Goal directed therapy to prevent Acute Kidney Injury
AKI – what we know!

- AKI is a heterogeneous disease with sudden loss of renal function
- Common 5% (non critical pts) to 30% (critically ill patients)
- Increasing incidence - multimorbid, older, polypharmacy ..... 
- Preventable
- Expensive (LOS, resources, CKD)
- Major Risk factor for CKD**
- No effective treatment (no silver bullet)
- Supportive therapy
<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>↑ ≥ 26.5 umol/L or 1.5 – 1.9 times baseline</td>
<td>&lt; 0.5 mL/kg/hour for 6 to 12 hours</td>
</tr>
<tr>
<td>2</td>
<td>↑ 2.0 to 2.9 times baseline</td>
<td>&lt; 0.5 mL/kg/hour for ≥12 hours</td>
</tr>
<tr>
<td>3</td>
<td>↑ 3.0 times baseline</td>
<td>&lt;0.3 mL/kg/hour for ≥24 hours, or anuria for ≥12 hours or the initiation of RRT</td>
</tr>
</tbody>
</table>

**AKI Stages**

KDIGO criteria correction of volume status and exclude obstruction

**Biomarkers**
Causes of AKI – Simplistic paradigm

- **Pre Renal**
  - Hypovolemia
  - ↓ Cardiac output
  - Vasomodulation
  - Systemic vasodilation

- **Post Renal**
  - Bladder Outlet
  - Ureteral
  - External

- **Intra Renal**
  - Vascular
  - Glomerular
  - Tubulo-interstitial

- **Heterogeneous Disease**
  - Incomplete understanding
AKI Morbidity and Mortality

broadly linear relationship between the severity of AKI and mortality risk

Mortality 36% in AKI stage 3
Identifying ‘at risk pts’ – poor

Delays detecting AKI

Appropriate management < 50 %

Avoidable 30 %

Appropriate referral
Goal directed therapy to prevent acute kidney injury

Nephrologist  Peri operative Team

“Before I begin, I’d just like to make it known that I didn’t volunteer to do this presentation.”
Pre operative
Risk identification
Bloods/urine
Optimising medications
Contrast
Illness/infection

Peri operative
Hemodynamics
Volume Management
Anaesthesia
Medications
Blood loss

Post operative
Bloods
Hemodynamics
Volume assess
Urine output
Medications

Discharge
Medications
Bloods
Follow up Planning

PREVENTION
INTERVENTION
Identify Risk factor for AKI

- Age
- Diabetes
- Chronic kidney disease
- Heart failure
- Hypertension and BP medications**
- Vascular disease
- Chronic liver disease (advanced)
- Acute critical illness

Goal directed therapy to prevent acute kidney injury
Recommended tests before elective surgery
by patient's physical status and surgery grade

ASA grade

1. Normal, healthy person
2. Mild systemic disease
3. Severe systemic disease
4. Severe systemic disease, constant threat to life

Offer
Consider
Surgery complexity
Examples

Minor
Excising skin lesion
Draining breast abscess

Intermediate
Excising varicose veins (leg)
Tonsillectomy
Knee arthroscopy

Major
Colonic resection
Thyroidecotomy
Total joint replacement

If over 65 and no ECG for 12 months

For people at risk of AKI:
If cardiovascular, renal or diabetes comorbidities

1. Acute kidney injury - people at risk include:
   - Intra-peritoneal surgery
   - eGFR < 60 mL/min/1.73 m²
   - Diabetes
   - Heart failure
   - Age 65 years +
   - Liver disease
   - Use of drugs with nephrotoxic potential in the perioperative period

2. American Society of Anesthesiologists

3. Tests such as (Activated) Partial Thromboplastin Time (APTT or PTT), and platelets

If no ECG for 12 months
If new symptoms of cardiovascular or renal disease
For people with chronic liver disease
Anaesthetist review for people with known or suspected respiratory disease
Medication Management

Prevent Hypotension and hypovolemia

Controversy – no consensus

Beta blockers (IHD) and statins ok

Minimise exposure to nephrotoxins

Dose adjustment in AKI

Goal directed therapy to prevent acute kidney injury
Continuation of ACEi/ARBs peri-operatively is reasonable (Level of evidence B)
Restart as soon as clinically feasible (Level of evidence B)

