New trends in the management of tetanus

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The prevalence of tetanus reflects a failure of immunization. Prompt diagnosis and prediction of severity are crucial for the prevention of early lifethreatening complications and the institution of appropriate management. The current symptomatic treatment of heavy sedation, paralysis and artificial ventilation for 3–5 weeks for moderate and severe tetanus, is, even in the best centers, still associated with unacceptably high mortality, due to the disease and complications of the therapy itself. It is especially inappropriate for the developing world where intensive care resources are minimal. New options reported to avoid artificial ventilation and sedation are dantrolene (Dantrium®, Procter and Gamble Pharmaceuticals), baclofen (Lioresal®, Novartis) and magnesium. Magnesium therapy has the advantages of controlling spasms and sympathetic over activity without sedation. This simplifies nursing care and minimizes the need for ventilatory support except in the very severe disease and the elderly. Magnesium is recommended as the first-line therapy in tetanus.

CONTENTS

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'Convulsions occasioned by wounds have by almost all authors since the days of Hippocrates, been pronounced as mortal, especially that called locked jaw'. Chalmers (1777).

Tetanus is one of the ancient diseases which still remains an enigma, with its treatment becoming ever more demanding both technologically and economically, with little reduction in mortality.

Despite a better understanding of the pathophysiology of the disease, which has been explored to a molecular level, no specific drug has been discovered which can counteract the toxin once it has bound to the nervous tissue and the disease established. Even today in the 21st century, treatment of tetanus is essentially symptomatic and management regimens have not significantly improved the outcome.

Epidemiology

Tetanus is still with us and it still kills, despite the declared intention of the World Health Organization to eradicate it by 1995. Deaths from tetanus are estimated to be in excess of one million a year. Since the expanded immunization program was established, tetanus has become essentially a disease of the developing world where 50% of deaths due to tetanus occur in neonates [1].

In the developed world, the reported incidence of adult and childhood tetanus is low. Approximately 12–15 cases are reported annually in the UK [2] and about 50–70 in the USA [3]. However, the true incidence is higher as under reporting is common [4–7]. In the USA, the completeness of overall reporting to the National Surveillance System between 1979 and 1984 was estimated to be 22–46% [4]. The risk of developing tetanus is higher in the very subset of the population in which it is most lethal, namely the elderly [5,8,9], the immunocompromised and drug abusers [8,10,11]. Neonatal tetanus has been almost totally eradicated by maternal immunization.

Prophylaxis

The prevalence of tetanus today reflects a failure of the healthcare delivery system to provide immunization, which still remains the best and cheapest method of preventing

deaths. Unlike many other infectious diseases, the disease itself does not confer immunity and prevention is only possible by routine vaccination and appropriate wound management. Initial vaccination consists of three injections performed at intervals of 4–8 weeks. Immunity is established only with the second injection [12], and the third prolongs its duration [13]. Boosters are needed at 10-yearly intervals.

Effective implementation of immunization programs therefore requires repeated contact between healthcare providers and the target population, which is an expensive exercise. The cost of getting the dose of vaccine to a child (US$15) is estimated to be 30-times the cost of the vaccine itself (US$0.5). Serological surveys in the UK and USA have demonstrated that 49–66% of patients over 60 years were found to have antibodies below the protective level [3,14]. Some had never been vaccinated and others had lost their immunity.

Tetanus remains a severe disease in the USA with a case fatality of 11% [8]. The disease primarily affects unvaccinated or inadequately vaccinated people. Despite the widespread availability of safe and effective immunization, only 13% of patients of the 124 cases reported between 1995 and 1997 had received primary vaccination [8]. In addition to decennial vaccination, the Advisory Committee on Immunization Practice (ACIP) has now recommended vaccination visits for all adolescents of 11–12 years and adults aged 50 years, to enable healthcare providers to review vaccination histories and administer vaccine if needed. Every contact with the healthcare system, particularly among older adults and drug users, should be used to review and update vaccination status. If tetanus is to be totally eradicated in the developed world, enhanced tetanus case surveillance is essential for regular evaluation of the tetanus immunization policy.

