first or second failed attempt at intubation, but in a rural centre, it might be contacting and preparing to transport a patient with a potentially difficult airway to a major centre. In essence these statements need to be translated into practical actions that can be exercised during clinical work.

Table 1. Key points of Crisis Resource Management[14].

Know the environment
Anticipate and plan
Call for help early
Exercise leadership and followership
Distribute the workload
Mobilise all available resources
Communicate effectively
Use all available information
Prevent and manage fixation errors
Cross (double) check
Use cognitive aids
Re-evaluate repeatedly
Use good teamwork
Allocate attention wisely
Set priorities dynamically

The key points also have considerable overlap. For example, effective delegation of roles by a leader could potentially be included in "Exercising leadership and followership" and "Distribution of the workload".

Interpretation and recall of (for example) 15 separate statements that reflect the ideal behaviours is not compatible with current theories of working memory. The Psychologist, George Miller's famous 1956 work suggested that only seven items (plus or minus two, depending on the circumstances) could be held in working memory[15]. It is unlikely that these diverse statements could all be recalled during complex clinical work, and highly improbable that they would be adequately interpreted and enacted.

The first two generations of the EMAC course were based on ACRM and referenced the key points of crisis management. In the second generation however, these principles were augmented by the emerging concepts of threat and error management being used in aviation CRM. The inclusion of concepts such as situation

awareness and prospective hazard identification helped to inform topics such as airway management planning and avoidance of cognitive tunnelling when working under stressful conditions.

A more evidenced-based approach to identification of the non-technical (team working) skills in anaesthesia was established by a group at the University of Aberdeen, in developing the Anaesthetists' Non-Technical Skills (ANTS) framework[16]. A comprehensive review of team working failures during critical events was teased out using interviews and focus groups. This created a large number of specific behaviours that were later clustered into four categories, each with between three and five elements. In turn, these elements had exemplars of behaviour that could be compared with those observed by the individuals in the team.

The ANTS framework took the idea of non-technical skills and made them more concrete for anaesthetists. They were now behaviours that could be observed and perhaps even scored to demonstrate the progression of a trainee's team working skills. However, there were difficulties in standardising these scoring systems and while useful for a research study, application into workplace-based training was difficult. Nevertheless, the framework gave an inventory, a curriculum and a lexicon to help educators understand the main behaviours involved in anaesthetic teamwork.

Table 2. The Anaesthetists' Non-Technical Skills framework[16].

Categories	Elements
Task management	Planning and preparing
	Prioritising
	Providing and maintaining standards
	Identifying and utilising resources
Team working	Coordinating activities with team
	Exchanging information
	Using authority and assertiveness
	Assessing capabilities
	Supporting others
Situation awareness	Gathering information
	Recognising and understanding
	Anticipating
Decision making	Identifying options
	Balancing risks and selecting options
	Re-evaluating

The third and latest version of EMAC uses an inventory of observable team behaviours[17]. This list includes a number of suggestions and exercises for the course participants to practise before attending the two-and-a-half-day simulation program, rather than expecting behavioural change to occur (and be sustained) in a short period outside of their normal work environment. Strategies such as speaking up (assertiveness), clinical handovers and delegation in crises are modelled and the participants given feedback during the course. This reflects best educational practice of inducing and maintaining behaviour change when returning to the clinical setting.

BEYOND THE NON-TECHNICAL SKILLS

As already noted, education alone is unlikely to improve perioperative safety. Careful, user-centred design of clinical settings, equipment, processes and organisational structures is required to ensure a safe, well-functioning system. Regulations, guidelines and standards from professional organisations such as ANZCA have to a large degree informed these aspects of safe anaesthetic care over the years. In additional to this, safety alerts are generated and disseminated through professional and regulatory bodies. Mature national and local reporting systems of medical device and pharmaceutical safety exist in high income countries where safety is well established. In low resource countries further safety measures and networks are required, but in richer areas routine anaesthesia is approaching levels of safety associated with ultrasafe industries. Having very safe conditions leads us to the next problem of how we can continue to improve when there are few incidents to learn from[18].

Newer theories of safety science include the concept of (organisational) resilience – the idea that organisations or systems can withstand stresses and adapt depending on the circumstances[19]. For example, during the influenza season a hospital may elect to suspend elective surgery, create additional spaces and resources for the new clinical load or find new ways to redistribute staffing to minimise the effects of the conditions. In an organisational sense this resilience is created by individuals making decisions to improve efficiency. Other examples include small, individual actions that seek to improve safety but aren't necessarily codified or recognised by the organisation[20]. Examples in anaesthesia might be laying out the anaesthesia work surface in a particular way to more easily identify the position of syringes or adopting a personal checklist for a particular operation to ensure nothing is missed. These individual actions represent active adaptations to maintain safe performance, often in the face of threats that operate to decrease safety margins such as production pressure and distraction. Prospectively identifying these adaptations has led to a new paradigm in safety science, that of "Safety II".