Goal directed therapy to prevent acute kidney injury
Withholding versus Continuing Angiotensin-converting Enzyme Inhibitors or Angiotensin II Receptor Blockers before Noncardiac Surgery

An Analysis of the Vascular events In noncardiac Surgery patients cOhort evaluationN Prospective Cohort

Conclusions: Withholding angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers before major noncardiac surgery was associated with a lower risk of death and postoperative vascular events. A large randomized trial is needed to confirm this finding. In the interim, clinicians should consider recommending that patients withhold angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers 24 h before surgery. (ANESTHESIOLOGY 2017; 126:16-27)

International, prospective, observational cohort study, non cardiac surgery

14,687 pts (4802 on ACEI/ARB – 1250 withheld)

Primary composite outcome – all cause death, stroke or AMI at 30d
Withholding Anti-hypertensives Peri operatively

Anti-hypertensive taken the morning of surgery independently associated post operative risk of AKI

Retrospective, multicentre, cohort study
AKI 10.3 %
Directly associated with number BP agents, age, length of surgery, blood loss, CAD
Perioperative management of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers: a survey of perioperative medicine practitioners

Sophie L.M. Walker, Tom E.F. Abbott, Katherine Brown, Rupert M. Pearse and Gareth L. Ackland

William Harvey Research Institute, QMUL, Queen Mary University of London, London, United Kingdom

Survey 2017 (predominantly UK)
Invited Peri op physicians (medicine and anaesthesia)
196 responses
Widespread uncertainty (experts)
Need large RCT to answer the question more definitively
Diuretics Peri operatively

Loop & Thiazide: 
- Hypovolemia → Hypotension
- Hypokalaemia → Muscle relaxants, arrhythmias, ileus
- Hyponatremia → Delirium

No consensus

Used in oliguric AKI - No evidence for their benefit

Intravenous frusemide (very effective)

Heart Failure pts should take diuretics including day of surgery

Post operatively individualise the therapy

Goal directed therapy to prevent acute kidney injury
Key Medications Requiring Dose Adjustment (or cessation) in AKI

Analgesics (morphine, gabapentin, pregabalin)

Antiepileptics (lamotrigine)

Antivirals (acyclovir, gancyclovir, valgancyclovir)

Antifungals (fluconazole)

Antimicrobials (almost all need dose adjustment in AKI)

exceptions of azithromycin, ceftriaxone, doxycycline, linezolid, moxifloxacin, nafcillin, rifampin

Diabetic agents (sulfonylureas, metformin)

Allopurinol

Baclofen

Colchicine

Digoxin

Lithium

Low-molecular-weight heparin

NOACs/DOACs
Intravenous Fluids and AKI

Multiple controversies

Type of fluids

Goal directed, liberal or restricted fluids
History of Intravenous fluids

1830

William Brooke O’Shaughnessy

iv Fluid Therapy
University of Edinburgh


1896

Hartog Jacob Hamburger

Dutch Physiologist

0.9 % saline
<table>
<thead>
<tr>
<th></th>
<th>O'Shaunessy 1831</th>
<th>Hamburger 1896 Saline</th>
<th>Sydney Ringer 1880 Ringer’s lactate 1930</th>
<th>Alexis Hartmann 1931</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sodium</strong></td>
<td>154 mmol/l</td>
<td>130 mmol/l</td>
<td>131 mmol/l</td>
<td></td>
</tr>
<tr>
<td><strong>Chloride</strong></td>
<td>154 mmol/l</td>
<td>109 mmol/l</td>
<td>111 mmol/l</td>
<td></td>
</tr>
<tr>
<td><strong>Potassium</strong></td>
<td>0</td>
<td>4 mmol/l</td>
<td>5 mmol/l</td>
<td></td>
</tr>
<tr>
<td><strong>Osmolarity</strong></td>
<td>308</td>
<td>273</td>
<td>275</td>
<td></td>
</tr>
</tbody>
</table>