Pathogenesis

Tetanus is a toxic infection caused by the obligate anaerobe *Clostridium tetani*. After entering a wound, the spore proliferates under anaerobic conditions and secretes two toxins, tetanolysin and tetanospasmin. Tetanolysin is capable of damaging viable tissue surrounding the wound and lowering the redox potential, thus optimizing conditions for bacterial multiplication. Tetanospasmin causes the clinical manifestations of the disease.

Once tetanospasmin is released, it spreads to the underlying tissue and circulates in the bloodstream from where it diffuses to nerve terminals throughout the body. The circulating toxin does not enter the central nervous system (CNS) directly, except at the fourth ventricle, as it cannot cross the blood–brain barrier. The toxin binds to the gangliosides on the membranes of nerve terminals and is then internalized and transported intra-axonally in a retrograde direction to the cell body at a rate of 75–250 mm a day. The transport of the toxin in the motor nerves takes 2–14 days to reach the CNS. The toxin migrates trans-synaptically from the cell body to the presynaptic inhibitory neurones.

Tetanus toxin inhibits the synaptic release of γ-amino butyric acid (GABA) and glycine, which are the main transmitters of the inhibitory system of the nervous system [15,16]. At a molecular level, tetanospasmin is synthesized as a single inactive polypeptide chain of 150 kDa consisting of three domains, which are connected by protease sensitive loops. The toxins are activated upon selective proteolytic cleavage, which generates a light (L) chain linked by a disulfide bridge to a heavy (H) chain. The amino terminus of the H chain is responsible for cell penetration and the carboxyl terminus for specific binding to neuronal cells.

After entry into the inhibitory neurones, the disulfide link is reduced and the L chain is released [17]. This acts presynaptically to prevent neurotransmitter release by a single site cleavage of synaptobrevin, which is the membrane protein necessary for the export of intracellular vesicles containing neurotransmitter [18]. Symptoms occur when the toxin inhibits the release of glycine and GABA in the inhibitory interneurones. The interneurones of the α-motor neurone are the first to lose their inhibitory control. The preganglionic sympathetic neurons in the lateral horns and the parasympathetic centers are affected by a similar mechanism. Autonomic dysfunction occurs some days after the onset of spasms, due to the slower transport in the autonomic nerves (longer pathway).

The toxin also acts at the neuromuscular junction where it reduces the release of acetyl choline [19]. This action, which is similar to the action of botulinus toxin, is not clinically evident (except in cephalic tetanus). This is because the inhibitory effects on the α-motor neurone predominate in tetanus, producing muscle rigidity and spasms rather than weakness [20].

The toxin travels along autonomic nerve endings to the spinal cord to enter the preganglionic sympathetic neurones of the lateral horn cells and the parasympathetic centers. The loss of inhibition of all these pathways leads to the clinical manifestations of tetanus, which consist of three main components namely muscle rigidity, muscle spasms and autonomic dysfunction (sympathetic and parasympathetic over activity). Due to the longer pathways, autonomic dysfunction occurs some days after the onset of spasms. There is a basal increase in sympathetic activity and episodes of intense hyperactivity involving both α- and β-receptors. This increase is caused by reduced inhibition of the postsynaptic sympathetic fibers and adrenal medulla, evidenced by outpourings of noradrenaline more than adrenaline in amounts comparable with those found in patients with phaeochromocytoma (about ten times the basal amounts) [21]. Other postulated causes of sympathetic over activity (SOA) are the increased release of thyroid hormone [22] and direct inhibition of the release of endogenous opiates [19].

Neuronal binding of toxin is thought to be irreversible and recovery requires the new growth of nerve terminals, which explains the long duration of the disease [19].

Management

During the first half of the 20th century, tetanus patients were treated with heavy sedation and nursed in quiet, dark rooms to reduce external stimulation. This method of treatment is still used in hospitals where ventilatory facilities are not available.

Here the mortality rate is as high as 80%; deaths being due to early respiratory failure secondary to spasms, obstruction by secretions, aspiration, exhaustion or infection [23].

The introduction of muscle relaxants, artificial ventilation and intensive care in the routine management of tetanus in the 1960s was a major landmark [24]. Trujillo, analyzing 641 cases of all grades of tetanus, found that such intensive care management reduced mortality from 43 to 15%. Causes of death changed from respiratory failure to cardiac causes due to marked autonomic dysfunction [23].

