MEDICINE

Tetanus

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SUMMARY
Although tetanus is not all that common in the UK, the pathophysiology and treatment (in particular the pharmacology and intensive care management) illustrate some important and interesting concepts. The reduction in mortality over the last three decades is due largely to the use of exceptionally heavy sedation rather than to muscle paralysis to control the spasms and prevent life-threatening effects of autonomic overactivity. The reduction in mortality has also been achieved by attention to detail and the improved care of long-term intensive care patients. The predominant site of action of tetanospasmin is thought to be the central inhibitory interneurones. The major effect may result from its influence on the release of the inhibitory neurotransmitters gamma-aminobutyric acid and glycine which allow increased rate of neuronal firing resulting in muscular rigidity, spasms and autonomic disinhibition. Inhibition of the release of enkephalins may add to the altered modulation of the autonomic nervous system. The botulinum-like action at the motor end-plate leads to decreased neuromuscular transmission between spasms increasing the risk of acute neuromuscular respiratory failure. Tetanolysin disrupts cell membranes damaging viable tissue, lowering redox potential which favours growth of anaerobic organisms.

INTRODUCTION
Changes in the treatment of tetanus over the past 25 years have reduced the mortality from approximately 30% to the exceptionally low figure of 6% in over 120 cases of adult tetanus in Groote Schuur Hospital, Cape Town. The reasons for this decrease in mortality are multifactorial, but probably the most important factor is the use of exceptionally heavy sedation rather than curarization to control spasms and prevent the potentially life-threatening effects of autonomic overactivity on the heart.¹

There are between 800 000 and 1 million deaths due to tetanus each year, of which about 400 000 are due to neonatal tetanus. Tetanus is most common in Africa and Asia where 80% of the deaths occur. Only 12–15 cases per year are reported in Britain each year.²

Tetanus and botulism (C. botulinum) are the most important toxin-mediated diseases associated with infection by the clostridia genus. Tetanus is caused by the exotoxin (tetanospasmin) from the anaerobic gram-positive bacillus Clostridium tetani. This ubiquitous organism occurs as spores in organic material particularly soil and the faeces of various animals and man. The toxin ascends intra-axonally in motor and autonomic nerve fibres although a small amount may reach the brain stem via the circulation and the lymphatics. Tetanospasmin (closely related to botulinum toxin) has a predilection for neural tissue and forms an irreversible bond with synaptosomes, thereby preventing the release of the contents of synaptic vesicles both in the spinal cord and in the central nervous system. The predominant site of action of tetanospasmin is thought to be the central inhibitory interneurones. Here the major effect may result from its influence on the release of the inhibitory neurotransmitters gamma-aminobutyric acid (GABA) and glycine, which allow increased rate of neuronal firing resulting in muscular rigidity and spasms and autonomic disinhibition. The botulinum-like action at the motor end-plate (inhibition of the release of acetylcholine) leads to decreased neuromuscular transmission between spasms increasing the risk of acute neuromuscular respiratory failure.

The portal of entry is usually a severe or untreated wound, often a neglected burn or an inadequately debrided compound fracture, occasionally a postpartum or post-abortion infection or non-sterile intramuscular
injection.² In a few cases (15–30%) the portal of entry is either trivial (e.g. rose thorn in the finger) or never isolated. The Public Health immunization programme with tetanus toxoid has dramatically reduced the incidence of neonatal tetanus in the Western Cape, but as yet we have seen only a moderate reduction in the incidence in adults. Most of the adult patients who we treat have no history of previous immunization, particularly the older age group. Features of special importance are the period from injury/inoculation to the onset of symptoms (incubation) and the time interval between the onset of symptoms to the onset of spasms (onset). In general, the shorter the period from injury to onset of symptoms and the shorter the time interval between symptoms and spasms, the more severe the tetanus will be. Incubation may vary from as short as 24 h to as long as many months. This interval may be a reflection of the distance the toxin must travel within the nervous system and the quantity of toxin released.²

**SPECIAL PROBLEMS**

**Maintenance of the airway**

The critical factor in patients with tetanus is to maintain a patent airway. Laryngospasm occurs commonly as part of generalized spasms and can often be precipitated by oral secretions or manipulations. Due to the inability to swallow, secretions are a problem and patients are unable to clear them adequately. These can lead to laryngospasm. Fatal laryngospasm has been recorded before any generalized muscular spasm has occurred. When the patient develops spasms, which are not controlled by a small dose of diazepam and dysphagia is present, they should have the airway protected by intubation and early tracheostomy due to the predictable long course of these patients. It is important to intubate early rather than take the chance of the patient developing laryngospasm. Due to the tendency to laryngospasm on any stimulation these patients should never be intubated without sedation and a muscle relaxant (general anaesthesia). The trismus always relaxes with succinylcholine which is usable at this stage, but not later, once prolonged disuse has taken place.