Safety II works on the principle that humans are not the weakest part of a system but the most adaptable and best able to identify risks that need modification. This is a marked change from the traditional model of safety (Safety I) that aims to remove the human from the processes as the least reliable component. Safety II recognises that in the majority of instances where the safety of the patient is threatened, it is only by the rapid action of a clinician that an adverse event is averted. By capturing and documenting these instances where a clinician made a change to avert or mitigate a disaster we can as a community place these into practice guidelines and make the system even safer. Safety II therefore recognises that learning can occur not only from adverse events and poor outcomes but also from events where safety was maintained, and no outcome occurred. It recognises more fully that safety is a "dynamic non-event" – in other words an active process by staff to prevent incidents that are largely invisible to reporting systems.

Resilience at an organisational level means that the health system can actively prevent incidents from occurring (foresight), can mitigate an adverse event from causing severe harm (coping), and can recover from the event once it has happened (recovery) and learn from it[21]. A Safety II approach to anaesthesia can enhance our ability to create this resilient system by learning from and strengthening the many more preventative actions that succeeded, rather than just identifying the ones that unfortunately failed.

THE FUTURE OF HUMAN FACTORS IN ANAESTHESIA

Anaesthetists have been at the forefront of safety in health. The advances in technology, processes and training over the past 50 years has been remarkable. There is every indication that we will continue to lead and become ever safer. Mortality from anaesthesia in high income countries has dropped from about 1:2000 anaesthetics in the 1950s to 1970s[22] to 1:57,000 in the latest ANZCA safety of anaesthesia report[23]. These improvements have occurred despite increasing numbers of surgical procedures being undertaken on increasingly older patients with a higher likelihood of coexisting diseases and advanced age. These safety improvements have resulted from improved technology and training and identification of hazards and their avoidance through design of equipment, processes and education.

Human factors will increasingly be implemented more formally in designing new interventions. By identifying when and where we are likely to make poor and difficult decisions, these cognitive processes can be helped through design of memory aids and equipment. A recent example has been the design of education, cognitive aids and airway equipment storage to prompt anaesthetists to make the difficult decision to transition to an emergency front of neck airway technique. In this case, a simple visual cognitive aid (the Vortex model) reminds the clinicians to try all three options for supraglottic airway management (facemask, tracheal tube and supraglottic airway) in the optimal conditions (for example, positioning, muscle relaxation). The design of the airway trolley and congruence between the symbols of the cognitive aid and trolley help all members of the team identify what is needed[24]. Supplementing the training of all the team members with this equipment and documentation helps develop the same understanding of the emergency should it occur. Having other team members with the same world-view (that is, a shared "mental model") allows them to speak up and advocate for the safety and continued oxygenation of the patient.

Ensuring a reduction in variation between clinical areas is also important. In the airway trolley example it makes sense to ensure the same equipment and training of staff occurs wherever airways are managed in an organisation. In that way, if an anaesthetic team are called to assist with a difficult airway in the intensive care unit or emergency department, the same understanding and equipment is available to the clinicians.

For human factors to be more broadly integrated into anaesthetic practice there needs to be a more comprehensive awareness of its scope and ability to solve the difficult clinical safety issues. The Chartered Institute of Ergonomics and Human Factors in in the UK recently released a white paper calling for human

factors expertise to be accessible to all health organisations across the country[25]. Having a designated human factors specialist that can take a thorough view of the systemic aspects of safety problems will likely have a greater effect than traditional education and clinical-only based solutions to problems. Like Chapanis' aircraft controls, the solutions to improved safety will often lie outside of areas that clinicians traditionally have expertise in. Our understanding of safety is evolving, and along with it we need to improve our basic knowledge of these areas and collaborate with human factors practitioners with complementary skills to our own.

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Feasibility of an open access collaborative anaesthesia knowledge base

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BACKGROUND

Anaesthetists, along with the wider medical community, are "drowning in information, but starving for knowledge". The dramatic increase in the quantity of medical knowledge and research has seen around 1 million papers added to the PubMed database each year in the biomedical field alone – around 2 per minute[1]. The personal distillation, critique, and translation of information of this magnitude for clinical practice has become an impossible task. Many techniques have been employed by clinicians in an attempt to surmount the insurmountable and stay abreast of current knowledge and practice; limiting sources of subscribed content, journal clubs, specials interest groups, conferences, tea-rooms, RSS feeds and Free Open Access Meducation (FOAM) among others.

The benefits of FOAM have been investigated in this journal previously[2], and include a low barrier to entry, a modern adult pedagogy and educational toolset, and the opportunity for disciplinary collaboration – harnessing the power of numbers via crowdsourcing content generation and quality control. Despite the desire among specialist anaesthetists to both consume and produce content, there is a need for the development of quality anaesthesia FOAM resources. Compared to our peers representing other medical specialties, we are languishing in our development of online education material – particularly in the format of an online knowledge database (Radiopaedia[3], WikEM[4], EyeWiki[5], LITFL[6], HemOnc[7] among others).

The aim of this article is to explore both the features of the ideal FOAM resource and the feasibility of creating a collaborative open access anaesthesia education resource across Australia and New Zealand.

