

REVIEW ARTICLE

Tetanus: a review of the literatureT. M. Cook*, R. T. Protheroe¹ and J. M. Handel*Department of Anaesthesia and Intensive Care, Royal United Hospital, Combe Park, Bath BA1 3NG, UK**¹Present address: Intensive Care Unit, Royal Adelaide Hospital, Adelaide, South Australia***Corresponding author**Br J Anaesth 2001; 87: 477–87***Keywords:** infection, tetanus; complications, autonomic dysfunction; intensive care, management; complications, death

Tetanus is now a rare disease in the developed world. However, it remains an important cause of death worldwide and is associated with a high case mortality, particularly in the developing world. There are an estimated 800 000–1000 000 deaths from tetanus each year.²⁸ Although the incidence in developed countries is low, the mortality in the group most at risk of contracting the illness, patients over 60 yr, remains above 50%.⁷⁸ Modern intensive care management should prevent death from acute respiratory failure,¹⁰⁹ but cardiovascular complications as a result of autonomic instability and other causes of death remain problematic. In this article, we review the epidemiology, pathophysiology, clinical features, and current management of tetanus.

Epidemiology

In spite of the World Health Organization's intention to eradicate tetanus by the year 1995, it remains endemic in the developing world and WHO estimated approximately 1000 000 deaths from tetanus worldwide in 1992. This included 580 000 deaths from neonatal tetanus, with 210 000 in South East Asia and 152 000 in Africa.⁴³ The disease is uncommon in developed countries. In South Africa approximately 300 cases occur each year,¹¹⁸ approximately 12–15 cases are reported each year in Britain⁴³ and between 50 and 70 in the USA.⁴⁵

Microbiology

Tetanus is caused by a Gram-positive bacillus, *Clostridium tetani*. This is a ubiquitous bacterium with a natural habitat of soil, but can also be isolated from stools of domestic animals and humans.¹¹⁸ It is a motile, spore-forming obligate anaerobe. The spore is incompletely destroyed by boiling but eliminated by autoclaving at 1 atmosphere pressure and 120°C for 15 min. It is rarely cultured, as the diagnosis of the disease is clinical. *Clostridium tetani*

produces its clinical effects via a powerful exotoxin. The role of the toxin within the organism is not known.⁷⁵ The DNA for this toxin is contained in a plasmid. Presence of the bacterium does not indicate infection, as not all strains possess the plasmid. Bacterial antimicrobial sensitivity has been little investigated.

Vaccination

As the organism is ubiquitous and infection does not confer immunity, prevention is through vaccination. Tetanus vaccine has been available since 1923. Routine vaccination began in the UK in 1961.⁵⁶ Vaccination is started at 2 months of age with three injections performed at monthly intervals.⁵⁶ The second injection confers immunity⁹⁶ with the third prolonging its duration.¹⁰³ A booster is given before the age of 5 yr.⁵⁶ Similar responses occur in older children and adults.⁸⁰ Neonatal immunity is provided by maternal vaccination and transplacental transfer of immunoglobulin. This may be impaired in the presence of maternal HIV infection.²⁷ Immunity is not lifelong. Revaccination at 10-yr intervals is recommended in the USA.⁴⁴ In the UK, two boosters spaced 10 yr apart are recommended in adulthood, so the recommendations do not extend to vaccination beyond the third decade.⁵⁶

In the USA, more than 70% of cases⁷⁸ and 80% of deaths⁴⁵ occur in those over 50 yr. Similar proportions are reported in Europe.⁸⁹ In the UK and USA, serological surveys have demonstrated an increasing proportion of patients with inadequate immunity as age increases: 49–66% of patients over 60 yr had antibody levels below the protective level.^{22 45 91 97 115} Some have never been vaccinated, while others have lost their immunity.⁸⁹

Pathophysiology

Under anaerobic conditions found in necrotic or infected tissue, the tetanus bacillus secretes two toxins: tetanospas-

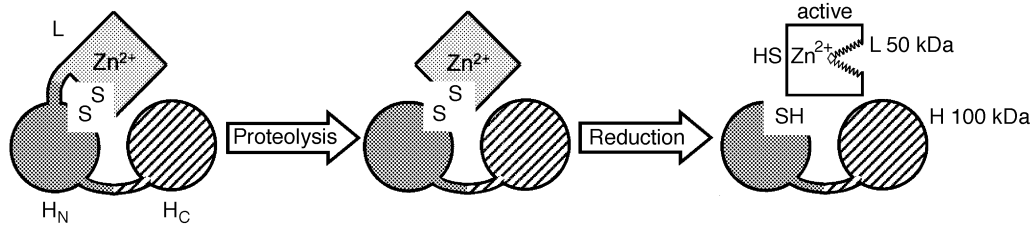


Fig 1 Scheme of the structure and mechanism of activation of tetanus and botulinum neurotoxins. The toxins are produced as an inactive single polypeptide chain of 150 kDa, composed of three 50 kDa domains, connected by protease-sensitive loops. The toxins are activated upon selective proteolytic cleavage, which generates two disulphide-linked chains: L (50 kDa) and H (100 kDa). The three domains play different functional roles in cell penetration: H_c is responsible for cell binding and H_n for cell penetration. Reduction takes place inside the nerve cells and liberates the activity of the L chain in the cytosol. L is a zinc-endopeptidase specific for protein components of the neuroexcitatory apparatus. Originally published in *Quarterly Review of Biophysics* 1995.⁷⁶