**Sympathetic overactivity**

Sympathetic overactivity remains the major cause of death in patients with tetanus once the early deaths from airway obstruction and the deaths from respiratory failure have been eliminated. The syndrome of sympathetic overactivity results in a tachycardia (or occasionally a profound bradycardia), marked fluctuation in blood pressure (both hypotension and hypertension), excessive salivation and sweating. This fluid loss may result in large fluid losses and clinically significant dehydration. The effect on the heart can give rise to

**Clinical manifestations**

Tetanus may be localized at the site of injury resulting in local pain and rigidity often with a low mortality. When local tetanus follows head, facial injuries or chronic otitis media, cephalic tetanus can occur which is a local variant (often involving cranial nerves particularly the seventh cranial nerve) but has a higher mortality.² Both of these may progress to the more common generalized form, which may present with pain, stiffness, rigidity, trismus (rigidity of the masseter muscles), dysphagia, opisthotonus and spasms. Spasms are usually worst during the first 2 weeks with autonomic instability following some days after the onset of spasms and often peaking during the second week of the disease. Rigidity may continue after the spasms and autonomic disturbances have started to improve.

The most useful classification of tetanus is given in Table 1. There are several scoring systems in an attempt to assess prognosis, including the Phillips score, the Dakar score and the Udwadia score.² The differential diagnosis includes dystonic drug reactions, meningitis/encephalitis, rabies, tetany, strychnine poisoning, facial pathology (jaw stiffness, dental abscess). In neonates, one also has to exclude hypocalcaemia, hypoglycaemia, meningitis and meningoencephalitis, seizures due to other aetiologies.²

<table>
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<th>Classification of grades of severity of tetanus</th>
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cardiomyopathy, ECG changes, dysrrhythmias and myocardial infarction. Basal catecholamine concentrations may be increased 10-fold with greater increase in sympathetic neuronal activity compared with adrenal medullary activity (noradrenaline more marked than adrenaline). This picture is similar to that seen in phaeochromocytoma and the histological changes in the hearts of patients dying from tetanus are similar to those of patients dying from phaeochromocytoma, the similarity probably being due to persistently raised concentrations of catecholamines. It is because of this complication that we have adopted the current method of treatment, which includes extremely heavy sedation, to the extent of having to provide IPPV. It is our unsubstantiated belief that stimulation causes overreaction of the sympathetic system in a similar way to that which affects the somatic system. Treatment by paralysis alone is not logical as this treats only the somatic system and leaves sympathetic stimulation untreated. We feel, therefore, that if one uses large doses of hypnotics sufficient to cause general anaesthesia, both the somatic and sympathetic nervous system will be inhibited centrally. This is preferable to using minimum sedation with muscle relaxation where the autonomic overactivity and ‘sympathetic storm’ will be unopposed.

**TREATMENT**

**Supportive**

**Tracheostomy**

A tracheostomy should be done under general anaesthesia in an operating theatre. Although percutaneous tracheostomy is now a routine technique in many intensive care units and may have certain advantages, it may not be available in all developing countries.

**Deep venous thrombosis prophylaxis**

This is important as thromboembolic complications are an important cause of mortality due to prolonged immobility, dehydration and sympathetic overdrive. Subcutaneous heparin 5000 IU 8-hourly and graded stockings are recommended.

**Ventilation**

Many patients with the generalized form of tetanus will require intubation and ventilation both for airway protection and respiratory support particularly if their forced vital capacity is less than 1200 ml (normal 4000–5000 ml) and their peak negative inspiratory pressure is less than $-35$ cm H$_2$O (normal $-75$ to $-100$ cm H$_2$O). Patients should all receive intermittent positive pressure ventilation (IPPV) with at least 5 cm H$_2$O of positive end expiratory pressure (PEEP) provided there is no contraindication to PEEP. In the later stages of the disease other modes of ventilation may be introduced to allow an appropriate component of spontaneous ventilation (synchronized intermittent mandatory, continuous positive airway pressure or biphasic positive airway pressure ventilation). This allows reduction of sedation (if the primary pathology is improving), may minimize muscle wastage and may reduce the likelihood of critical illness neuropathies or myopathies.

