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Tetanus

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Abstract Despite long-standing availability of a vaccine, tetanus continues to cause high morbidity and mortality throughout the world. In the developed world, the elderly have traditionally been most at risk due to decline in protective antibody levels, however recent cases have occurred in younger people, particularly injecting drug users. Much of the management is supportive, although treatment aimed at preventing toxin release and uptake into the central nervous system should be given. Recent studies have focussed on optimizing antitoxin effect and improving control of muscle spasms and cardiovascular instability. This paper reviews these and other current concepts regarding the pathophysiology and management of tetanus.

Introduction

Tetanus is a toxin-mediated disease caused by the bacterium *Clostridium tetani*. Although relatively rare in the developed world, it has recently received particular attention following an outbreak in the UK.[1] It derives its name from the Greek word 'tetanos' meaning 'contract' and has been known since antiquity, with descriptions appearing in the Edwin Smith papyrus of ancient Egypt (ca. 1600 BC), the writings of Aristotle (ca. 400 BC) and the Ayurvedic texts of ancient India (C 400 AD).[2,3] Routine vaccination began in the UK in 1961, and the disease has been central to the WHO's Expanded Programme on Immunization since 1974.[4] The implementation of good immunization programmes has led to a global decline in incidence.[5] Nevertheless the disease continues to be an important global cause of morbidity and mortality, affecting an estimated 700,000–1,000,000 people every year.[6,7]

Despite this, there has been little contemporary research into disease treatment and evidence of beneficial effect of most therapy is poor.[6] As most disease occurs in the developing world, there is a desperate need for simple interventions that do not require sophisticated facilities, such as mechanical ventilation. This paper reviews the current knowledge of tetanus, with particular focus on evidence from recent clinical trials.

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Epidemiology

Tetanus is primarily a disease of unvaccinated individuals and occurs wherever public health programmes are poor, thus the majority of cases arise in the developing world. *C. tetani* is an ubiquitous organism, able to persist as resistant spores in soil, faeces and dust.[8] Therefore, unlike other infectious diseases, non-immune individuals remain vulnerable irrespective of the immune status of the surrounding population.

In the UK, cases are under-reported by an estimated 54–64%,[9] and just four cases were reported in 2002.[10] In the same year 25 cases were reported in the USA.[11] These cases mostly occurred in older patients in whom serum antibody concentrations are lowest. A recent study of 180,000 people in the USA showed only 50% of those over 60 years old had adequate serum concentrations of anti-tetanus antibody.[12] However, unvaccinated people of any age are at risk, as illustrated by the recent cluster of cases amongst injecting drug users in the UK, where 20 cases have occurred since July 2003.[1] Immunization details are incomplete, but 8 out of 10 recalled no or incomplete immunizations and only 1 out of 8 patients had protective levels of antibodies. This patient experienced only mild disease.

In some circumstances, standard immunization regimes may be insufficient. Both malaria and HIV have been shown to reduce transplacental transfer of antibody,[13,14] and neonatal tetanus has been reported despite 'protective' maternal concentration of antibody.[15]

Postexposure immunization and/or antitoxin is recommended for incompletely immunized patients or those sustaining high-risk wounds.[16] Nevertheless, this is often overlooked. In 2002, Cassel reported inadequate tetanus management in British hospitals, resulting in 27% of admissions to a plastic surgery unit requiring further action.[17] Similar results have been reported elsewhere.[18,19] These deficiencies in immunization and prophylaxis mean that complete tetanus eradication is unlikely and the disease will continue to occur.

