Tetanus and the Anaesthetist

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Tetanus is an acute, often fatal disease caused by the exotoxins produced by
Clostridium tetani. It was first described more than two thousand years ago. The disease
is characterised by generalised muscle rigidity, autonomic instability and sometimes
convulsions. It is preventable by adequate immunisation programs, but remains
common world wide. Although predominantly a disease of developing countries, the
management of tetanus remains a challenge to critical care specialists in developed
countries because,

- Tetanus presenting in its early stages, when it is most amenable to treatment, is often
  unrecognized. Severe and even fatal cases are under reported.
- The incidence in developed countries is increasing and at risk populations include
  the elderly, the immunocompromised and intravenous drug abusers.
- Severe tetanus requires prolonged intensive care and organ support, with the
  associated complications including nosocomial sepsis.
- Autonomic dysfunction in severe tetanus is difficult to control and is a significant
  cause of mortality.
- Reports in the literature relating to the management of severe tetanus are sometimes
  conflicting. They constitute only level 3 or 4 evidence.

Pathophysiology
Tetanus is caused by Clostridium tetani, an anaerobic Gram-positive bacillus. The
mature organism forms a terminal spore which is resistant to oxygen, moisture and
extremes of temperature and is capable of surviving decades. Spores exist ubiquitously
in soil and in animal and human faeces. Following entry into a wound, spores proliferate as the vegetative form, if the local tissue oxygen tension is sufficiently low. The usual mode of entry is through a puncture wound or laceration, although tetanus may follow surgery, burns, gangrene, chronic ulcers, dog bites, injections such as with drug users, dental infection, abortion and childbirth. Tetanus neonatorum usually follows infection of the umbilical stump. The injury itself may be trivial, and in as many as 29% of cases there is no history or evidence of a wound. The oxidation-reduction potential of the tissues is lowered by factors such as the presence of necrotic tissue, pus and foreign bodies.

In the vegetative form, spores produce two toxins: tetanospasmin and tetanolysin. Tetanolysin is capable of further damaging otherwise viable tissue surrounding an infected wound, optimizing conditions for bacterial multiplication. Tetanospasmin causes the clinical manifestations of tetanus. This toxin is distributed widely by the blood stream, entering the nervous system at the neuromuscular junction (NMJ) of alpha-motor neurons. Once tetanospasmin is bound to the NMJ, inhibition of transmitter release is permanent and recovery depends on the formation of a new synapse. Toxin is then carried by retrograde axonal transport to the cell body and migrates trans-synaptically to other neurones. The cells most commonly affected by tetanospasmin are the alpha-motor neurone, parts of the sympathetic nervous system and the spinal inhibitory cells.

The action of spinal inhibitory cells is mediated at a local level by glycinergic interneurones. Release of glycine from these cells is directly inhibited by tetanospasmin, preventing the damping down of reflex muscle action. The consequent loss of inhibition leads to the clinical manifestations of tetanus, the characteristic rigidity and spasms.

A further inhibitory system connecting the brain stem to the spinal cord, mediated by the transmitter gamma-aminobutyric acid (GABA) is also affected by tetanospasmin. There is thought to be blood borne spread of toxin from the entry site to the brain at the area of the floor of the fourth ventricle, where the blood-brain barrier is non-existent. This may explain why trismus and neck rigidity are early manifestations of the disease.

**Active immunoprophylaxis**

Natural immunity to tetanus does not occur. The disease may both relapse and recur. Victims of tetanus must be actively immunised. Tetanus toxoid is a cheap and effective vaccine, which is thermally stable. It is a non-toxic derivative of the toxin which, nevertheless, elicits and reacts with antitoxic antibody. A serum antibody titre of 0.01 units/ml is universally quoted as being protective. However, this figure was extrapolated directly from animal experiments and there are reports of tetanus in individuals with much higher serum antibody titres. The diagnosis of tetanus should not be excluded on the basis of toxin-neutralising antibody ≥ 0.01 units/ml, if the history and clinical features are supportive.