min and tetanolysin. Tetanolysin is capable of locally damaging otherwise viable tissue surrounding the infection and optimizing the conditions for bacterial multiplication.⁸⁷

Tetanospasmin leads to the clinical syndrome of tetanus. This toxin may constitute more than 5% of the weight of the organism.⁷⁴ It is a two-chain polypeptide of 150 000 Da which is initially inactive. The heavy chain (100 000 Da) and the light chain (50 000 Da) are linked by a protease sensitive loop that is cleaved by tissue proteases leaving a disulphide bridge linking the two chains. The carboxyl terminus of the heavy chain binds to neural membrane and the amino terminus facilitates cell entry.¹²⁰ The light chain acts pre-synaptically to prevent neurotransmitter release from affected neurones. Released tetanospasmin spreads to underlying tissue and binds to gangliosides GD_{1b} and GT_{1b} on the membranes of local nerve terminals. If toxin load is high, some may enter the bloodstream from where it diffuses to bind to nerve terminals throughout the body. The toxin is then internalized and transported intra-axonally and retrogradely³⁹ to the cell body.⁶⁵ Transport occurs first in motor⁹ and later in sensory and autonomic nerves (Fig. 2).¹¹⁶ Once in the cell body the toxin can diffuse out so affecting and entering nearby neurones. When spinal inhibitory interneurons are affected symptoms occur.¹¹ Further retrograde intraneural transport occurs with toxin spreading to the brainstem and midbrain. This passage includes retrograde transfer across synaptic clefts by a mechanism that is unclear.

After internalization into inhibitory neurones the disulphide bonds linking the light and heavy chains are reduced, liberating the light chain. The effects of the toxin result from prevention of the release of neurotransmitters.^{21 23 24} Synaptobrevin is a membrane protein necessary for the export of intracellular vesicles containing neurotransmitter. The tetanospasmin light chain is a zinc metalloprotease, which cleaves synaptobrevin at a single point, thereby preventing neurotransmitter release.^{84 100} The toxin has a predominant effect on inhibitory neurones, inhibiting release of glycine and gamma-aminobutyric acid (GABA).^{21 23 24} Interneurones inhibiting alpha motor neurones are first affected and the motor neurones lose inhibitory control. Later (because of the longer path) pre-

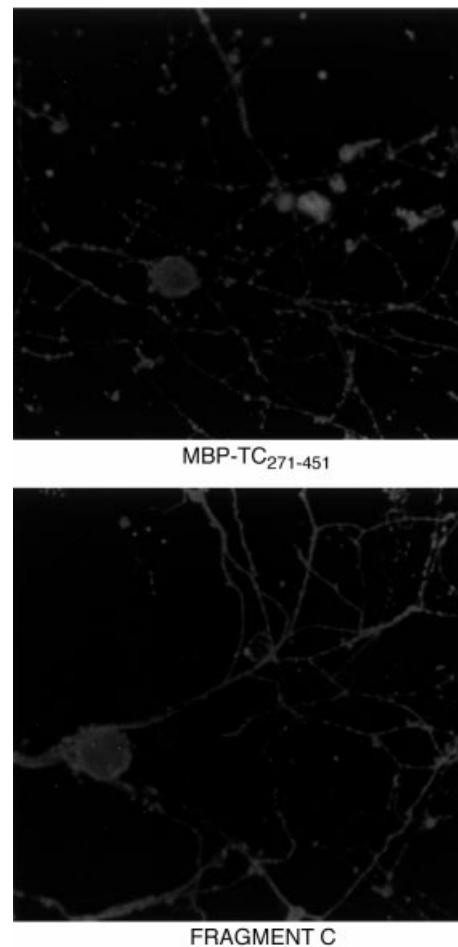


Fig 2 Radio-labelled fragment C of tetanus toxin in the dorsal root ganglion showing tetanus toxin within axons and nerve cell bodies. (Kindly provided by Dr N. Fairweather of Department of Biochemistry, Imperial College, London.)

ganglionic sympathetic neurones in the lateral horns and the parasympathetic centres are also affected. Motor neurones are similarly affected and the release of acetylcholine into the neuromuscular cleft is reduced.¹¹ This effect is similar to the action of the closely related botulinum toxin, which produces a flaccid paralysis.⁷⁵ However, in tetanus the



Fig 3 Risus sardonicus. (Kindly provided by Dr J. Farrar and Dr C. Parry of the University of Oxford Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Viet Nam.)