CHARACTERISTICS OF THE IDEAL FOAM RESOURCE

Free

The ideal FOAM resource would be provided without cost or any form of paywall associated with its use, institutional or otherwise. Content would be also freely useable by the end-user under a Creative Commons International License.

Open access

The ideal FOAM resource would provide open-access material globally, without restriction. Aside from commenting privileges to avoid abuse, removing the requirement for registration to access material would facilitate ease of access.

Format

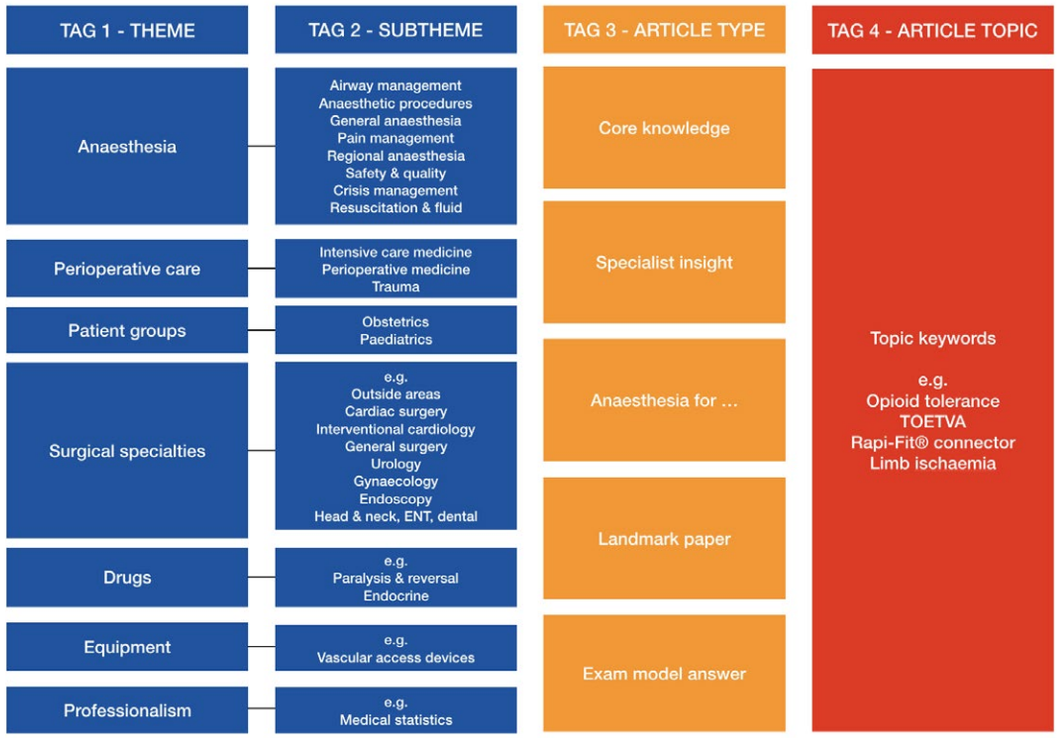
An ideal FOAM resource would be a collaborative "wiki" – a complete compendium of current anaesthesia knowledge and practice where content can be generated, collaborated on, and indexed with some consensus achieved. Content would cover all of the knowledge base in anaesthesia required for the provision of safe and competent clinical care, drawn from the Australian and New Zealand College of Anaesthetists 2013 Curriculum. By covering all anaesthesia-related content, populism and the over-publication of "hot" topics and the bias this entails would be avoided.

Articles of different "flavour" would be utilised in order to address specific domains of content: "notes" for base anaesthesia content; "insights" for commentary on controversial or best-practices; and "papers" for critical analysis of landmark research.

Articles of similar material would be published according to a consistent format for clarity and continuity across the database. These would include drug references, anaesthesia considerations for specific medical conditions and surgical procedures, and regional anaesthesia guides.

Content would be organised and easily filtered within the database by multilayered indexing of articles with "tags" according to theme and article type. For example, an article describing the anaesthetic implications of opioid tolerance may have the tags "perioperative care", "perioperative medicine", "core knowledge", and "opioid tolerance". An article discussing the landmark RELIEF trial may have the tags "anaesthesia", "resuscitation and fluid", "landmark paper", and "RELIEF" (see Figure 1).

Figure 1. An example of anaesthesia tag taxonomy.



A high level of quality in content produced

The ideal FOAM resource would provide up-to-date content of exceptional quality and accuracy. To achieve this, authorship should be restricted, with content generated only by specialist anaesthetists with formal specialist recognition or anaesthetists-in-training with specialist supervision. Authors should declare any conflicts of interest and affiliations and provide their contact information to the editors. Seeking a broad range of practicing clinical anaesthetists and experts from within the anaesthesia community as authors would avoid the bias associated with over-representation by any one author in particular. Seeking authors with special interests from sub-specialty centres or specialist interest groups for authorship of specific topics may produce material of higher accuracy and quality.