Pathophysiology

Tetanus occurs after contamination of a wound with material containing *C. tetani* spores. Injuries are mostly minor abrasions to the limbs, and in approximately 20% of cases, no entry site can be found.[20] Infections arising from surgical wounds, injection sites or postpartum are associated with higher case-fatality rates (43–72%), compared to limb or unknown entry sites (14–16%).[20]

Anaerobic conditions within the wound allow the spores to germinate and multiply. *C. tetani* is a Gram-positive anaerobic bacillus that produces a highly potent neurotoxin. The DNA sequences of both bacteria and toxin are now known.[21,22] Tetanus toxin is similar in structure to botulinum toxins, consisting of heavy and light chains joined by a disulphide bond.[23] The heavy chain is necessary for neuronal uptake and transport of the toxin in the motor neurone, whereas the light chain is a zinc-dependent endopeptidase responsible for the toxin's pathological actions.[24] The *N*-terminal domain of the heavy chain may be involved in interneuronal sorting and trafficking, whereas the C terminal is necessary for specific binding and neuronal uptake of the toxin.[25] This region has four carbohydrate binding sites and has been shown to interact with polysialogangliosides and glycosylphosphatidylinositol (GPI)-anchored glycoproteins.[24,26] These are both components of microdomains of the membrane known as lipid rafts and it has been hypothesized that these areas mediate specific toxin binding.[25]

Once inside the motor neurone, the toxin undergoes retrograde transport to reach the soma of the motor neurone, then trancystosis to the γ-amino butyric acid (GABA) inhibitory interneurones where it cleaves vesicle-associated membrane protein (VAMP or synaptobrevin), preventing release of neurotransmitter and blocking inhibitory pathways.[24] The precise mechanism of retrograde transport is unknown, although the toxin may use a synaptic vesicle recycling pathway, thereby avoiding degradation. This may be the same pathway as used by nerve growth factor (NGF), which also undergoes retrograde transport and accumulates within the cell bodies of motor nerves without degradation. Recently, tetanus toxin and NGF have been shown to share the same transport carriers and exhibit similar retrograde transport kinetics in vivo.[25]

Inhibition of inhibitory pathways is apparent in motor and autonomic systems. Symptoms arise 1–2 weeks after infection (termed the incubation period) (Fig. 1). Muscle tone increases over a period of days (period of onset) progressing to spasms. This gives rise to symptoms of muscle stiffness, pain and dysphagia and the classic signs of hypertonia, trismus and muscle spasms. Spasm of the facial muscles produces the characteristic 'risus sardonicus' whereas spasm of paravertebral muscles results in opisthotonus. Spasms may be spontaneous or result from external stimuli and are maximal during the first 2 weeks of illness. Towards

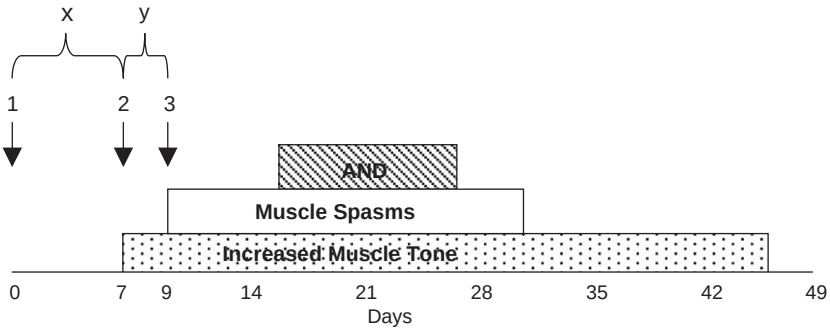

Fig. 1 Natural history of severe tetanus. AND—Autonomic disturbance; 1—wound; 2—first symptom; 3—first spasm; *x*—incubation period; *y*—period of onset.

the end of the first week, in severe disease, disinhibition of the autonomic nervous system becomes apparent, with fluctuating hypertension, tachycardia, pyrexia and profuse sweating. Hypertension is associated with increased systemic vascular resistance and little change in cardiac output.[27] Less commonly hypotension and bradycardia occur.[28] Profuse bronchial and salivary secretions are characteristic and gastrointestinal disturbance may also be seen.[3,29] Periods of autonomic disturbance have been associated with elevated catecholamine concentrations,[30] although these measurements used old and unreliable assays and these findings have been disputed.[31] Non-oliguric acute renal failure has been reported in association with autonomic dysfunction.[32] Dehydration and rhabdomyolysis may also contribute to renal dysfunction.[33,34]

Disease severity may be graded, most commonly using a modified version of the score proposed by Ablett,[29,35] which divides patients into four grades of severity based upon intensity of spasms, respiratory compromise and autonomic involvement. Severe disease is associated with short incubation period and period of onset, entry site, age, tachycardia and pyrexia on admission (Table 1, Fig. 2).[36,37] Combinations of these and other variables have been used to create prognostic scores.[38–40] However, these scores were published over 26 years ago and require statistical validation with current clinical data as their performance with contemporary data is unknown.