In adults, a full immunization course consists of three toxoid doses, given at an optimal interval of 6-12 weeks between the first and second doses, and 6-12 months between the second and third doses. Neonates have immunity from maternal antibodies. Children over 3 months should be actively immunized, and need four doses in total. Two or more doses to child-bearing females over 14 years will protect any child produced within the next five years. Pregnant women who are not immunised should
thus be given two spaced-out doses two weeks to two months before delivery. Booster
doses should be given routinely every ten years, but the full immunisation course
should not be repeated.

Side-effects of tetanus toxoid are uncommon and not life-threatening. They are
associated with excessive levels of antibody due to indiscriminate use. Common
reactions include urticaria, angio-oedema and diffuse, indurated swelling at the site of
injection.

**Diagnosis**

The diagnosis of tetanus relies on clinical assessment. There is no diagnostic
laboratory test and blood cultures are positive in less than half of cases. The absence
of an obvious wound does not exclude the diagnosis.1 The most common differential
diagnosis is dystonic reaction to tricyclics. Others include strychnine poisoning, local
temporomandibular disease, local oral disease, convulsions, tetany, intracranial
infections or haemorrhage and psychiatric disorders.

Suggested criteria for the clinical diagnosis of tetanus are:

1. An illness characterized by the acute onset of hypertonia and/or painful muscular
   contractions (usually of the jaw and neck) and generalized muscle spasms, without
   any other apparent causes such as drug reactions, other central nervous system
   disorders, or hysteria.
2. No history of contact with strychnine.
3. Subsequent disease course consistent with tetanus.

**Clinical presentation**

The incubation period (i.e. time from injury to onset of symptoms) varies from 2 to
60 days. The period of onset (i.e. from first symptom to first spasm) similarly varies.
However, nearly all cases (90%), present within 15 days of infection.4 The incubation
period and the period of onset are of prognostic importance, with shorter times
signifying more severe disease.

The presenting symptoms are pain and stiffness. Stiffness progresses to rigidity, with
difficulty in mouth opening — trismus or lockjaw. The rigidity becomes generalised,
with the facial muscles producing a characteristic clenched-teeth expression called
risus sardonicus. The disease then descends, to affect the trunk and limbs. Typical
spasms, with flexion and adduction of the arms, extension of the legs and opisthotonos,
are very painful and may be so intense that fractures and tendon separations occur.1
Spasms are caused by external stimuli, e.g. noise and pressure. As the disease worsens,
even minimal stimuli produce more intense and longer-lasting spasms. Spasms are life
threatening when they involve the larynx and/or diaphragm.

Neonatal tetanus presents most often on day 7 of life,5 with a short (one day) history
of failure of the infant to feed. The neonate displays typical spasms that can be easily
misdiagnosed as convulsions of another aetiology. In addition, because these infants
vomit (as a result of the increased intra-abdominal pressure) and are dehydrated
(because of their inability to swallow), meningitis and sepsis are often considered first.

Autonomic dysfunction occurs in severe cases,5,6 and begins a few days after the
muscle spasms (see below). If tetanus of uterine origin is associated with autonomic
dysfunction, the prognosis is very poor.

Local tetanus is an uncommon mild form of tetanus with a mortality of 1%. The
signs and symptoms are confined to a limb or muscle, and may be the result of
immunization. Cephalic tetanus is also rare. It results from head and neck injuries, eye infections and otitis media. The cranial nerves, especially the seventh are frequently involved, and the prognosis is poor. This form may progress to more generalized disease. In heroin addicts, tetanus seems to be severe with a high mortality, although reported numbers are small.

**Autonomic dysfunction**

Sympathetic overactivity in tetanus was first described by Kerr and others in 1968.\(^5\) The hallmarks were reported to be fluctuating tachycardia and hypertension, sometimes followed by hypotension, cardiac dysrhythmias, peripheral pallor, sweating and pyrexia. These are associated with increased plasma and urinary concentrations of catecholamines, increased oxygen consumption and carbon dioxide production.