Contributors would list their name, role, and institution for transparency and accountability. Content would be kept up to date by allowing articles to be editable and employing a plan for periodic revision to ensure accuracy as medical knowledge evolves. Articles would require a publication date.

Peer-review

The ideal FOAM resource would have an avenue for both pre- and post-publication review. For example, content produced by a specialist-in-training would be reviewed by their supervisor, and subsequently reviewed by another specialist anaesthetist prior to submission for publication. There would be an editorial group of medical practitioners who ensure content is of sufficient quality prior to publication. There should be an online avenue for direct feedback and commentary from end-users on published content that notifies both the original authors and the editors to the need for clarification or correction.

Promotion of critical appraisal skills

There is concern that, in its power of distillation, online education content may be of detriment to the development of skills in critical appraisal, as primary material has often already been appraised and synthesised into a narrative form. This separates learners from the primary literature and deprives them of the opportunity to develop the required skill of critical appraisal of literature expected of a medical practitioner. An ideal FOAM resource should present the summation of knowledge for a theme, but also address the primary sources, a discussion of their quality, and any conflict among the evidence base. A discussion of the alternate positions held and some degree of qualitative analysis of viewpoints should be undertaken. Particularly contentious topics should be addressed as such, with authors publishing a critical appraisal of the topic explicitly.

Avoidance of simplification

A risk of FOAM content is the tendency toward oversimplification of complex medical knowledge in order to improve the consumability and popularity of content in a medium associated with short attention times (1 in 3 spend less than 15 seconds reading an online article[8]). An insufficient depth of knowledge may lead to erroneous decision-making. The ideal FOAM resource would address this by ignoring said pressures, and setting a benchmark for content as sufficient for safe clinical practice as a specialist anaesthetist. There should be no length limit for content.

A balanced approach to novel research and practices

FOAM promotes the rapid dissemination and uptake of new knowledge in the light of emerging evidence. This has the potential to improve the traditionally slow translation of practice-changing knowledge to clinical practice (thought to be around 17 years[9]). The ideal FOAM resource would mitigate any risk associated with the rapid uptake of novel research and practices by providing an honest and balanced assessment of practices as they emerge, aiming to reflect accepted community practice, and being cautious in any recommendations provided without evidence of efficacy or safety. Content should be curriculum-driven rather than trend-driven.

Discoverability

The ideal resource would be easily discoverable for the user; well-known by word-of-mouth within the anaesthesia community and with high online visibility via Search Engine Optimisation (SEO) without the need for commercial-style broadcast. The resource should therefore have a blog-style landing page, an associated RSS feed for subscription, as well as a Facebook and Twitter article feed for social media presence. There would be access provided for external database searches.

Conflict-free funding

An ideal FOAM resource would be funded by a benevolent source and not seek monetisation. The source of funding should not carry any conflict of interest; for example, industry funding or advertising.

FEASIBILITY OF AN OPEN ACCESS COLLABORATIVE ANAESTHESIA EDUCATION RESOURCE

Workload

The tacit and theoretical knowledge required of a competent anaesthesia specialist is considerable. A thematic analysis of the ANZCA curriculum performed by the authors has returned 1702 discrete topics across 7 themes and 48 sub-themes[10]. Specific topics may warrant several articles to address in their entirety. Furthermore, this count does not include the need to address landmark research papers, the breadth of specific surgical procedures, or individual examples of anaesthesia equipment.

A complete database would be a compendium of knowledge across all these topics; conservatively, this may reach up to 3000 articles. For all content to be covered within 5 years, the platform would need to publish approximately 11 articles per week.

Of course, the entire knowledge base does not need to be present upon launch of the platform for it to be useful educationally and generate discussion, particularly if the priority of topics addressed over time is strategically decided. The experience of similar projects in other medical fields is that of beginning with a small collection of articles at launch that grows exponentially over months to years as a critical mass of users is gathered. EyeWiki was launched after being seeded with 94 articles, and within 3 months it registered over 6500 contributions and edits to articles[11].

Revision

Additionally, there is a workload associated with revision of published content to ensure accuracy as medical science progresses. If we accept 24 months as an appropriate lapse in time before revision is necessary, this equates to ~30 revisions per week. However, the revision of a topic would be associated with a much lower workload than its initial generation, and would be tied to the original author.

Comment moderation

There will be a workload associated with the moderation and analysis of comments.

The 1% rule of internet participation[12] suggests that 10% of users contribute to discussion, while only 1% of users generate new content. Based on this rule and the projected traffic, an estimate of comments per article per day can be generated. The responsibility of moderating comments and incorporating this into revisions of the original content would be a shared responsibility between the editor and the author of the article.

Workforce

There is obviously a significant workload at hand. Do we have a sufficient workforce to realise this vision? Investigation of models for sustainable, open-educational resources have shown that selection of authors by locality is most likely to lead to success[13]. With more than 6400 fellows and 1500 anaesthetic trainees registered with ANZCA[14], we are well-positioned among specialties with regards to a potential workforce. Harnessing the global workforce is also possible as the prominence of a database grows. The experience of other wiki-style databases[15] suggests that content leads to traffic which, in turn, yields more contributions and content, and so on.