In the last two decades, heavy sedation, muscle paralysis and artificial ventilation have been the cornerstones of treatment, mortality depending to a great extent on the facilities available. In the developed world where intensive care has improved markedly, the mortality ranges from 20 to 40% in severe tetanus [9,25]. Deaths are mainly due to complications of the treatment itself or cardiovascular complications from uncontrolled sympathetic over activity (SOA). On the other hand in the developing world where tetanus is mostly prevalent, this method of treatment is inappropriate since the required intensive care facilities are limited or nonexistent. Despite these problems there have been no significant advances in the treatment of tetanus.

It is therefore appropriate to review the current methods of treatment and evaluate better alternatives so that mortality from tetanus can be reduced.

The issues that need to be addressed are:

• Early diagnosis
• Specific treatment
• Prevention of early complications
• Symptomatic treatment
• New options

Early diagnosis

Early diagnosis enables early treatment, which is crucial for survival. Tetanus is unique, in that diagnosis is based only on clinical observation with laboratory investigations being virtually of no value except as a negative finding. Clinical diagnosis takes into account a history of injury and requires a high index of suspicion to recognize the first symptom and progression of the disease. Although the disease pattern is characteristic in most cases, there may be variants from the classical presentations. A definitive diagnosis is essentially dependent upon the clinician and his familiarity with the disease.

History of injury

Tetanus follows an injury with an incubation period that can vary from 3 to 21 days. In 15–30% of patients there is no evidence of a recent wound [19], as the injury is often too trivial to be noticed, or the portal of entry may be atypical, such as infections of the skin and middle ear [26], dental caries [27], septic abortion or intramuscular injections. Thus, the exclusion of tetanus due to the absence of an obvious injury is unwise.

Clinical features

In the developing world, the diagnosis is rarely missed as physicians are familiar with the disease. In the developed world where tetanus is rare, symptoms are often mistaken for more common problems (TABLE 1). This may lead to early lifethreatening complications, as treatment is often delayed due to wrong diagnosis.

The degree of severity varies with the load of toxin produced at the wound site. The first symptom is due to rigidity of muscles supplied by the cranial nerves, trismus being the commonest presentation, followed by risus sardonicus and neck stiffness. In moderate tetanus, rigidity extends to cause severe dysphagia and generalized rigidity affecting the trunk more than the limbs. In severe tetanus, spasms occur which can embarrass respiration. In very severe tetanus, autonomic dysfunction occurs and is often the cause of death.

The spatula test is a practical simple bedside test found to be positive for 349 out of 350 patients [28]. A spatula is used to touch the back of the pharyngeal wall. A reflex contraction of the masseters gives a positive result while a typical gag reflex is considered negative for tetanus. In the authors' experience this test performed during the stage of trismus has always been successful in the early diagnosis of tetanus, thus ensuring appropriate management.

Neonatal tetanus presents around the 7th day, with failure to feed for approximately 24 h followed by generalized spasms [29]. A history of immunization during pregnancy would exclude the diagnosis, as neonatal tetanus is completely preventable except possibly in HIV positive mothers [30].

Unusual forms of presentation are seen in cephalic and local tetanus. The diagnosis of cephalic tetanus is often missed as it presents with paralysis of the cranial nerves (commonly with facial paralysis and diplopia), after wounding of the head and neck. Progression to generalized tetanus is associated with a high mortality [27,31].

Table 1. Differential diagnosis of tetanus.

Symptom	Differential diagnosis
Trismus	Alveolar/dental pathology
	Tempero–mandibular disease
Neck stiffness	Muscle spasm,
	Meningitis
Dysphagia	Acute pharyngeal disease
Spasms	Strychnine poisoning
	Inctracranial lesions
	Drug-induced dystonic reactions
Neonatal tetanus	Sepsis
	Meningitis
	Convulsions

Local tetanus occurs in approximately 2% of cases with flaccidity or rigidity and spasms restricted to muscles near the wound. It is usually associated with a low toxin load and the incubation period is long and spasms may spread from one limb to the other [32].

Specific treatment

Though the pathophysiology of the disease has been explored to a molecular level, no specific drug has been discovered which can counteract the toxin once it is bound to nervous tissue and the disease established. The only specific treatment is eradication of the organism from the wound and neutralization of the circulating toxin, which should be given irrespective of severity.