Proposed mechanisms for autonomic dysfunction include:\(^1,^7\)

- The effect of toxin on the brainstem and autonomic interneurones causing impairment of inhibitory pathways. This is the most likely mechanism.
- A direct effect of toxin on the myocardium.
- Loss of inhibition of the adrenal medulla with increased adrenaline secretion.
- Direct inhibition of the release of endogenous opiates by tetanospasmin.
- Increased release of thyroid hormone.\(^1,^2\)

Fluctuations in blood pressure and heart rate appear to be related to changes in systemic vascular resistance, rather than cardiac output or left ventricular filling pressure.\(^6\) Noradrenaline is increased disproportionately relative to adrenaline, suggesting a direct sympathetic mechanism rather than humoral release. Another possible cause is a seizure-like discharge causing a sudden tachycardia and vasoconstriction, increasing central venous and arterial pressure. Cessation of this seizure-like activity results in hypotension, bradycardia, decreased central venous pressure and vasodilation.

Sympathetic overactivity seems to predominate in this process, but it is possible that effects on parasympathetic nervous system have been largely overlooked and underreported. For example, sudden cardiac arrest is a common complication of severe tetanus but its cause has not always been ascribed to autonomic dysfunction.\(^7\) Preterminal bradycardia, salivation and increased bronchial secretions have also been reported. It should be noted that such patients have often also been on beta-adrenergic blocking agents, which confuses the interpretation of their signs.

**Management**

The management of patients with tetanus has five goals: neutralisation of circulating toxin (i.e. passive immunisation), eradication of the organism and removal of the source of toxin, control of rigidity and spasms, management of autonomic dysfunction and general supportive care. Many anaesthetic drugs and techniques may be of value in the control both of spasms and autonomic dysfunction.

**Passive immunization**

Human antitetanus serum has now largely replaced equine serum (ATS), as it is less antigenic. Although never prospectively tested, the present dosage recommendation is 3000-6000 units IM (or IV if available).\(^1,^2\) It has been suggested that patients who are unimmunised or whose immunisation status is unknown should be given human rich antiserum on presentation with contaminated wounds. No controlled study has shown
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this to be more effective than wound toilet and penicillin administration. Intrathecal administration of antitetanus serum is still controversial. A large meta-analysis reported it to have no advantage over the intramuscular route.8

The side effects of human antitetanus serum include fever, shivering and chest or back pains. Cardiovascular parameters need to be monitored, and the infusion may need to be stopped temporarily if significant tachycardia and hypotension present. If human antiserum is not available, equine ATS can be used after testing and desensitization.1

Eradication of the organism

Wound care

Once human antitetanus toxin has been given, the infected site should be thoroughly cleaned and all necrotic tissue extensively debrided. Hysterectomy is advocated for tetanus associated with septic abortion or childbirth. Wound debridement may not always be practicable, for example in drug addicts or those with no obvious wound.

Antibiotics

Tetanus spores are destroyed by antibiotics. The vegetative form (bacillus) is sensitive to antibiotics in vitro. However, in vivo efficacy depends on the antibiotic concentration at the wound site, and large doses may be required. Recommended antibiotic regimens include:

1. Metronidazole 500 mg IV 8-hourly for 10 days: The drug has a spectrum of activity against anaerobes, is able to penetrate necrotic tissue, and has been shown to be more effective than penicillin in this situation.9
2. Penicillin G 1-3 MU IV 6-hourly for 10 days. Penicillin is a GABA antagonist in the CNS, and may aggravate the spasms.

Overall penicillin is the antibiotic of choice. Erythromycin, tetracycline, chloramphenicol and clindamycin are alternatives.2

Control of rigidity and spasms

In the early stages of tetanus, the patient is most at risk from laryngeal and other respiratory muscle spasm. Therefore, if muscle spasms are present, the airway should be urgently secured by endotracheal intubation or tracheostomy. If respiratory muscles are affected, mechanical ventilation is instituted. In severe tetanus, spasms usually preclude effective ventilation and muscle relaxants may be required. No one drug or class of drugs has been shown to be consistently effective in controlling rigidity and spasms in severe disease. A wide range of drugs suppressing central and/or peripheral nervous activity has been used, both singularly and in combination. Neuromuscular blocking agents (NMBAs) are often combined with heavy sedation to control severe spasms. There is no consensus on the most appropriate NMA to use in tetanus. Pancuronium bromide may cause tachycardia and hypertension, by stimulating noradrenaline release from sympathetic nerve endings, but has been used safely in tetanus. Neuromuscular blockade has been avoided by using agents such as dantrolene, intrathecal baclofen and propofol.10,12 Heavy sedation alone may prevent muscle spasms and improve autonomic dysfunction (see below).