Fig 4 Left facial nerve palsy and recent scar in patient with cephalic tetanus. (Kindly provided by Dr T. M. Cook, taken at the University of Oxford Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Viet Nam.)

disinhibitory effect on the motor neurone overwhelms any diminution of function at the neuromuscular junction. Medullary and hypothalamic centres may also be affected. Tetanospasmin has a cortical convulsant effect in animal studies.^{14 19} Whether these mechanisms contribute to intermittent spasm and autonomic storms is unclear. The pre-junctional effect on the neuromuscular junction may lead to considerable weakness between spasms⁷⁵ and might account for both the paralysis of cranial nerves observed in cephalic tetanus⁵⁷ and myopathies observed after recovery.⁷⁵ In other species, tetanus produces an illness characterized by flaccid paralysis.⁷⁵

Uncontrolled disinhibited efferent discharge from motor neurones in the cord and brainstem leads to intense muscular rigidity and spasm, which may mimic convulsions. The reflex inhibition of antagonist muscle groups is lost and agonist and antagonist muscles contract simultaneously. Muscle spasms are intensely painful and may lead to fractures and tendon rupture. Muscles of the jaw, face, and head are often involved first because of their shorter axonal pathways. The trunk and limbs follow but peripheral muscles in the hands and feet are relatively spared.

Disinhibited autonomic discharge leads to disturbances in autonomic control, with sympathetic overactivity and excessive plasma catecholamine levels.

Neuronal binding of toxin is thought to be irreversible. Recovery requires the growth of new nerve terminals^{11 33 98} which explains the prolonged duration of tetanus.

Clinical features

Tetanus usually follows a recognized injury. Contamination of wounds with soil, manure, or rusty metal can lead to tetanus. It can complicate burns, ulcers, gangrene, necrotic snakebites, middle ear infections, septic abortions, childbirth, intramuscular injections, and surgery. Injuries may be

trivial and in up to 50% of cases the injury occurs indoors and/or is not considered serious enough to seek medical treatment.^{37 78} In 15–25% of patients, there is no evidence of a recent wound.

There is a clinical triad of rigidity, muscle spasms and, if severe, autonomic dysfunction. Neck stiffness, sore throat, and difficulty opening the mouth are often early symptoms.^{4 37} Masseter spasm causes trismus or ‘lockjaw’. Spasm progressively extends to the facial muscles causing the typical facial expression, ‘risus sardonicus’, and muscles of swallowing causing dysphagia (Fig. 3). Rigidity of the neck muscles leads to retraction of the head. Truncal rigidity may lead to opisthotonus and respiratory difficulty with decreased chest wall compliance.

In addition to increased muscle tone, there are episodic muscular spasms. These tonic contractions have a convulsion-like appearance affecting agonist and antagonist muscle groups together. They may be spontaneous or triggered by touch, visual, auditory, or emotional stimuli. Spasms may vary in severity and frequency but may be strong enough to cause fractures and tendon avulsions.¹¹ Spasms may be almost continual, leading to respiratory failure.⁶⁹ Pharyngeal spasms are often followed by laryngeal spasms and are associated with aspiration and life-threatening acute airway obstruction.

In the commonest form of tetanus, *generalized tetanus*, muscles throughout the body are affected. The muscles of the head and neck are usually affected first with progressive caudal spread of rigidity and spasm to affect the whole body. The differential diagnosis includes orofacial infection, dystonic drug reactions, hypocalcaemia, strychnine poisoning, and hysteria.

With lower toxin loads and peripheral injuries *local tetanus* is seen. Spasm and rigidity are restricted to a limited area of the body.³⁵ Mortality is greatly reduced. An exception to this is *cephalic tetanus* when localized tetanus



Fig 5 Severe opisthotonos in tetanus neonatorum. (Kindly provided by Dr J. Farrar and Dr C. Parry of the University of Oxford Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Viet Nam.)