The task of gathering an initial critical mass of content and authors is critical to future growth. This is not without difficulty, however. Intuitively, and as others have described[16], medical specialists and specialists-in-training are time-poor and have many conflicting priorities such as clinical care, teaching, academia and research, organisational roles, examinations, as well as personal commitments. Specialists are typically well-compensated for their time, and it would be unlikely that this project would have the resources for a monetary incentive for contributions; there is limited prestige associated with an emerging website.

Potential models to encourage participation and authorship could include:

- Raising awareness and shaping culture; presence at conferences and regional meetings, cross-promotion with other education initiatives, social media.
- Collaboration across teaching hospitals (a collaborative "community of practice").
- Collaboration with the relevant anaesthesia college(s).
- Collaboration with anaesthesia societies.
- Collaboration with specialist interest groups.
- Incorporating production of content into expectations of trainees in training centres; for example, the 283 provisional fellows in Australia and New Zealand in general or sub-specialist training.
- Collaboration with trainees preparing for examinations or fulfilling the Scholar Role requirement to critically appraise a paper.
- Collaboration with presenters who prepare material for departmental meetings, journal clubs, and conference presentations.
- Recognition as an accredited avenue to generate CPD points.

Platform

The technical requirement for developing an appropriate platform is not significantly troublesome. Wiki source-code is open-source and freely available. Alternatives for the tech-savvy are widely available, such as the ubiquitous WordPress©. Alternatives focused on being more easily accessible for the tech novice, like Wix©, are also widely available.

Cost

There is a cost incurred with hosting online content. This is primarily associated with the costs of domain registration and the use of third-party servers to store data. Costs are small initially, but would escalate with increased content size and traffic. The hiring of a website developer, if employed, would be associated with significant cost.

Sources of funding should be conflict-free and not compromise the need for a free platform for the end-user, and have been explored[14]. Costs could be borne or shared across the following models:

- An endowment model with a central benevolent fund where interest gained is used to cover cost.
- A membership model with associated rewards, for example, access to an offline mobile application.
- An institutional/governmental model with annual commitment by relevant bodies (ANZCA, Australian Society of Anaesthetists, anaesthesia departments) or governmental initiatives.
- Educational grants.
- Altruistic donation by end-users.
- An associated publication fee tied to authorship.

MOVING FORWARD

So where to from here? Development of the ideal collaborative anaesthesia education resource as described in this article is both overdue and attainable. Chan et al have called for the engagement and participation of three types of modern scholar[17]:

- "Translational teachers" – those authors dedicated to the task of engaging the community in education.
- "Critical clinicians" – a digitally-active base of clinicians who provide meaningful critique of material.
- "Interactive investigators" – researchers who engage with the community to ensure that research findings are relevant and adapted to clinical practice.

By personally embracing this mantra, and answering the call to collaborative education, we are set to take full advantage of its benefits in advancing anaesthesia practice and improving patient outcome.

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Management

A resilience engineering approach to out-of-hours healthcare: The SAFE initiative

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A resilience engineering approach to out-of-hours healthcare: The SAFE initiative

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INTRODUCTION

The difference in the model of care in most hospitals between the standard working day and out-of-hours is stark. The vast majority of medical manpower and resource is invested in daytime care, where the eyes of senior medical, nursing and executive staff, as well as funders, are focused. Out-of-hours medical care has traditionally been delivered by a skeleton staff of junior medical officers with on-call support from off-site seniors.

In recent years increasing attention has been placed on out-of-hours outcomes, and potential harms associated with the traditional model. A large study in the UK demonstrated an increased risk of death associated with out-of-hours admissions[1]. Although this study may have been overinterpreted in the past, particularly by politicians and healthcare funders, there certainly appears to be an association between admission outside the normal working week and increased mortality, even after correction for baseline risk. This association has subsequently been further demonstrated in other healthcare jurisdictions, including Australasia[2-5].

In addition to the signal of increased risk of mortality associated with out-of-hours admission, further evidence exists of harm associated with the out-of-hours model. A large registry study, again from the UK NHS, demonstrates reduced chance of return of spontaneous circulation and subsequent survival to hospital discharge after inpatient cardiac arrest[6]. This association with worsened outcomes persists even after exclusion of intra-procedure cardiac arrest, which would be expected to occur mostly in-hours and have a good outcome.

Traditional out-of-hours models have been associated with failures of essential care elements. These include delays to medical review, delayed investigation and follow up of investigation, and delays to commencement of therapy[3,7]. Additionally, early warning scores are less consistently applied and escalated out-of-hours[8].

Although these results have caused concern, they have become known at a time when, both in Australia and internationally, healthcare budgets are coming under increasing pressure. This prevents solutions that include allocation of additional resources out-of-hours. Solutions to out-of-hours healthcare therefore require careful consideration of alternative care models.