Table 1 Features associated with poor outcome in tetanus.

Increasing age, or neonatal tetanus[37,36]
Short incubation period[36]
Short period of onset[36]
Short time from first symptom to admission[38]
Fever on admission[37,36]
Tachycardia on admission[37,36]
Severe disease or spasms on admission[38]
Puerperal, IV entry site, postsurgery, burns[37,36,20]

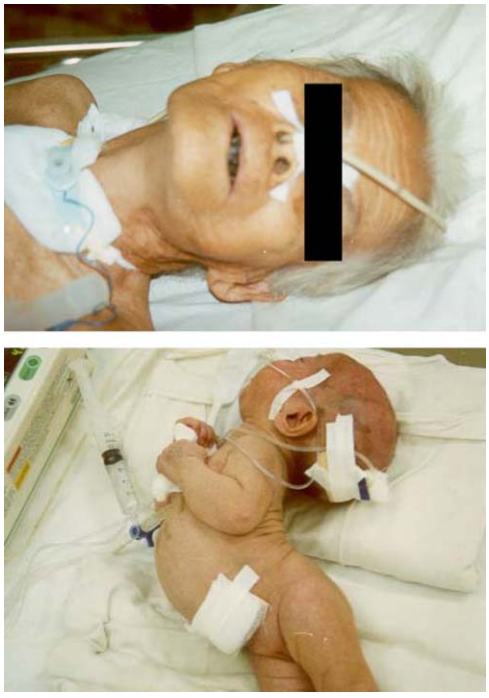

Fig. 2 Acute tetanus. Prognosis is worst at the extremes of age.

Management

The priorities in tetanus management are maintenance of airway and ventilation. Spasms of pharyngeal and laryngeal muscles are common

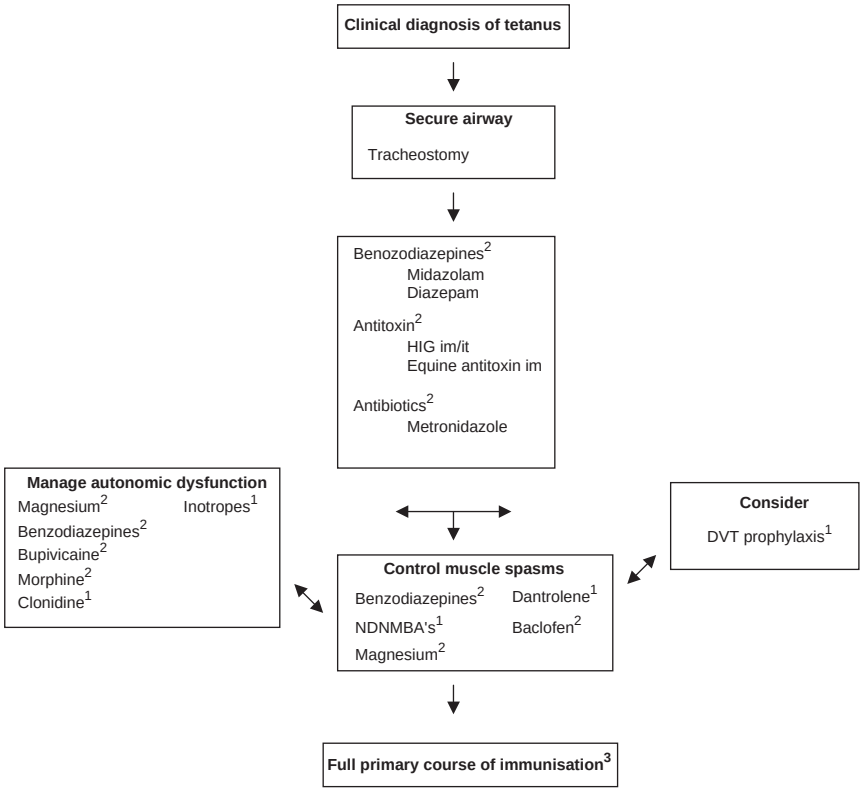

Fig. 3 Flow diagram showing the management of tetanus. 1—limited evidence; 2—some evidence; 3—good evidence.

and may occur in isolation. Profuse secretions, trismus and hypersensitivity of the larynx mean tracheostomy is the preferred method of securing the airway,[41,42] especially as patients often require long periods of mechanical ventilation (Fig. 3).