Fig 6 Severe spasm with flexion of the arms in tetanus neonatorum. Dr J. Farrar and Dr C. Parry of the University of Oxford Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Viet Nam.

from a head wound affects the cranial nerves; paralysis rather than spasm predominates at presentation (Fig. 4), but progression to generalized tetanus is common and mortality is high.⁵⁷

Tetanus neonatorum causes more than 50% of deaths from tetanus worldwide⁴³ but is very rare in developed countries.⁷⁸ Neonates present within a week of birth with a short history of failure to feed, vomiting, and 'convulsions'. Seizures, meningitis, and sepsis are differential diagnoses (Figs 5 and 6). Spasms are generalized and mortality is high. Poor umbilical hygiene is the cause of the disease but it is entirely preventable by maternal vaccination, even during pregnancy.²⁶

Before the introduction of artificial ventilation, many patients with severe tetanus died from acute respiratory failure.¹⁰⁹ With the development of intensive care it became apparent that severe tetanus was associated with marked autonomic instability.^{37 64} The sympathetic nervous system is most prominently affected. Clinically, increased sympathetic tone causes persistent tachycardia and hypertension. Marked vasoconstriction and pyrexia are seen. Basal plasma catecholamine levels are raised.⁶³ 'Autonomic storms' occur with marked cardiovascular instability. Severe hypertension and tachycardia may alternate with profound hypotension, bradycardia, or recurrent cardiac arrest.^{64 110} These alterations are a result of, predominantly, rapid alterations in systemic vascular resistance rather than cardiac filling or performance.^{58 108} During these 'storms' plasma catecholamine levels are raised up to 10-fold, to similar levels to those seen in pheochromocytoma.^{31 62 108} Norepinephrine is affected more than epinephrine.^{31 108} Neuronal hyperactivity rather than adrenal medullary hyperactivity appears to predominate.^{108 111}

In addition to the cardiovascular system, other autonomic effects include profuse salivation and increased bronchial

secretions. Gastric stasis, ileus, diarrhoea, and high output renal failure may all be related to autonomic disturbance.

The involvement of the sympathetic nervous system is established.⁶⁴ The role of the parasympathetic system is less clear. Tetanus has been reported to induce lesions in the vagal nuclei,⁸ while locally applied toxin may lead to excessive vagal activity.⁵ Hypotension, bradycardia, and asystole may arise from increased vagal tone and activity.^{37 111}

Natural history

The *incubation period* (time from injury to first symptom) averages 7–10 days, with a range of 1–60 days. The *onset time* (time from first symptom to first spasm) varies between 1–7 days. Shorter incubation and onset times are associated with more severe disease. The first week of the illness is characterized by muscle rigidity and spasms, which increase in severity. Autonomic disturbance usually starts several days after the spasms and persists for 1–2 weeks. Spasms reduce after 2–3 weeks, but stiffness may persist considerably longer. Recovery from the illness occurs because of re-growth of axon terminals^{11 33 98} and by toxin destruction.²⁵

Severity grading

Several grading systems (Phillips, Dakar, Udwadia) are reported.^{86 111 113} The system reported by Ablett is most widely used (Table 1).¹

Altered cardiovascular physiology

There have been relatively few studies of the effects of tetanus on the cardiovascular system. One problem is that the haemodynamic effects of both complications and

Table 1 Ablett classification of severity of tetanus¹

Grade	Clinical features
I	Mild: mild to moderate trismus; general spasticity; no respiratory embarrassment; no spasms; little or no dysphagia.
II	Moderate: moderate trismus; well-marked rigidity; mild to moderate but short spasms; moderate respiratory embarrassment with an increased respiratory rate greater than 30; mild dysphagia.
III	Severe: severe trismus; generalized spasticity; reflex prolonged spasms; increased respiratory rate greater than 40; apnoeic spells; severe dysphagia; tachycardia greater than 120.
IV	Very severe: grade III and violent autonomic disturbances involving the cardiovascular system. Severe hypertension and tachycardia alternating with relative hypotension and bradycardia, either of which may be persistent.

treatment may mask the true effects of the disease itself. Udwadia studied 27 patients with Ablett grade III/IV disease who were stable and not on drugs likely to alter haemodynamics.¹¹¹ Nineteen had uncomplicated and eight complicated tetanus (with pneumonia, ARDS, sepsis). His extensive studies examined cardiovascular features of the disease: changes during poorly controlled spasms, during intense relaxation, during recovery, and the effect of fluid loading in tetanus compared with the effect in healthy volunteers. He also studied patients during periods of considerable cardiovascular instability because of autonomic storms.

Severe uncomplicated tetanus was marked by a hyperkinetic circulation. Tachycardia was universal with hypertension, raised stroke volume index, and raised cardiac index. Other findings were low normal systemic vascular resistance and normal left- and right-sided filling pressures. These findings were similar to those of James and Manson.⁵⁸ The hyperkinetic state was exaggerated during poor relaxation and increased spasm activity. The haemodynamic abnormalities became less marked during periods of full muscular relaxation but measurements only gradually returned to normal ranges during recovery from the disease. A fluid challenge of 2000 ml increased left heart filling pressures and cardiac index but these effects were very transient. During autonomic storms with marked cardiovascular instability, patients fluctuated from a hyperstimulated state of hypertension (arterial pressure up to 220/120 mm Hg) and tachycardia (heart rate 130–190 beats min⁻¹) to one of profound depression with hypotension (as low as 70/30 mm Hg), bradycardia (50–90 beats min⁻¹) and a fall in CVP (reducing from 6 to 1 cm H₂O). Invasive monitoring showed these changes to be a result of a rapid, marked alteration in systemic vascular resistance index (SVRI), falling from 2300 to less than 1000 dynes s cm⁻⁵ m⁻². There was little change in cardiac index or filling pressures. Patients with grade IV disease were less likely than those with less severe disease to raise cardiac index or cardiac work indices in response to fluid load or during alterations in vascular resistance seen during autonomic storms. One patient with severe sustained hypertension was found to have massively raised vascular resistance with SVRI greater than 4500 dynes s cm⁻⁵ m⁻². In complicated tetanus, measurements varied widely with no consistent findings.