THE SITUATION AT ROYAL PERTH HOSPITAL (RPH)

RPH is a 450-bed inner metropolitan hospital. It acts as the tertiary centre for over 725,000 Western Australians. In addition, RPH is the major trauma centre for Western Australia, with the provision of most major medical and surgical specialties. Historically, out-of-hours healthcare was provided by a small number of Resident Medical Officers (RMOs), normally in post-graduate years (PGY) 2, 3 or 4, with support from offsite specialist teams, available for phone support or, if needed, physical attendance. The first support for the RMOs out-of-hours was the medical admissions registrar, normally in PGY 3-6. In 2015, major reconfigurations of healthcare delivery across Western Australia led to significant changes in the workforce configuration at Royal Perth Hospital. This created significant pressures on the medical workforce, with severe shortages, particularly of on-call middle-grade medical staff.

After reconfiguration, concerns were raised about the safety of the out-of-hours system, particularly in light of the international literature. Note was made of the fact that although RPH had a Standardised Mortality Ratio (SMR) of 0.71 overall, the mortality of out-of-hours admissions was much higher, at 0.98 from Health Roundtable data[9]. Although as with other centres it was possible to explain this at least partially through unaccounted variation in case mix and acuity, there was further signal of concerns with the out-of-hours model. A series of severe adverse event reports highlighted issues with the delivery of care out-of-hours.

Through Root Cause Analyses (RCAs), these issues were investigated. These investigations highlighted concerns around uncertain roles, unclear handover, and reactive models of care. Policy interventions focusing on roles and responsibilities, and handover processes, including the introduction of standardised iSOBAR handovers, were implemented. However, these were ineffective in reducing the rate of adverse events, and so a different approach was required.

SAFETY 1.0 AND THE PRINCIPLES OF SAFETY 2.0

The described process of identification of an adverse event, with investigation of causative factors through some form of RCA, followed by recommendations to address these factors, is an example of a Safety 1.0 process. Other similar processes include investigations of hospital-acquired blood stream infection and morbidity review panels. These Safety 1.0 processes share many common features, and have formed the basis of much of the progress on patient safety over the past decades. Particular successes of the Safety 1.0 process have included those where an engineering solution is feasible, including the introduction of enteral syringes, physically incompatible with IV access devices, and the use of non-interchangeable anaesthetic gas connectors.

However, there are limitations to Safety 1.0. For instance, in a study of 5 years of significant investment in RCA and patient safety in Georgia, there was no significant fall in the rate of critical incidents[10]. In addition, there are certain situations where adverse events continue, despite repeated attempts to fix the root causes, an example of this is the RPH out-of-hours situation. This has led to the recognition that although Safety 1.0 processes are the mainstay of safety thinking, they are not complete.

Safety 1.0 makes several assumptions that may not be reliable. The first is that the system being examined is decomposable – in other words, it can be broken down into a series of discrete steps, where an error can be identified and fixed, then the system reassembled to work correctly. This assumption is normally correct for simple systems; however, it is often not the case for modern complex healthcare systems. The second major assumption is that the way that work is done matches the way that work is imagined – that most work in the healthcare environment follows policy and normal procedure, and that therefore safety breaches can be detected by deviation from policy, and prevented by more rigorous enforcement of policy. However, in practice, normal work as done has considerable variability outside policy, much of which actually enhances safety, and efforts to prevent this are counterproductive.

Safety 2.0 is an alternative approach to safety, where, philosophically, instead of reducing the number of events that go wrong, as in Safety 1.0, the emphasis is on making as many things go right as possible[11]. It emphasises much more a complete understanding of work as done rather than work as imagined, so that the full range of variability is understood and that conditions that favour safe working can be reproduced. The method is by necessity more time consuming but has greater power to change complex systems.

Resilience engineering is a related concept, where Safety 2.0 principles are used to design a system that adapts to unforeseen circumstances, and acts to restore safe conditions without external input. These systems need the capacity to self-monitor, respond, learn and adapt without external input.

RESILIENCE ENGINEERING FOR OUT-OF-HOURS HEALTHCARE

At RPH, a series of Safety 1.0 investigations and interventions had failed to resolve the safety concerns out-of-hours. It was therefore decided that a Safety 2.0 approach may be more effective. A working group, composed of an ICU consultant, senior nurse, and a medical administrator was formed, who undertook a detailed investigation of overall work conditions out-of-hours. The focus of the investigation was on how work was normally conducted, rather than on rarer adverse events. Several themes emerged. Firstly, the work was poorly organised. Some members of medical staff would be so busy that they were unable to safely review patients in a timely fashion, while others may be under-occupied. There was no communication of this between the staff, as there was no overall leadership. There was additionally minimal governance or oversight over the night junior medical staff, as they often rotated from diverse day teams, or a relief pool that made it difficult to provide feedback or training. At times workload was extremely high, with no ability to filter or redistribute work. Additionally, there was limited ability to proactively manage patients; there was no system to identify patients at risk of deterioration and review them proactively, other than *ad hoc* handover from the day team to the night team (a process which was often poorly attended as thought to offer little value).