**Physiotherapy and occupational therapy**

These patients need regular chest physiotherapy and often require a bronchodilator in the nebulizer. Due to the excessive secretions, both oral and bronchial, they are particularly prone to develop nosocomial pneumonias and areas of atelectasis. It is important to try and reduce the amount of secretions, which accumulate between the vocal cords and the tracheostomy cuff as this may predispose to lower respiratory infection due to microaspiration (continuous ‘vocal aid’ suctioning may help in this regard). Patients might require an additional intravenous injection of diazepam or might need to be paralysed to enable adequate physiotherapy. However, regular tracheal suctioning is essential to prevent atelectasis, lobar collapse and pneumonia. Immobility considerations are important and passive range-of-motion exercises must be instituted to maintain muscle strength and prevent deformities and contractures. Splints may be required. Physiotherapy and occupational therapy would also be required during the rehabilitation phase.

**Intravenous lines**

A central line inserted under aseptic techniques must be used because of the intravenous penicillin (although there is a shift away from the use of penicillin to other antibiotics as will be mentioned later) which is usually given for the first 10 days. As soon as this line is no longer needed it should be removed as it is just another source of infection. We try not to have any intravenous lines once the autonomic instability and spasms are well controlled on nasogastric tube medication.

**Fluid balance**

This is important due to increased losses from sweating, salivation and GIT losses. Being fluid replete may help to manage the autonomic instability. Acute renal failure is fairly common in generalized tetanus and may be
due to the fluid shifts, cardiovascular instability and rhabdomyolysis.

Feeding

A nasogastric tube (NGT) should be passed on admission and can be used immediately for drugs provided there is no ileus and nasogastric feeds can be commenced as soon as possible. The regular tube feeds with additional supplementation with vitamins and trace elements must be given. The daily caloric requirements in well-controlled tetanus will be within 15% of the predicted requirements. Early enteral feed is recommended. If this is not possible then total parenteral nutrition should be commenced early. Some units would advocate prophylaxis for stress ulcers if the patient is not being fed enterally and this may be appropriate during the period of high sympathetic outflow.

Special nursing care

A few points in the nursing care should be carefully verified:

(a) Meticulous tracheostomy care using low-pressure cuff tracheostomy tubes to try and prevent tracheal stenosis. These must be inflated correctly against a manometer.

(b) Tracheostomy securing tapes to be tied tightly with a 2-finger space only.

(c) The patient who is unable to breathe on his/her own, either because of heavy sedation or if he/she is paralysed, must have someone specially looking after him/her continuously.

(d) Use a constant-volume ventilator with all alarms correctly set.

(e) Meticulous care of pressure areas to prevent the development of bedsores.

(f) Routine oropharyngeal care (regular suctioning, dental suction, ‘vocal-aid’ suctioning).

(g) Routine ocular care (all heavily sedated patients).

(h) Pay particular attention to drip sites, tracheostome, urinary catheter and nasogastric tube to minimize the incidence of infection. The condition and the treatment may immunosuppress these patients making them more prone to infection. Strict aseptic technique and constant nursing surveillance to recognize life-threatening situations early are essential.

(i) Slight external stimuli such as noise or tactile stimulation can trigger muscle spasms and autonomic instability. The environment therefore needs to be kept as quiet and dark as possible. The nurses can co-ordinate care and contact activities by personnel from all disciplines in an effort to decrease incidence of stimulation and maintain a calm environment.

(j) Psychological care for both the patient and relatives is important and may best be co-ordinated and addressed by the nursing team who spend the most time with the patient and family. They may then bring it to the attention of the rest of the multidisciplinary team.

(k) The clinical course of tetanus is often unpredictable (particularly if there are associated complications of prolonged critical illness including ventilator-associated pneumonias, generalized sepsis, gastrointestinal haemorrhage, thromboembolic complications). All these patients should therefore be closely monitored throughout their illness and for a period of recuperation thereafter.

After the initial airway and autonomic problems it is often the level of nursing care of these long-term patients which dictates the morbidity and mortality.

Specific

Surgical debridement

The patient should be carefully examined for a wound. Early surgical debridement is an essential part of the therapy as this obligate anaerobe requires devitalized tissue, which is potentiated by the production of Tetanolysin, a substance which disrupts cell membranes damaging viable tissue. It should include wide excision of the site of infection under general anaesthesia. It can be done under general anaesthesia at the same time as the tracheostomy. If the tetanus progresses (worsening autonomic instability and spasms) for more than 5–10 days following institution of adequate therapy, further exploration and debridement of the original wound should be undertaken as foreign bodies may frequently be missed on initial exploration.