The hyperkinetic circulation is largely because of increased basal sympathetic activity and muscle activity, with a lesser effect from raised core temperature. The low-normal SVRI is because of extensive vasodilation in metabolically active muscles. As oxygen extraction ratio does not alter in tetanus, the increased demand must be delivered by increased blood flow. Poor spasm control exaggerates these effects. Fluid loading causes only a transient rise in filling pressures, cardiac index, and LVSWI, because the circulation is widely vasodilated and hence is a high capacitance system in comparison to normal controls. In uncomplicated tetanus, the cardiovascular system, therefore, mimics that of the normal patient undergoing intense exercise. Grade IV patients appear less able to increase cardiac performance and, therefore, are more susceptible to profound hypotension and shock during acute vasodilatory storms. The mechanism is unclear but may relate to sudden withdrawal of catecholamine stimulation or a direct action of tetanus toxin on the myocardium. Altered myocardial function may be because of persistently raised catecholamine levels⁹⁵ but abnormal function may occur even in the absence of sepsis or high catecholamine levels.⁵⁴

Altered respiratory physiology

Muscular rigidity and spasms of the chest wall, diaphragm, and abdomen lead to a restrictive defect. Pharyngeal and laryngeal spasms predict respiratory failure or life-threatening airway obstruction. Poor cough from rigidity, spasms, and sedation leads to atelectasis and the risk of pneumonia is high. The inability to swallow copious saliva, profuse bronchial secretions, pharyngeal spasms, raised intra-abdominal pressure, and gastric stasis all increase the risk of aspiration, which is common. Ventilation/perfusion mismatching is also common. Consequently, hypoxia is a uniform finding in moderate or severe tetanus even when the chest is radiologically clear.¹¹² Breathing air, oxygen tensions of between 5.3–6.7 kPa are common. In artificially ventilated patients, increased A-a gradients persist.¹¹² Oxygen delivery and utilization may be compromised even without super-added lung pathology. Acute respiratory distress syndrome may occur as a specific complication of tetanus.¹¹¹ Minute ventilation may be altered by a variety of causes. Hyperventilation may occur because of fear, autonomic disturbance, or alteration in brainstem function.⁷¹

Hypocarbica (PCO_2 4.0–4.6 kPa) is usual in mild to moderate disease.¹¹² Hyperventilation ‘storms’ may lead to severe hypocarbica ($PCO_2 < 3.3$ kPa). In severe disease, hypoventilation from prolonged spasms and apnoea occurs.⁶⁹ Sedation, exhaustion and altered brainstem function may also lead to respiratory failure. Respiratory drive may be deficient leading to recurrent life-threatening apnoeic periods.¹¹²

Altered renal physiology

In mild tetanus, renal function is preserved. In severe disease reduced glomerular filtration rate and impaired renal tubular function are frequent.¹⁰¹ Contributory causes of renal failure include dehydration, sepsis, rhabdomyolysis, and alterations in renal blood flow secondary to catecholamine surges. Renal failure may be oliguric or polyuric. Clinically important renal impairment is associated with autonomic instability⁵¹ and histology is normal or shows acute tubular necrosis.¹⁰¹

Management

Treatment strategies involve three management principles: organisms present in the body should be destroyed to prevent further toxin release; toxin present in the body, outside the CNS should be neutralized; and the effects of toxin already in the CNS should be minimized.

Neutralization of unbound toxin

Human tetanus immune globulin 3–6000 units is given i.m.^{2 4 48}

Removal of the source of infection

Where present, obvious wounds should be surgically debrided.^{2 37 48} Penicillin has been widely used for many years but is a GABA antagonist and associated with convulsions.⁶¹ Metronidazole is probably the antibiotic of choice. It is safe and comparative studies with penicillin suggest at least as good results.^{3 121} Erythromycin, tetracycline, chloramphenicol, and clindamycin are all accepted as alternatives.^{2 4 37 48}