Neutralization of circulating toxin

The toxin circulates in the bloodstream during the early part of the incubation period but by the time clinical symptoms occur, most of the toxin has become firmly bound to the nervous system and cannot be accessed. Even if parenteral antitoxin is given as soon as the diagnosis is made, it can only neutralize the residual circulating toxin.

In an attempt to inactivate the toxin bound to nervous tissue, antitoxin has been administered intrathecally. Though several studies have reported the value of this technique [9,33,34], a meta analysis failed to support their use in neonatal tetanus [35]. In adults, the only truly randomized trial by Vakil was stopped when results favored the group not treated intrathecally [36]. The safety of intrathecal treatment is still debatable as some studies have reported no complications during hospitalization [37,38], one study reported transient blindness and transverse myelitis after intrathecal administration [39]. It should be noted that in the USA, equine tetanus antitoxin (ATS) is formulated for intravenous and intramuscular use, but human tetanus immunoglobulin (HTIg) is approved only for intramuscular administration. Neither has been approved for intrathecal use. Concerns have been raised regarding safety of HTIg given by intravenous or intrathecal route since the US preparation of HTIG is not filtered and contains thimerosal and aggregates of immunoglobulins. Some European manufacturers produce HTIG in a formulation that does not contain thimerosal. There is a need for well-designed controlled trials to study the efficacy and immediate and late complications of intrathecal therapy.

Intramuscular HTIg is the antitoxin of choice. The optimum dose is still debatable but 500 units are recommended, as the traditional larger doses of 3000–6000 units are of questionable benefit [40]. ATS is still used in many countries (in doses of 5000 units intramuscularly and 5000 units infiltrated around the wound) due to the nonavailability of HTIG. However, sensitivity reactions are common which often precludes its use. Therefore, parenteral antitoxin is recommended and should be administered as soon as tetanus is diagnosed before wound debridment, to counteract any toxin released during the procedure.

Eradication of the organism

Eradication of the organism is effected by antibiotics and wide wound debridment under anesthesia whenever an injury is identified. This is most effective after the injury but unfortunately most wounds implicated in tetanus are so trivial that it is either ignored or treated with home remedies. Though it has been stated that wound debridment is of no value after the disease has been established and that antibiotics are of no value after wound debridment, [19], it may be preferable to ensure that no further toxin is manufactured at wound level.

Antibiotics

Antibiotics are especially useful in the absence of an identified wound. Penicillin, which is effective against most clostridial infections, was the traditional antibiotic for tetanus. It is no longer recommended as it is GABA antagonist and can aggravate the spasms of tetanus [41]. Furthermore, the presence of concomitant colonizing β-lactamase-producing organisms, such as *Staphylococcus aureus* and *Escherichia coli* would inactivate the little penicillin that finds its way to the essentially anaerobic wound.

Metronidazole (Flagyl®, GD Searle and Co., IL, USA) is preferred as it is rapidly bactericidal against the whole spectrum of obligate anaerobes and its pharmocokinetic attributes ensure its distribution at effective therapeutic concentrations even to anaerobic tissues. In the treatment of experimental tetanus in mice, metronidazole was shown to be more active than penicillin and tetracycline. A randomized trial comparing penicillin and metronidazole showed a significantly lower mortality rate, better progress of the disease and response to treatment with metronidazole [42], and it has now emerged as the antibiotic of choice. It is given in a dose of 500 mg intravenously every 8 h for 7–10 days.

Prevention of early complications

Pulmonary aspiration and laryngeal obstruction are common causes of mortality in tetanus if the airway is not isolated in time. There is a high risk of aspiration resulting from poor cough due to muscle rigidity and sedation, inability to swallow saliva, pharyngeal spasms, gastric stasis and increased intra-abdominal pressure during spasms. In very severe cases, spasms occur within 24 h of the first symptom, increasing rapidly in frequency and duration, allowing hardly any time for securing the airway before laryngeal obstruction and/or aspiration occurs.

Therefore, it is recommended that once the diagnosis is established, patients should be transferred to an intensive care unit (ICU) for monitoring and further care. Though this is the ideal and safest method, it is not practicable as intensive care beds are at a premium and not required for mild tetanus, which does not progress further. Further treatment therefore depends on selecting patients who will require intensive care and in practice this is done by predicting the severity of the disease.