Management of autonomic dysfunction

More than thirty years since the syndrome was first described, management of
autonomic dysfunction is still sub-optimal. As with control of spasms, no one drug or class of drug has been shown to be consistently effective in the control of autonomic dysfunction. Treatments include the use of heavy sedation, peripheral adrenergic blocking agents, morphine, magnesium sulphate, baclofen, clonidine, chlorpromazine, ganglion-blockers and atropine, often in combination. Other strategies include epidural analgesia and atrial pacing.

Evaluation of treatment is complicated by the lack of defined criteria for the diagnosis of autonomic dysfunction in tetanus. Studies differ in the haemodynamic variables monitored and their method of measurement. Catecholamine concentrations are not always reported and the method of measurement may have been inaccurate in some of the older studies. Lastly, there is no standardisation of other aspects of management. In retrospective studies, it is impossible to distinguish cases of true autonomic dysfunction from, for example, drug withdrawal syndromes, stress response in the setting of inadequate sedation, labile blood pressure in a patient with poorly-controlled pre-existing cardiovascular disease, or the systemic inflammatory response syndrome.

**Beta-adrenergic blocking agents**

These were the earliest drugs advocated for the management of autonomic dysfunction. Propanolol was used at first, but it may result in profound hypotension, severe pulmonary oedema and cardiac arrest.7 Labetalol has been used for its combined alpha- and beta effects, either alone or in combination with propanolol.5 However, it has less effect on alpha blockade than on beta blockade. From the literature, it appears that combined alpha- and beta-blockade denervates the circulation and makes circulatory support during periods of hypotension difficult. Esmolol, an ultra-short acting beta-blocker, reduces catecholamine release in shocked animals and has been used in tetanus.13 In one report, it provided haemodynamic stability with good control of tachycardia and hypertension. However, arterial catecholamine concentrations remained markedly increased. This may be of concern as control of the haemodynamic disturbance without reduction in catecholamine levels has been associated with fatal myocardial necrosis in phaeochromocytoma. This situation might be aggravated in tetanus by the direct action of the toxin on the myocardium.

**Post-ganglionic and alpha-adrenergic blocking agents**

Bethanidine, guanethidine and phentolamine were used as adjuncts to propranolol by Prys-Roberts and Kerr, with apparent beneficial effect.14 Other similar agents that have been used include trimetaphan, phenoxybenzamine and reserpine. A disadvantage of this group of drugs is that induced hypotension may be difficult to reverse and withdrawal can result in rebound hypertension.

**Morphine**

Morphine acts centrally to reduce sympathetic tone to the heart and vascular system. Morphine helps control cardiovascular instability, but it is unclear whether catecholamine concentrations are reduced. Gastrointestinal effects such as constipation and ileus may compound the effects of autonomic dysfunction.

**Magnesium sulphate**

Magnesium inhibits release of humoral and neuronal catecholamines and reduces
the sensitivity of alpha-adrenergic receptors. It has been used to treat autonomic
dysfunction with varying success, appearing to reduce pulse rate, vasoconstriction and
catecholamine concentrations when used with sedatives.\textsuperscript{15, 16} Negative inotropic effects
are minimised, but not eliminated, if hypocalcaemia is avoided. Marked neuro-
muscular blockade is associated with the use of magnesium; with the simultaneous use
of NMBAs, this may predispose to prolonged weakness during the recovery phase.
Intravenous magnesium sulphate is given in doses similar to those used for the
treatment of pre-eclampsia, keeping serum levels in the range 2.5-4.0 mmol/l.

\textbf{Epidural blockade}

Lumbar epidural blockade with local anaesthetic agents has controlled cardio-
vascular instability and reduced serum catecholamine concentrations. Epidural
blockade provides sympathetic blockade, neuromuscular blockade and analgesia.\textsuperscript{17}
There are only individual case reports of this technique and they provide insufficient
evidence to draw firm conclusions on its value.