Control of rigidity and spasms

Avoidance of unnecessary stimulation is mandatory, but the mainstay of treatment is sedation with a benzodiazepine. Benzodiazepines augment GABA agonism, by inhibiting an endogenous inhibitor at the GABA_A receptor. Diazepam may be given by various routes, is cheap and widely used, but long acting metabolites (oxazepam and desmethyldiazepam) may lead to cumulation and prolonged coma. Doses as high as 100 mg h⁻¹ have been reported.⁷² Midazolam has been used with less apparent cumulation.⁵⁰ Additional sedation may be provided by anticonvulsants, particularly phenobarbitone (which further enhances GABAergic activity)⁶⁰ and phenothiazines, usually chlorpromazine.²⁵

Propofol has been used for sedation with rapid recovery on stopping the infusion.^{13 83}

When sedation alone is inadequate, neuromuscular blocking agents and intermittent positive pressure ventilation may be required for a prolonged period. Traditionally, the long acting agent pancuronium has been used.³⁶ However, pancuronium inhibits catecholamine re-uptake and could worsen autonomic instability in severe cases. There have been isolated reports of worsening hypertension and tachycardia associated with its use.^{18 40} But Dance reported no difference in complications in those treated with pancuronium compared with other neuromuscular blocking drugs.²⁵ Vecuronium is free from cardiovascular side-effects and histamine release but is relatively short-acting.^{40 88} The use of an atracurium infusion in tetanus for 71 days has been reported.⁸¹ In this patient, with normal renal and hepatic function, there was no cumulation of laudanosine, the epileptogenic metabolite of atracurium. Longer-acting agents are preferable as they lend themselves to administration by intermittent bolus rather than requiring infusion. Prolonged use of aminosteroid neuromuscular blocking agents (vecuronium, pancuronium, rocuronium, and pancuronium), particularly by infusion, has been associated with critical illness neuropathy and myopathy,⁴¹ but this has not been reported in tetanus. Of the newer agents, pipecuronium and rocuronium are long acting ‘clean’ agents but are expensive. Individual drugs have not been compared in randomized trials.

The use of dantrolene to control refractory spasms has been reported in one case.¹⁰⁷ Neuromuscular blocking drugs were unnecessary after its administration, paroxysmal spasms stopped and the patient’s condition improved.

Sedation with propofol has allowed control of spasms and rigidity without the use of neuromuscular blocking drugs.¹³ Examination of the EMG and neuromuscular function during propofol boluses.¹² showed an 80% reduction in EMG activity without alteration of function at the neuromuscular junction. However, drug levels were closer to anaesthetic than sedative concentrations and mechanical ventilation would be required.

Intrathecal baclofen (a GABA_B agonist) has been reported in several small series with varying success.^{32 92 99} Doses ranged from 500 to 2000 µg each day, given as boluses or infusion. Larger doses and boluses were associated with more side-effects.³² In all the reports, a significant number of patients developed coma and respiratory depression necessitating ventilation.^{32 99} In some cases, adverse effects were reversible with the GABA_A antagonist flumazenil, but this is not reliable.³² The technique is invasive, costly and facilities for artificial ventilation must be immediately available.

Control of autonomic dysfunction

Many different approaches to the treatment of autonomic dysfunction have been reported. Most are presented as case

reports or small series. There is a lack of comparative or controlled studies. In general, outcome measures have been limited to haemodynamic data rather than survival or morbidity. Non-pharmacological methods of preventing autonomic instability rely on *fluid loading* of up to 8 litres day⁻¹.^{66 120}

Sedation is often the first treatment. Benzodiazepines, anticonvulsants, and particularly morphine are frequently used. *Morphine* is particularly beneficial as cardiovascular stability may occur without cardiac compromise.^{18 93 94} Dosages vary between 20 and 180 mg day⁻¹. Proposed mechanisms of action include replacement of endogenous opioids,¹¹ reduction in reflex sympathetic activity and release of histamine.⁸⁵ Phenothiazines, particularly chlorpromazine are also useful sedatives; anticholinergic and α -adrenergic antagonism may contribute to cardiovascular stability.^{58 90}

Initially β -adrenergic blocking agents, such as propranolol, were used to control episodes of hypertension and tachycardia,^{37 64 90} but profound hypotension, severe pulmonary oedema and sudden death were all found to occur.^{17 37 58} Labetolol, which has combined α - and β -adrenergic blocking effects has been used, but no advantage over propranolol was demonstrated (possibly because its α activity is much less than its β activity^{31 34}) and mortality remained high.¹¹⁷ In recent years, the short-acting agent, esmolol, has been used successfully.⁶⁸ Although good cardiovascular stability was achieved, arterial catecholamine concentrations remained elevated.

Sudden cardiac death is a feature of severe tetanus. The cause remains unclear but plausible explanations include sudden loss of sympathetic drive, catecholamine-induced cardiac damage and increased parasympathetic tone or 'storms'. Persisting beta block could exacerbate these causes because of negative inotropism or unopposed vasoconstrictor activity, leading to acute cardiac failure, particularly as sympathetic crises are associated with high systemic vascular resistance and normal or low cardiac output. Isolated use of β -adrenergic block with long acting agents, therefore, cannot be recommended.