Prediction of severity

Several grading systems have been used for assessing severity but the system reported by Ablett is the most widely used (TABLE 2) [43].

Table 2. Ablett classification of severity of tetanus [30].	
Grade I (mild)	Trismus, with little or no dysphagia
Grade II (moderate)	Trismus, marked dysphagia and generalized muscle rigidity, with fleeting spasms, not embarrassing respiration
Grade IIIa (severe)	Trismus, dysphagia and generalized muscle rigidity with severe spasms, embarrassing respiration
Grade IIIb (very severe)	Grade IIIa with autonomic dysfunction

Severity should be predicted before the onset of spasms to protect the airway. Unfortunately, the existing methods of predicting severity are not fool-proof and can only act as guidelines. The most common method relies on the incubation period, which is the time from the injury to the first symptom, and onset time, which is the period from the first symptom to the first spasm. The duration of these periods are inversely related to the severity. An incubation period of more than 14 days is said to predict Grade I while 7 days or less predicts Grade IIIb level of severity [43]. Unfortunately, there are many drawbacks to this assessment:

- There may not be a history of obvious injury
- An incubation period of over 14 days does not always guarantee a mild course [44], possibly because severity also depends on the timing of the innoculum in relation to the injury
- The virulence of the organism
- The immune state of the patient
- The onset time is more reliable but does not fulfil the need to predict severity prior to spasms

Phillips took into consideration additional factors for a severity index, which was intended for comparison of patient groups but could also be used for prediction [45]. He assigned a scale for each of four variables: incubation period (>14 days as 1 and <7 days 5), site of injury (1–5), state of immunity (0–10) and other complicating factors (0–10). The summation of these scores provides a severity index, with less than 9 predicting mild, 9–19 moderate and greater than 19, severe tetanus.

The site of infection is not always of prognostic importance but some sites, such as umbilical, uterine and head and neck, are consistently associated with high mortality. Intramuscular injections of quinine have a reported mortality of 96% [46], the acidic pH causing ischemia and tissue damage, an ideal milieu for the multiplication of the organism. High mortality has also been reported in drug addicts developing tetanus probably due to the fact that heroin is often 'cut' with quinine. Thus, a history of quinine injections for malaria and drug addiction is relevant to the prediction of severity.

Since the outcome of the disease is influenced by comorbid disease and age, these categories should also be treated as high risk and early transfer to the ICU would be appropriate.

Protecting the airway

Urgent tracheotomy and arrangements for transfer to ICU must be made prior to spasms and therefore early diagnosis, prediction of severity and timing becomes crucial in preventing life threatening complications. Tracheotomy should be carried out within 24 h of diagnosis in all patients predicted to develop moderate and severe tetanus and buys time even if transfer to ICU is delayed. Insertion of the tracheal tube after the onset of spasms does not prevent aspiration.

Prediction of severity is not fool-proof. It is therefore essential that even patients predicted to develop the mild form of tetanus, must be closely monitored for extension of rigidity and intake limited to clear fluids orally. If rigidity spreads and dysphagia becomes marked, tracheotomy should be performed without delay. Once the airway is isolated feeding can be commenced without danger of aspiration.

Symptomatic treatment

The key to symptomatic treatment consists of controlling spasms and autonomic dysfunction while providing adequate ventilation, oxygenation and nutrition, and preventing complications. Current therapy requires quality intensive care for 33–40 days [10,25].

Control of rigidity & spasms

Heavy sedation, almost reaching anesthetic levels, controls the less severe spasms but not the rigidity. Artificial ventilation is required due to reduced chest compliance. Bolus doses of neuromuscular blocking agents (NMBAs) are needed during nursing procedures, such as mouth care and limb physiotherapy. In the more severe forms, supplementation with NMBAs is required as sedation alone is inadequate to control spasms.

Drugs suppressing central or peripheral nervous activity have been used both separately and in combination for the control of spasms. Degrees of success have been claimed for a variety of drugs though no valid comparative studies are available and the dose of sedatives is often limited by cardiovascular side effects. In practice, the cost of drugs (prolonged therapy in large doses) has to be balanced against the advantages of rapid recovery of the newer drugs.