\textbf{Clonidine}

Clonidine is a selective partial agonist for alpha\textsubscript{2}-adrenergic receptors with a 200-
fold selectivity for the alpha\textsubscript{2}-receptor over the alpha\textsubscript{1}. Alpha\textsubscript{2} agonists have both
peripheral and central effects on the cardiovascular system. Acting centrally, clonidine
causes hypotension and bradycardia. The precise mechanisms of action is not fully
understood, but is thought to involve inhibition of sympathetic outflow and
potentiation of parasympathetic nervous activity, increasing vagal tone. Acting
peripherally, clonidine inhibits the release of nor-adrenaline from prejunctional nerve
endings. It also produces marked sedation and anxiolysis, decreases spontaneous
motor activity and potentiates the sedative and anaesthetic actions of other drugs. Two
case studies report the use of clonidine in the management of autonomic dysfunction
in tetanus with conflicting results.\textsuperscript{16, 18} Clonidine is available as an oral, intravenous,
intrathecal and transdermal preparation. Dexmedetomidine, a superselective alpha\textsubscript{2}-
adrenergic agonist related to clonidine but more potent and more selective, may prove
to be more effective in the management of autonomic dysfunction.

\textbf{Inhalational anaesthetic agents}

Nitrous oxide, halothane and isoflurane have all been reported as being used in the
management of tetanus.\textsuperscript{14, 19} Nitrous oxide and halothane were shown to adequately
control haemodynamic instability. Isoflurane, in relatively high concentrations, was
shown to control spasms but the case reported did not demonstrate significant
autonomic dysfunction. Many intensive care units lack the facilities for the
administration, monitoring and scavenging of such agents, limiting the potential
usefulness of this treatment strategy.

\textbf{Other drugs and treatment strategies}

A continuous infusion of atropine has been advocated for the management of
parasympathetic dysfunction.\textsuperscript{20} Atrial pacing may be of use in the treatment of
hypotension and bradycardia associated with autonomic dysfunction.\textsuperscript{21} Other treatments that have been reported as isolated case studies include sodium nitroprusside,
steroids, hypothermia and hyperbaric oxygen.\textsuperscript{1, 2}

Drugs of potential benefit include sodium valproate, angiotensin converting enzyme
(ACE) inhibitors and adenosine. Sodium valproate blocks GABA-aminotransferase and is therefore an inhibitor of GABA metabolism. Angiotensin II increases noradrenaline synthesis and facilitates its release from nerve endings. Inhibition of angiotensin II synthesis may therefore reduce sympathetic overactivity in tetanus. Adenosine has actions that include reduction of presynaptic noradrenaline release and antagonism of the inotropic effects of catecholamines. Adenosine, therefore, has potential for use in sympathetic overactivity. However, to date its use has been largely experimental with clinical use limited to isolated bolus doses.22

Supportive treatment
Steps should be taken to prevent contractures, nosocomial pneumonias and deep vein thrombosis. The patient (including the mother if a neonate is afflicted) must be actively immunised. Where possible, supportive psychotherapy should be offered to both patient and family.

Complications
Muscle spasms disappear after 1-3 weeks, but residual stiffness may persist. Although most survivors recover completely by 6 weeks, cardiovascular complications, including cardiac failure, arrhythmias, pulmonary oedema and hypertensive crises can be fatal. No obvious cause of death can be found at autopsy in up to 20% of deaths.

Conclusion
Severe tetanus remains a clinical challenge. Although autonomic dysfunction was first described more than thirty years ago and, despite the extensive range of pharmacological agents available, its control remains difficult in severe cases. Current evidence is often anecdotal as controlled trials are difficult to conduct. There are advocates for the use of epidural blockade, magnesium sulphate and esmolol to control spikes of hypertension and tachycardia, in addition to sedation and neuromuscular blockade. Further assessment of the use of dexmedetomidine, to control autonomic dysfunction, and dantrolene and intrathecal baclofen, to control spasms, is needed. Finally, it should not be forgotten that tetanus is completely preventable by adequate immunisation programs.

References