Postganglionic and α -adrenergic blocking agents such as bethanidine, guanethidine, and phentolamine have been successfully used with propranolol,^{62 90} along with other similar agents such as trimetaphan, phenoxybenzamine, and reserpine.⁸⁷ A disadvantage of this group of drugs is that induced hypotension may be difficult to reverse, tachyphylaxis occurs and withdrawal can lead to rebound hypertension.

The successful management of autonomic disturbance with i.v. *atropine* has been reported.³⁰ Doses of up to 100 mg h⁻¹ were used in four patients. The author argues that tetanus is a disease of acetylcholine excess. He suggests these extremely high doses achieve not only muscarinic but also nicotinic block providing autonomic block, central sedation, and even neuromuscular block. Block of the

parasympathetic nervous system was reported to markedly reduce secretions and sweating.

The α_2 -adrenergic agonist *clonidine* has been used orally or parenterally, with variable success. Acting centrally, it reduces sympathetic outflow, thus, reducing arterial pressure, heart rate, and catecholamine release from the adrenal medulla.¹⁶ Peripherally, it inhibits the release of norepinephrine from pre-junctional nerve endings. Other useful effects include marked sedation and anxiolysis. Two case reports reported opposing results, one with good control¹⁰⁵ and one with no alteration in haemodynamic instability.¹⁵ Gregorakos used i.v. clonidine 2 $\mu\text{g kg}^{-1}$ tds in 17 of 27 patients treated over 12 yr.⁴⁶ The group randomized to receive clonidine had a significantly lower mortality than those receiving conventional treatment.

Epidural^{49 104} and *spinal bupivacaine*¹⁰² have been reported to reduce cardiovascular instability. However, catecholamine infusions were required to maintain adequate arterial pressure.

Magnesium sulphate has been used both in artificially ventilated patients to reduce autonomic disturbance^{58 72} and in non-ventilated patients to control spasms.⁶ Magnesium is a pre-synaptic neuromuscular blocker,⁷⁹ blocks catecholamine release from nerves and adrenal medulla,¹¹⁴ reduces receptor responsiveness to released catecholamines,⁷⁹ is an anticonvulsant¹¹⁹ and a vasodilator.⁵³ It antagonises calcium in the myocardium and at the neuromuscular junction and inhibits parathyroid hormone release so lowering serum calcium. In overdose, it causes weakness and paralysis,⁷⁷ with central sedation^{10 82} although the latter is controversial.⁵⁸ Hypotension and bradyarrhythmia may occur.⁷³ It is, therefore, mandatory to maintain levels in the therapeutic range. In the report by James and Manson, patients with very severe tetanus were studied and magnesium was found to be inadequate alone as a sedative and relaxant, but an effective adjunct in controlling autonomic disturbance. Serum concentrations were difficult to predict and regular monitoring of serum magnesium and calcium levels were required.⁵⁸ Muscular weakness was apparent and ventilation was required in all cases. Attygalle and Rodrigo⁶ studied patients at an earlier stage of the illness yet all cases were probably severe and had undergone tracheostomy. They used similar doses of magnesium to try to avoid sedatives and positive pressure ventilation. They reported successful control of spasms and rigidity. Magnesium concentrations were predictable and readily kept within the therapeutic range, by using the clinical sign of the presence of a patella tendon reflex. In both studies, the absence of hypotension and bradycardia was in contrast to the results with beta block. Both authors agreed that tidal volume and cough may be impaired and secretions increased. Ventilatory support must be immediately available.^{7 59} More work is necessary on the role of magnesium both with regard to its physiological effect on neuromuscular function in the presence of tetanus and to establish what role, if any, it has in the routine management of severe tetanus.

Several drugs show potential for use in the future. *Sodium valproate* blocks GABA-aminotransferase, thereby inhibiting GABA catabolism. In animal studies, this prevents the clinical effects of tetanus toxin.⁴² *Angiotensin converting enzyme inhibitors* may also help by inhibiting the synthesis of angiotensin II, which increases norepinephrine synthesis and release from the nerve endings.¹²⁰ *Dexmedetomidine*, a more potent α_2 -adrenergic agonist than clonidine, may also have an effect in reducing sympathetic overactivity.⁸⁷ Finally, *adenosine*, which reduces presynaptic norepinephrine release and antagonizes the inotropic effects of catecholamines, has theoretical potential.⁸⁷ To date, its clinical use in this setting has not been discussed.

Supportive intensive care treatment

Weight loss is universal in tetanus.³⁷ Contributory factors include inability to swallow, autonomic induced alterations in gastrointestinal function, increased metabolic rate from pyrexia and muscular activity and prolonged critical illness. Nutrition should, therefore, be established as early as possible. Enteral nutrition is associated with a lower incidence of complications and is cheaper than parenteral nutrition. Percutaneous gastrostomy may avoid the complications associated with nasogastric tube feeding⁵² and is easily performed on the intensive care unit under sedation.