Sedatives

Sedatives in large doses are often given in combination to control rigidity and spasms. Benzodiazapines and barbiturates are GABA agonists and have gained a traditional place as sedatives for tetanus, being inexpensive in the long-term. Phenobarbital is given in doses of up to 240 mg every 8 h and amylobarbital of up to 600 mg over 24 h. Diazepam (Valium®, Roche Pharmaceuticals, NJ, USA) is the more popular drug and intravenous doses of 15–100 mg/h are used, while doses as high as 3400 mg/day have been reported [47]. Metabolic acidosis may occur with these doses of diazepam probably due to the effects of the solubilizing vehicle propylene glycol. Major disadvantages of diazepam are the tendency to venous

thrombosis, tolerance, withdrawal symptoms and prolonged residual sedation due to active metabolites with long half-lives (96 h). Withdrawal symptoms include aggressive behaviour and noncooperation, which is disturbing to the patients and the nursing staff.

Midazolam (Versed®, Roche Pharmaceuticals, NJ, USA) is now preferred to diazepam as it does not cause venous thrombosis and offers less cumulation, although recovery may be delayed with long-term use. Its cost is a limiting factor in the developing world [48–50].

Chlorpromazine (Thorazine®, GlaxoSmithKline, UK) (25–50 mg every 8 h) is used in combination with GABA agonists and has the advantage of being an α-blocker, which is useful in suppressing sympathetic over activity but may be a problem in the presence of hypotensive episodes.

Propofol (Diprivan®, AstraZeneca, UK) has been successfully used in severe tetanus according to case reports and does not seem to be associated with tolerance, addiction or withdrawal symptoms [51,52]. An infusion of 3.5–4.5 mg/kg/h following a loading dose of 50 mg obviates the need for other sedatives. Added advantages are reduction of muscle rigidity and rapid recovery. The suppression of metabolism, which is independent of its sedative effects, significantly reduces oxygen consumption and may also be beneficial in tetanus. However, its efficacy in the control of SOA has not been assessed and it may itself contribute to cardiovascular instability. Its use alone or in combination in patients with severe tetanus requires further investigation. The relatively high cost precludes its long-term use in many centers.

Neuromuscular blocking agents

Neuromuscular blocking agents used in tetanus should be inexpensive and have a long duration of action without cardiovascular side effects. Pancuronium (Pavulon®, Organo, NJ, USA) is popular in the developing world due its low cost and long duration. There have been isolated reports of worsening cardiovascular instability as pancuronium inhibits catecholamine reuptake in severe SOA but Dance reported no difference with pancuronium when compared to alcuronium [53]. It should, however, preferably be avoided in severe cardiovascular instability.

Vecuronium (Norcuron®, Organon, NJ, USA) would be the drug of choice due to the absence of cardiovascular side effects [54]. Prolonged use of aminosteroid NMBAs (vecuronium, pancuronium, rocuronium [Zemuron®, Organon, NJ, USA]) particularly by infusion has been associated with critical illness neuropathy and myopathy, though this has not as yet been reported in tetanus [55]. Atracurium (Tracrium®, DSM Pharmaceuticals Inc., NC, USA) has been used as an infusion with no serious accumulation of metabolites [56] but has been reported to cause cardiovascular instability [54]. Both these drugs are expensive in the long-term, which precludes their use in the developing world. New long-acting agents, such as pipecuronium and rocuronium, are 'clean' but expensive.

Control of autonomic dysfunction

Basal SOA is characterized by resting tachycardia and depression of bowel motility and bladder function. Episodes of severe SOA with fluctuating tachycardia, labile hypertension and sweating occur both with and without stimulation.

Increased parasympathetic activity causes profuse salivation and bronchial secretions. Episodes of bradycardia and hypotension, often leading to cardiac arrest have been explained on the basis of increased parasympathetic activity but many attribute it to sudden withdrawal of sympathetic activity, as the bradycardia does not usually respond to atropine. Cardiac arrest in tetanus has also been attributed to myocardial damage caused by high catecholamine levels [57] and toxic damage to the brainstem [58].

All these signs of autonomic dysfunction do not necessarily occur concurrently and its severity varies from patient to patient.

Criteria for the diagnosis of SOA in tetanus have not been defined. Cardiovascular instability due to spasms and inadequate sedation must be excluded. Criteria should include a time interval from the onset of spasms, adequate sedation in ventilated patients and spontaneous fluctuations in blood pressure and heart rate in the absence of external stimuli and spasms.