Anti-tetanus serum

About 1500–6000 units of human tetanus immunoglobulin (HTIG) should be given intravenously. A dose of 500 units may be as effective as the larger doses. Should this not be available the patient should receive 40 000 units of anti-tetanus serum (horse) intramuscularly and 40 000 units intravenously following a test dose as there is a 20% incidence of anaphylactic reactions. If the patient reacts to the test dose the anti-tetanus serum can be skipped. The true value of this therapy has not been validated and the rapidity with which the tetanospasmin fixes irreversibly to neural tissue may limit its value. The benefit of intrathecal HTIG is, as yet, not confirmed.

Antibiotics

Patients should be treated with intravenous benzylpenicillin in a dosage of 1 megaunit 6-hourly.
Metronidazole 500 mg intravenously 8-hourly (or rectal after a few days) is a safe and adequate alternative and in a prospective, open, non-randomized clinical trial those patients who received metronidazole had a lower mortality and a shorter hospital stay. This may be because penicillin acts as a competitive antagonist to GABA. It does not readily cross the blood brain barrier but in high cumulative doses may cause CNS excitability. In tetanus, these effects may worsen the effects of the toxin at the GABAergic neurons. Erythromycin, tetracycline, vancomycin, clindamycin, doxycycline and chloramphenicol would be alternatives to penicillin and metronidazole if those were unavailable or unusable in individual patients. Patients who have tetanus often have a pyrexia which might be as high as 40°C and this may be due to pyrogens, metabolic stimulation, muscular activity caused by the tetanus or due to toxin effects on the medullary centres of the brainstem. It can be expected and need not necessarily be indicative of an ongoing infection.

**Facilitative**

**Heavy sedation**

Diazepam is the mainstay of the hypnotic drugs. It has a wide margin of safety, can be given orally (via a nasogastric tube), rectally or intravenously and is a sedative, anticonvulsant and a muscle relaxant. It is also cheap and available in most parts of the world. It does have a long cumulative half-life and has active metabolites. Initially, it can be given intravenously in 10 mg increments until the patient is stabilized. In patients with severe tetanus an infusion of thiopentone sodium may be necessary in addition to the diazepam to achieve adequate control. As soon as the patient can receive oral medications via a nasogastric tube diazepam should be given orally as should all the other drugs. Diazepam is then given as required and doses greater than 1 g/day may be necessary. It is initially started in a dosage schedule of approximately 20 mg 4–6-hourly and if this is insufficient the time interval between doses is reduced until the patient is receiving diazepam in doses that may exceed 100 mg 2-hourly. At this stage, if further sedation is still necessary, the dose of diazepam can be further increased but barbiturates and/or a phenothiazine should be added in addition. Chlorpromazine is a useful sedative with alpha-adrenergic and anticholinergic effects.

Morphine may be a useful addition for its sedation properties, which may not compromise cardiac performance. However, the opioids may contribute towards unwanted gastrointestinal effects (e.g. gastroparesis, prolonged ileus or constipation) which one should try to avoid or may need further management should they occur. When necessary, we have given 240 mg phenobarbitone 8-hourly orally (alternatively up to 600 mg of amylobarbitone over 24 h), 1 g diazepam over 24 h orally and 150 μg clonidine 8-hourly orally. In addition, occasional thiopentone infusions have been necessary. It is important, however, to space the doses of different drugs and try to give one drug at a time to avoid hypotension. Dosage of hypnotics is obviously far in excess of what a normal patient would tolerate and important signs to watch for overdosage are hypothermia and hypotension. This occurs particularly when the effects of the tetanus are wearing off. With the institution of therapy, the clinical severity of the disease should not progress and its severity may then be assessed by the amount of sedative drugs required. The tetanus usually runs its self-limiting, natural course within 3–4 weeks and the sedatives are usually reduced at this time after which it may take a week or more for the patient to wake sufficiently to be considered for extubation. If the spasms or autonomic instability recur then the patient is resedated for a further week and then weaning is attempted again. Even with the long-acting benzodiazepines (diazepam), one should look for signs of withdrawal (more of a problem with the shorter-acting benzodiazepines like midazolam) and the dose may need to be reduced slowly.