Once the patient is stable, specific treatment aimed at eliminating further toxin release and uptake should be instituted. A thorough search for an entry site should be made, and any necrotic tissue removed. Metronidazole should be given for 7–10 days to eradicate the causative bacteria. Penicillin may also be used, but is associated with higher requirements for sedatives and muscle relaxants,[43] and, in one open randomized controlled trial (RCT) of 175 patients, significantly worse mortality rates (24% vs. 7%, $P<0.01$).[44] This may be related to structural similarities between penicillin and GABA, which allow penicillin to act as a competitive GABA antagonist.[45]

Antitoxin is administered to neutralize any unbound toxin. It is available as two preparations: equine or human immune globulin (HIG). One double blind RCT has compared the two in 135 neonates and found no difference in mortality.[46] Equine preparations are cheaper and widely used in the developing world, but are associated with more adverse reactions; therefore HIG (100–300 IU/kg) is the treatment of choice.[43]

There has been a long-standing debate over the optimal route of antitoxin administration after Ildirim demonstrated decreased progression of tetanus and reduced mortality in those given intrathecal antitoxin.[47] These data led to a series of studies and a meta-analysis of these, published in 1991, reported that a modest benefit was seen in adults treated by the intrathecal route using equine antitoxin, but not HIG, and no benefit in neonates.[48] However, the results of a recent study conflict with this finding.[49] In this study, 120 Brazilian patients aged >12 years were randomized to receive 1000 IU intrathecal and 3000 IU intramuscular HIG or 3000 IU intramuscular HIG alone. Disease severity and presence of spasms were recorded daily and disease progression was assessed from these data, although it is unclear exactly how this was done. The authors report a significant reduction in disease progression in those treated with intrathecal antitoxin. Duration of spasms, mechanical ventilation and hospital stay were reduced in this group, whilst non-significant reductions in mortality and proportion requiring mechanical ventilation also occurred. The study was not fully blinded and the outcome assessment subjective, reliant on a doctor's assessment of disease severity. Nevertheless, the consistency of findings across all

outcome measures suggested a genuine treatment effect.

Benzodiazepines (diazepam or midazolam intravenously) are the traditional first-line treatment in tetanus, although, like other tetanus therapy, there is little evidence to support their use. A recent Cochrane review[50] identified only two suitable studies enrolling a total of 134 children, and concluded that although diazepam was more effective than phenobarbitone and chlorpromazine, evidence was not sufficient to recommend a change in clinical practice. Nevertheless, benzodiazepines, which augment GABA action, are theoretically an appropriate choice and are used widely.[3,43] High doses are used commonly, and doses of 100 mg/h or 480 mg/day have been reported.[51,52] Propofol has also been used in tetanus, without adjunctive neuromuscular blocking agents.[53,54] However, high doses were required, thus access to mechanical ventilation necessary.[29]

Severe spasms require non-depolarizing neuromuscular blocking agents (NDNMBAs) to provide adequate muscle relaxation. Traditionally, tubocurarine has been used[27,55] as its ganglion-blocking effects have been desirable. Modern drugs with minimal cardiovascular effects are now recommended. Satisfactory results with vecuronium, pipecuronium and atracurium have been reported.[20,27,29,56] Pancuronium, with its sympatheticomimetic effects, should be avoided as it has been associated with worsening of autonomic instability.[27,57] A recent retrospective study has reported successful use of intrathecal baclofen in tetanus.[58] Twenty-one patients were treated using infusions through a subarachnoid catheter. Satisfactory spasm control was reported and the treatment described as safe and efficacious, although one patient died of meningitis and seven catheters were noted to be colonized.