**physiological**
Intravenous Fluids and AKI

Early goal-directed therapy no effect on mortality or need for RRT

Fluid overload deleterious

Numerous methods to assess fluid responsiveness

- none are ideal in isolation, multiple repeated assessments recommended

Intravenous fluids should be used judiciously in patients with AKI who are not “volume responsive.”
Colloid Versus Crystalloid

Colloids - Albumin, hydroxyethyl starches (HES) & gelatins

Oncotic gradients expand the intravascular space

Crystalloids equilibrate across intravascular and extravascular spaces

Significant practice variation – ‘doctor preference/culture’
Albumin

safe, expensive, alternative for resuscitation of critically ill patients – SAFE trial
useful in septic shock and cirrhotic patients.
Should be avoided in patients with traumatic brain injury (↑ risk for death)

HES

Differing molecular weights, molar substitutions & tonicities
Cheaper than Albumin
Renal toxicity with hyper-oncotic HES - proximal tubule vacuolization and swelling (osmotic nephrosis)

Crystalloid Versus Hydroxyethyl Starch (CHEST) Study
↑ risk for RRT in the group that received HES (7.0% vs 5.3%)

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock
The CRISTAL Randomized Trial

No difference in RRT requirement or mortality at 28 days

JAMA 2013
Isotonic 0.9% saline solution chloride content - 154 mmol/l vs 110 mmol/l
Risk hyperchloremic metabolic acidosis

↑ renal vascular resistance
↑ renin activity
↓ GFR

↑ Extravascular volume
↓ Renal cortical perfusion

Physiologic Balanced Salt Solution V Normal Saline Solution

SALT-EM Study
Balanced crystalloids lower rate of composite Outcome of death from any cause, new RRT or persistent renal dysfunction

Await PLUS Trial
Plasma-Lyte 148 v Saline (PLUS) study
Intravenous Fluids and AKI

Type of Fluid?

Volume? Restrictive v Liberal

How to give it? Goal directed!

Excess Fluids ↑ AKI
renal compartment syndrome
renal venous congestion
↓ renal oxygenation

Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery

Restrictive was associated with higher rate of AKI

Australasian Resuscitation in Sepsis Evaluation (ARISE) trial
USA - Protocolized Care for Early Septic Shock (ProCESS) trial
UK - Protocolised Management in Sepsis (ProMISe) trial

Failed to demonstrate that early GDT improves survival compared with non-protocolized standard resuscitation
Intravenous Fluids and AKI

**Goal directed fluid therapy**
should optimise stroke volume and tissue oxygen delivery
Minimize excess fluid administration once no haemodynamic benefit

How do we recognise who will respond from fluid bolus or who will have deleterious outcome?
## PREDICTING FLUID RESPONSIVENESS

<table>
<thead>
<tr>
<th>Static tests</th>
<th>less sensitive, less specific and less useful than dynamic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical static endpoints</td>
<td>BP, HR, JVP, Cap refill, UO</td>
</tr>
<tr>
<td>CVP/PCWP</td>
<td></td>
</tr>
<tr>
<td>CXR</td>
<td>Pulmonary oedema</td>
</tr>
<tr>
<td>PICCO</td>
<td></td>
</tr>
<tr>
<td>Lactate or SvO2</td>
<td></td>
</tr>
</tbody>
</table>

### Dynamic tests

<table>
<thead>
<tr>
<th>Passive leg raising</th>
<th>pulse pressure change, PPV, VTI (echo), NICCOM, carotid Doppler flow, or ETCO2 (if ventilation and metabolic status constant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-expiratory occlusion test</td>
<td>Occluding the circuit at end-expiration prevents the cyclic effect of inspiration to reduce left cardiac preload and acts like a fluid challenge</td>
</tr>
</tbody>
</table>

### Ultrasound

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>subaortic velocity time index (VTI) allows measurement of stroke volume, EDV approximates preload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung ultrasound</td>
<td>Detect lung water</td>
</tr>
<tr>
<td>IVC ultrasound</td>
<td>generally limited to mechanically ventilated patients in sinus rhythm</td>
</tr>
<tr>
<td>Aortic blood velocity</td>
<td></td>
</tr>
</tbody>
</table>
My approach to the BP, fluids and GDT