We also considered why adverse events didn't occur more often. We identified that the senior cadre of night nurses provided a resilient backbone to the system. Where they were involved, they could often mobilise medical resource to proactively manage situations, and understood the organisation well enough to arrange escalation to on-call senior or critical care medical staff in order to prevent harm. Although their role was well recognised by nursing staff, it was inconsistently recognised by medical staff, resulting in the loss of their valuable assistance in certain circumstances.

Finally, we considered what the differences were between the day and night that resulted in the negative outcomes. What was different about the daytime that was protective? Although the superficial answer is that more staff are present, we realised that there was more to it than this. Successful clinical teams during the day have a culture that helps drive good outcomes. They have motivated junior and senior medical staff, who delegate decisions, both upwards and downwards, appropriately. They have a sense of ownership, and try to resolve clinical problems and advance care, rather than passively hoping that the next duty shift will resolve the problems. Additionally, they knew who their sickest patients were, and focused on these individuals to manage them proactively, rather than waiting to be told that they have deteriorated.

THE SAFE PROGRAM

When redesigning the out-of-hours system into the SAFE (Safety After hours For Everyone) program, we attempted to address the concerning features of existing out-of-hours work by adapting the principles identified in successful daytime teams, and integrating the senior nurses into the medical team. The SAFE team covers all inpatient areas at RPH that do not have a dedicated medical team (that is, excludes the emergency department, ICU, operating theatres, state trauma unit and medical admissions units). The team operates from 4pm to 8am during the week, and 24 hours over the weekend and public holidays. Core features of SAFE that distinguish it from existing out-of-hours systems include:

- Significant senior executive buy-in to the idea of upgraded out-of-hours care. This allows investment in out-of-hours care, but also facilitates change management where there may be resistance in some quarters to established practice.
- The formation of a department of out-of-hours care. This allows:
  - The appointment of a head of department. This provides a single point of contact and accountability for out-of-hours care and allows out-of-hours issues to be represented to executive consistently. It also facilitates bilateral positive and negative feedback between the night and day staff.
  - Recognition for training. By being recognised for RMO and registrar training, junior medical staff can be appointed to the team for consistent terms. This allows the formation of a team culture of supportive and shared working, consistent hand over and communication. A strong patient safety culture is formed through mutual trust and respect, and transparent reporting and accountability. It also encourages understanding of the issues associated with out-of-hours healthcare through repeated exposure and continuity of care.
  - Appointment of permanent staff. The existing cadre of senior nurses were permanently integrated into the team, allowing clear accountability and shared working, training and development with the medical staff.
  - Specific morbidity and mortality sessions addressing out-of-hours issues.
  - Accountability for process and professionalism – important care process issues such as communication and hand over can be audited with clear accountability.
  - Development of trust and understanding between in and out-of-hours teams.
- Development of a clear team structure.
  - RMOs are assigned to wards; normally covering about 60 patients each overnight. Although part of SAFE, and attending the SAFE team handover, they are embedded for their shift in the ward, and are expected to spend most of the shift present on the ward. After handover, they are expected to make themselves known to the shift coordinators, and undertake a board round, where the shift coordinator briefly hands over each patient's diagnosis and any major concerns at the ward patient board, so that they are familiar with issues and concerns on the ward.
  - A dedicated medical registrar provides medical leadership for the team, and provides direct support to the RMOs, reviewing and advising, and where needed liaising with specialists outside the team. The medical registrar also leads the hospital wide medical emergency team (MET) response.
  - A clinical nurse specialist supports the ward nursing staff, providing expert advice in the management of unwell ward patients, including organ support, transfer, as well as leading the nursing team at MET calls. Allocates nursing resource as required between wards.

  - The team is led by the clinical lead, a nurse consultant in after-hours care. The clinical lead maintains oversight of the whole team's workload, along with a knowledge of patients of concern in the hospital, and allocates medical resource as required, while ensuring that patients of concern are being proactively managed, and that forward progress is maintained. They have a role in both supporting the management of individual patients, and coordinating the team's response across the hospital.
  - The on-site team is supported by the on-call specialist primary teams. Responsibility and governance of the patients is retained by the parent team. Close liaison is maintained, supported by policy led mandatory consultant notification criteria, such that any significant change in patient condition must be discussed with the responsible specialist.
- Formation of an organisation-wide "patient of concern" list. Consultation with a wide variety of ward staff resulted in identification of a series of criteria, predicting the patients most likely to deteriorate in the foreseeable future. These criteria are listed in Figure 1. These patients form the basis of the team hand over; the RMO is expected to see every patient of concern in their area at least once per shift and maintain closed loop communication with the clinical lead to confirm forward progress. If there is any residual concern, the clinical lead can review the patient in person or assign the registrar to review.
- Every patient arriving in a SAFE area during operational hours receives a "SAFEty check" (Figure 2). This is a way for the area RMO to take ownership of the patient, by formally confirming clinical stability, that a senior is aware of the patient and that a plan has been made and actioned, as well as confirming basic treatment measures such as DVT prophylaxis are appropriately prescribed.
- The outcome of the combination of formal handover of patients of concern, board round at the start of the shift, and SAFEty checks is that the RMOs have a comprehensive picture of the patients in their area, in particular those most likely to deteriorate, with a shared mental model with the other members of the team as to where pressure in the hospital exists, so that they may mutually support.
- Scheduled shift "catch-ups" where the whole team reconvenes to confirm that all patients of concern are progressing, discuss any issues, and reallocate workload where required. This also presents an opportunity for focused and relevant teaching on current issues by the senior nurses and registrars.
- The strong integration of the MET service with the SAFE model results in a MET leadership team with both an active interest in MET management, and significant and rapidly developing experience in MET management even for new team members. All patients undergoing MET activation automatically become patients of concern, allowing follow up by the MET team members. This has significant advantages over MET teams drawn from other areas who often have little continuity of care after the MET, and less experience of managing MET activations.
- Strong emphasis on individual and team wellbeing. It was recognised that continuous out-of-hours working presented risk to the individuals within the team. Support was built into the system, particularly with team based rostering and preferential allocation to teams and roster patterns.
- Formal and informal education programs, primarily registrar led, in emergency management and acute care including simulation.