Recently, there has been interest in using magnesium sulphate to treat severe tetanus. Magnesium causes muscle relaxation, vasodilatation and reduces catecholamine release,[52,59,60] all of which may be desirable in tetanus. Attygale and Rodrigo treated 40 patients with magnesium, increasing infusion rates until spasms were controlled, serum levels were >4 mmol/l, or the patella reflex disappeared.[61] Only 2 patients required NDNMBAs to control spasms. Of the 24 patients aged <60 years, only 7 required mechanical ventilation, although 10 of the 16 over 60-year olds did. No patient required additional treatment for autonomic instability. The authors state a larger than expected proportion of patients did not require mechanical ventilation, although no control data was supplied.

James and Manson conducted an open study of magnesium sulphate in 10 patients with severe autonomic disturbance.[62] These patients were already receiving high dose sedation with diazepam, morphine, chlorpromazine and phenobarbitone yet continuing to experience spasms and cardiovascular instability. Comparisons were made between the greatest fluctuations of systolic blood pressure (SBP) and heart rate in the 48 h prior to treatment with those in the 7 days of treatment. The authors reported satisfactory cardiovascular control in all except one patient who died of sepsis. Haemodynamic measurements in 6 patients showed no change in cardiac index, but reduced heart rate and increased stroke volume. By using each patient as their own control, problems of adequately matching a control group with such small numbers of patients were overcome. However, as comparisons were made before and after therapy, it is impossible to say that benefits observed were not influenced by patient recovery. Thus, although two positive studies have been published supporting the use of magnesium sulphate in tetanus, changes in practise should await a larger RCT.

Other drugs reported in the management of autonomic dysfunction include morphine (up to 200 mg/day)[57,63,64] and clonidine.[27] Epidural bupivicaine has also been shown to significantly reduce heart rate and blood pressure variation in tetanus,[65,66] but no RCT has been performed.

Beta-adrenergic receptor blockade is controversial, as it has been reported to be associated with sudden cardiac arrest and unresponsive hypotension.[67] A series of 15 patients treated with oral and intravenous labetolol reported that BP fluctuations were poorly controlled, 3 patients died of sudden cardiac arrest and 3 following profound and unresponsive hypotension.[68] The short-acting drug esmolol may be better,[69] although no study to support its use has been published.

Tetanus patients are susceptible to complications such as nosocomial infections (particularly ventilator acquired pneumonia),[70] deep vein thrombosis and pulmonary embolus.[3] Gastro-intestinal bleeding may occur, but is usually limited. Muscle spasms and hypertonia make nursing care and physiotherapy difficult and the recovery period may be prolonged.

Recovery occurs due to neuronal regrowth and toxin degradation.[71,72] Adult patients tend to make a full recovery.[73] The prognosis of neonatal tetanus is worse. Few long-term studies have been performed, but there are indications of increased cerebral palsy, learning and behavioural problems, especially in those with frequent hypoxic episodes.[74,75]

Before discharge from hospital, patients require a full primary vaccination course, as tetanus does not result in natural immunity. Recurrent tetanus has been documented when only booster immunization was performed after tetanus.[76]

Summary and future directions

Much is now known about the action of tetanus toxin within the nervous system, however this knowledge has not yet been translated into novel therapeutic approaches. Attempts have been made to synthesize specific toxin inhibitors, either zinc chelators or endopeptidase inhibitors, but have only been tested in vivo.[77–79] Specific therapy still consists of antibiotic and antitoxin administration, and recent evidence indicates that disease progression may be reduced or reversed if antitoxin is administered intra thecally. Encouraging preliminary data also exists suggesting magnesium sulphate may be beneficial in treating spasms and autonomic disturbance of established tetanus. However, as no control patients have been enrolled into these studies, results should be interpreted cautiously. Nevertheless, therapies that reduce the need for costly interventions are urgently needed in the developing world, and more work is required to answer these questions. Equally, although tetanus treatment remains unsatisfactory, prevention is possible if vaccination and primary care programmes are effective, thus these measures should remain the focus of anti-tetanus strategy.

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