GOLDILOCKS APPROACH

No ACEi/ARBs
No Diuretics

More liberal IVT
No HES fluids

0.9 % Saline or physiological

Goal directed therapy to prevent acute kidney injury
Goal directed therapy to prevent acute kidney injury

Hemodynamic Support: Blood Pressure Targets

No clear evidence of benefit
- Dopamine
- Fenoldopam
- Atrial natriuretic peptide
- Calcium channel blockers
- Diuretics
- Erythropoietin
- Insulin growth factor
- N-Acetylcysteine
- Statins
- Aminophylline/theophylline
Contrast induced AKI

Transient small increase in serum creatinine
Few days after intravascular iodinated contrast (esp hyperosmolar)
Usually self-limited course
Increased short- and long-term mortality
Progression to CKD

Risk Factors

CKD (esp low GFR & proteinuria)
Diabetes
Hypovolemia
Volume of contrast/multiple doses
Intra arterial

Treatment = Prevention!
Isotonic IV fluids
1 ml/kg/h infusion 12 hours pre & post
3 ml/kg/h 1 hour pre & 1.5 ml/kg/h 4 hours post

Goal directed therapy to prevent acute kidney injury
Renal Replacement Therapy (RRT)

- Hyperkalemia
- Metabolic Acidosis
- Volume overload
- Symptoms of uraemia

**Timing**

**Modality**
- HD/CRRT

**Dose**

**Discontinuation**

**Goal directed therapy to prevent acute kidney injury**
Risk, Prevention and Recognition

Some AKI is Predictable, Preventable and/or Recognised Late

Risk Assess for AKI
The risk of AKI is contributed to by the acute insult and background morbidity

Background
- Elderly (>65)
- CKD
- Cardiac failure
- Liver disease
- Diabetes
- Vascular disease
- Background nephrotoxic medications

Acute STOP
- Sepsis and hypoperfusion
- Toxicity
- Obstruction
- Parenchymal kidney disease

Prevent AKI - The 4 'M's
- Monitor Patient (observations and EWS, regular blood tests, pathology alerts, fluid chart, urine volumes)
- Maintain Circulation (hydration, resuscitation, oxygenation)
- Minimise Kidney Insults (e.g. nephrotoxic medications, diuretics, ACE/ARB, dopamine, surgery or high risk interventions, iodinated contrast and prophylaxis, hospital acquired infection)
- Manage The Acute Illness (e.g. sepsis, heart failure, liver failure)

Recognise AKI
- 1.5 rise from recent baseline creatinine, >26 rise in 48 hours, prompt from National algorithm or 6 hours of oliguria

AKI Develops

INSTITUTE CARE BUNDLE
- Prevent AKI progression by rapid diagnosis, supportive care, specific therapy and appropriate referral
Goal directed therapy to prevent acute kidney injury
Improving the management of Acute Kidney Injury in a District General Hospital: Introduction of the DONUT bundle

Anisha Bhagwanani, Rory Carpenter, Aqeelah Yusuf
King's Mill Hospital, Sherwood Forest NHS Trust

D – Dehydration
O – Obstruction
N – Nephrotoxins
U – Urine
T – Think sepsis

Goal directed therapy to prevent acute kidney injury
Care Bundles for Acute Kidney Injury: Do They Work?

Nicholas M. Selby\textsuperscript{a, b} Nitin V. Kolhe\textsuperscript{b}

\textsuperscript{a}Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine, University of Nottingham, Royal Derby Hospital Campus, and \textsuperscript{b}Department of Renal Medicine, Royal Derby Hospital, Derby, UK
Think Kidneys

AKI Prevention

AKI is common

Considerable harm

Significant costs

Preventable

Course modifiable

Rich vein research

Pre operative

Peri operative

Post operative

Discharge

Improve Recognition diagnosis

Improve AKI care

Improve Recovery

Improve Discharge Follow up

Goal directed therapy to prevent acute kidney injury
Medications Commonly Associated With ATN

- Aminoglycosides (tobramycin, gentamycin)
- NSAIDs (and celecoxib)
- ACEi
- ARB
- Amphotericin
- Cisplatin
- Foscarnet
- Iodinated contrast
- Pentamidine
- Tenofovir
- Zolendronic acid