The SAFE program commenced in January 2016.

Figure 1. Patient of Concern criteria. ADDS = Adult Deterioration Detection Score.
See Midodrine chapter in this edition of *Australasian Anaesthesia*.

Within 24 hours of: ▪ MET call ▪ ICU Discharge ▪ Behavioural emergency ▪ CARE phone activation
Modified MET criteria in a patient whose Goals of Care would support ICU admission
Receiving organ support in non-specialist area (eg. NIV outside the respiratory ward, oral vasopressor use)
Physical or chemical restraint
ADDS score greater than 4 or rise of 2

Figure 2. SAFEty Check.

SAFE TEAM – SAFETY CHECK
Date of review:___/___/_____ Time of review: _____
Current ADDS score: _____ ☐ No clinical concerns
Reason for check:
☐ Post admission ☐ Post Transfer ☐ Post Op
Has been checked:
☐ Medical/Surgical Plan ☐ Plan actioned
☐ Usual meds charted ☐ Analgesia charted
☐ DVT Prophylaxis ☐ Oxygen
☐ IV fluids ☐ IV cannula
Document below any actions taken
Signature:_____
Printed Name:_____

OUTCOMES OF THE SAFE PROGRAM

SAFE was conceived primarily as a patient safety improvement program, and has widely been regarded as successful. SAFE was implemented as part of an overall organisational drive to improve safety, and no results can be interpreted in isolation. The overall hospital Hospital Standardised Mortality Ratio (HSMR[9]) has fallen from 0.71 in 2015 before SAFE implementation, to 0.54 in 2018, among the lowest in Australia.

One of the key focuses of the SAFE initiative was addressing the discrepancy in mortality between admissions in and out-of-hours. Before SAFE implementation, the in:out-of-hours standardised mortality ratio was 0.98. By mid-2018, the ratio had fallen to 0.38. This improvement in out-of-hours mortality exceeds the overall improvement in mortality, suggesting that the SAFE model, and the resultant changes in after-hours care, have been key to the overall improvement in mortality.

Staff satisfaction has been extremely high with the new model. Feedback to postgraduate education from the RMOs in SAFE has consistently been positive, with SAFE being rated as among the best terms in the hospital for teaching, support and overall experience. Particularly valued are the team-based working and the close relationship with senior nursing staff – this has created a real sense of mutual respect. Also of note, the RMOs feel much more confident in their ability to access senior support out-of-hours.

Nursing staff feedback has identified improved confidence in the after-hours medical team. It is now easier to identify and contact the correct doctor, and where required a senior review in more prompt. More confidence is expressed in the ability of the team to identify and monitor deteriorating patients. The presence of the clinical lead as a single point of contact in the event of uncertainty or conflict was highly rated.

Overall, the feedback was that the overall quality of care had improved since implementation, with a reduction in the time to review sick patients, and in task response and completion times.

Clearly with the implementation of the SAFE program, an initial financial investment was required. However, due to the consistent presence of an out-of-hours junior doctor, daytime junior medical staff find it far easier to handover work. As time went on, the registrars also developed confidence handing over clinical problems to the SAFE team. The result of this was an immediate drastic reduction in unplanned RMO and intern overtime at the time of implementation, with a slower reduction in registrar overtime over the 3 months following implementation. This reduction has been sustained over time. The result of this significant savings in overtime has been that with the Western Australian medical contracts, the implementation of the model has been near cost neutral.

CONCLUSION

Through application of resilience engineering principles, out-of-hours care at Royal Perth has been reimagined into a proactive, team based department. This has been associated with significant improvements in overall and out-of-hours mortality, and staff satisfaction with out-of-hours work, at minimal marginal cost. Although the specific features of the system are specific to the hospital, many of the ideas and principles can be implemented in any equivalent sized hospital.

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