Infective complications of prolonged critical illness including ventilator-associated pneumonia are common in tetanus.^{46,112} Securing the airway early in the disease and preventing aspiration and sepsis are logical steps in minimizing this risk. As artificial ventilation is often necessary for several weeks³⁷ tracheostomy is usually performed after intubation. The percutaneous dilatational method^{20,47} appears particularly suitable for patients with tetanus.^{29,70} This straightforward bedside procedure avoids transfer to and from the operating theatre with the attendant risk of provoking autonomic instability. Prevention of respiratory complications also involves meticulous mouth care, chest physiotherapy, and regular tracheal suction, particularly as salivation and bronchial secretions are greatly increased. Adequate sedation is mandatory before such interventions in patients at risk of uncontrolled spasms or autonomic disturbance and the balance between physiotherapy and sedation may be difficult to achieve.

Other important measures in the routine management of patients with tetanus, as with any long-term critical illness, include prophylaxis of thromboembolism, gastro-intestinal haemorrhage, and pressure sores. The importance of psychological support should not be underestimated.

Complications

Complications are listed in Table 2. These may occur as a result of the disease, for example, laryngospasm; as a consequence of simple treatment, for example, sedation

Table 2 Complications of tetanus. Life-threatening complications are indicated by an asterisk (*)

Body system	Complication
Airway	Aspiration* Laryngospasm/obstruction* Sedative associated obstruction*
Respiratory	Apnoea* Hypoxia* Type I* (atelectasis, aspiration, pneumonia) and type II* respiratory failure (laryngeal spasm, prolonged truncal spasm, excessive sedation) ARDS* Complications of prolonged assisted ventilation (e.g. pneumonia) Tracheostomy complications (e.g. tracheal stenosis)
Cardiovascular	Tachycardia*, hypertension*, ischaemia* Hypotension*, bradycardia* Tachyarrhythmias, bradyarrhythmias* Asystole* Cardiac failure*
Renal	High output renal failure* Oliguric renal failure* Urinary stasis and infection
Gastro-intestinal	Gastric stasis Ileus Diarrhoea Haemorrhage*
Miscellaneous	Weight loss* Thromboembolus* Sepsis and multiple organ failure* Fractures of vertebrae during spasms Tendon avulsions during spasms

leading to coma, aspiration or apnoea; or intensive treatment, for example, ventilator-associated pneumonia.

Mortality and outcome

Case fatality rates and causes of death vary dramatically according to the facilities available. Trujillo and colleagues reported a reduction in mortality from 44 to 15% after the introduction of intensive care treatment.¹⁰⁹ In developing countries, without facilities for prolonged intensive care and ventilatory support, deaths from severe tetanus exceed 50% with airway obstruction, respiratory failure, and renal failure as prominent causes. A mortality of 10% has been suggested as an acceptable goal in developed countries.⁹⁸ Modern intensive care should prevent death from acute respiratory failure but as a result, in severe cases, autonomic disturbance becomes more apparent. Trujillo reported that 40% of deaths after introduction of ICU care were a result of sudden cardiac death and 15% a result of respiratory complications. Before ICU was established, 80% of historical controls died as a result of early acute respiratory failure.¹⁰⁹ Important complications of ICU care include nosocomial infections, particularly ventilator-associated pneumonia, generalized sepsis, thromboembolism, and gastrointestinal haemorrhage. Mortality varies with patient age. In the USA, mortality in adults below 30 yr may approach zero, but in those over 60 yr is 52%.⁷⁸ In Portugal,

between 1986 and 1990 all age mortality varied between 32 and 59%.⁹² In Africa, mortality from neonatal tetanus without artificial ventilation was reported as 82% in 1960¹⁰⁶ and 63–79% in 1991.³⁸ With artificial ventilation available this may be as low as 11%⁶⁷ but other authors report rates close to 40%.²⁶

Severe cases of tetanus generally require ICU admission for approximately 3–5 weeks.^{26 37 58 72 92 109 111} Recovery can be expected to be complete, with return to normal function. However, in one of the few follow-up studies in survivors of tetanus, persisting physical and psychological problems were frequent.⁵⁵

Conclusions

Tetanus is fortunately a rare disease in the UK and is entirely preventable by vaccination. It remains a major health problem worldwide. In developed countries, several cases present every year in the elderly and unimmunized population. Mortality in these cases remains high. Prolonged intensive care support may be necessary but most treatment is based on limited evidence. Major therapeutic challenges lie in the control of muscular rigidity and spasms, the treatment of autonomic disturbance and the prevention of complications associated with prolonged critical illness. Return to normal function can be expected in those who survive.

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