**Muscle relaxants**

Muscle relaxants are now used only intermittently to control severe spasms or to enable adequate physiotherapy. They have no beneficial effect towards the autonomic instability and make it difficult to assess the signs of anaesthesia when the patient is paralysed. Muscle relaxants that may be used include pancuronium, vecuronium, rocuronium and atracurium. Pancuronium and atracurium may, however, reduce haemodynamic stability due to catecholamine effects or histamine release. It must be remembered that problems have been reported with the extended use of non-depolarizing muscle relaxants. Agents like dantrolene and baclofen have been used with varying success. Heavy sedation alone may provide adequate neuromuscular relaxation. Sedation with propofol may allow control of spasms and rigidity without additional relaxant with appropriate effects noted on EMG. With our heavy sedation regimen described above, we have also found little need for neuromuscular blocking agents.

**Further management of autonomic disturbance**

Sedation, which is useful for controlling spasms and rigidity, is also the first step in reducing autonomic instability and is essential in the management of tetanus. If the resting heart rate is more than 120 beats/min with adequate sedation, propranolol may be given in a starting dose of 10 mg twice daily by mouth. Concerns about beta-blockade and sudden death have, however, been
raised. The use of alpha-blockade should be avoided because it complicates the management without adding any positive contribution to the therapy. Alpha-blocking agents may have a small role if a patient has an unopposed vasoconstrictor response to beta-blockade. Labetalol (combined alpha- and beta-blockade) or the use of the short-acting agent esmolol may have a role although it is expensive and does not decrease catecholamine levels. Other components of autonomic instability may be treated with magnesium, which is cheap and reduces both catecholamine release and receptor responsiveness with few side-effects in the ventilated patient. Magnesium sulphate should be given as a 5 g loading dose over 20 min and then followed by an infusion of between 2 and 3.5 g/h for up to 4 weeks in ventilated patients. Appropriate monitoring of both Mg$^{2+}$ and Ca$^{2+}$ levels is required. James found this to improve the autonomic instability when used as an adjunct with appropriate sedation. Other therapies including spinal bupivacaine and more extensive use of clonidine need further investigation.

Tetanus itself induces no immunity and these patients all require active immunization with tetanus toxoid. (Toxoid 0.5 ml by intramuscular injection on discharge with a follow-up booster at 2 months and again at 6 months.)

OUTCOME

Mortality of this condition is 6–10% usually due to autonomic dysfunction or nosocomial infections especially pneumonias. Treatment of this condition can be very rewarding as full recovery is the norm among survivors although this may not be so for neonatal tetanus.

PREVENTION

Active immunization

A booster should follow three intramuscular injections of tetanus toxoid every 7 years. Alum absorbed tetanus toxoid is very effective at preventing tetanus with a failure rate of 4 in 100 million immunocompetent individuals. Neonatal tetanus can be prevented by immunization of women during pregnancy. If a wound has the possibility of being contaminated with dirt, faeces, soil or saliva or there is a lot of devitalized tissue then HTIG should be considered (250 units by intramuscular injection).

FUTURE TREATMENT POSSIBILITIES

- Increased use of propofol may have benefits but has cost implications.
- Corticosteroids have been reported to be of benefit in tetanus. They should not be recommended, however, unless further appropriately conducted studies show an acceptable risk:benefit ratio.
- Pyridoxine (vitamin B6) may help to increase GABA concentrations. Early studies in neonatal tetanus suggest that there may be some benefit with the use of this agent.
- Further use of intrathecal baclofen and/or the use of magnesium as a way of avoiding ventilation.
- Remifentanil.
- Dexmedetomidine.
- Enalaprilat.
- Intrathecal therapy with antitetanus serum remains of unproven benefit and safety.
- Single-dose vaccine.
- Alternate ventilation and ITU support.
- Interactions with HIV and how this may influence transplacental transfer of tetanus-specific maternal IgG, presentation, treatment and outcome.

CONCLUSION

Although tetanus is not common in the UK, the pathophysiology and treatment (in particular the pharmacology and ITU management) illustrate some important and interesting concepts. The reduction in mortality over the last three decades is due largely to the use of exceptionally heavy sedation rather than to muscle paralysis to control the spasms and prevent life-threatening effects of autonomic overactivity. The reduction in mortality has also been achieved by attention to detail and the improved care of long-term ITU patients. There is huge discrepancy between the incidence and related morbidity and mortality between the developed and developing world with over 400 000 neonatal deaths a year.

REFERENCES