If more sophisticated measurements are possible, fluctuating systemic vascular resistance coinciding with fluctuating blood pressure and significant increases in plasma and urinary catecholamine concentrations would establish the presence of SOA [59].

When cardiovascular instability was first recognized as being due to SOA in 1968 [60], combinations of α- and β-adrenergic antagonists were recommended [61]. In the late 1970s, reports of fatal cardiovascular failure and cardiac arrest appeared [62], and those drugs though effective were considered unpredictably dangerous. Heavy sedation was reintroduced, not only to control spasms but also autonomic dysfunction. This method, however, does not reliably control SOA and supplementary treatment is often required.

The wide range of therapeutic agents used to date reflects the dissatisfaction of clinicians with the existing drug regimens. There is no consensus as to which drug is the most appropriate, as most reports in the literature relating to treatment are anecdotal, involving small numbers of patients. The difficulty in finding a drug which controls autonomic dysfunction in the whole range of severity could be due to the variation in plasma concentrations achieved, individual variation in response or the varying degrees of severity of the disease.

A regimen is required which will stabilize the cardiovascular system whilst preserving compensatory mechanisms to avoid sudden collapse and death. Data supported by pulmonary artery catheter studies show that labile arterial pressure results from changes in the systemic vascular resistance (SVR) rather than changes in cardiac output and left ventricular filling pressures [63]. The SVR becomes elevated with the progress of the disease but can vary widely within minutes. The ability to increase myocardial contractility becomes important in coping with episodes of low SVR (when the heart must compensate by increasing cardiac output) and high SVR

(when the heart has to maintain an adequate cardiac output in the face of increased afterload). A number of drugs have been used with varying success but none of them entirely fulfils the above criteria.

Two different approaches have been used in the management of SOA, namely peripheral adrenergic blockade and suppression of catecholamine release.

Combined α- & β-blockade

Combined α- and β-blockade, although effective in reducing SOA, denervates the cardiovascular system thus rendering it incapable of coping with hypertensive episodes and renders pressure support difficult during hypotensive episodes. This would explain the many reports of cardiac failure and arrest in patients treated with propranolol [62] and labetalol (Normodyne®, Schering Plough, NJ, USA) [64]. Esmolol with its short duration of action is more suitable and has been used as an infusion during the hypertensive crises [65]. Even here, there is danger from its negative inotropic effects and its cost was reported to be US$450 a day.

Using invasive hemodynamic monitoring with individualized cardiorespiratory support for the management of severe SOA, Udwadia reported a mortality of 6.5% in 32 patients [63]. Unfortunately this form of management, which involves long-term invasive monitoring, is not possible in most centers dealing with tetanus and does not prevent the high catecholamine levels.

Suppression of catecholamine release

Suppression of catecholamine release has been recognized as the more logical method of controlling SOA in tetanus. Heavy sedation is claimed to reduce catecholamine levels but may also interfere with cardiac compensatory mechanisms due to its peripheral mechanisms of action.

Morphine acts centrally to reduce sympathetic tone in the heart and vascular system resulting in bradycardia and hypotension. It induces peripheral arterial and venous dilatation mediated by a reflex reduction in sympathetic α-adrenergic tone. Morphine as an adjunct to deep sedation has been successfully used to control cardiac instability in tetanus without itself causing cardiac compromise [66]. It is unclear whether catecholamine concentrations are reduced but replacement of endogenous opiates may be another mechanism of action. Reported doses to suppress SOA vary from 240 to 2500 mg a day and are useful in combination with benzodiazapines. However, other investigators have observed that tolerance developed rapidly and that morphine had little effect on instability occurring with spasms and stimulation [67]. Additionally, it causes constipation and paralytic ileus thus compounding the gastrointestinal effects of SOA. Despite these side effects, morphine constitutes an important component of heavy sedation in tetanus.

Clonidine (Catapres®, Boehringer Ingelheim Pharmaceuticals Inc., CT, USA) is a partial agonist for α_2 adrenergic receptors. It causes hypotension by central action as it reduces sympathetic outflow and catecholamine release and peripherally by inhibiting the release of noradrenaline from the pre-junctional nerve endings. Clonidine has been used for the control of SOA in tetanus but with conflicting results [68,69] and needs further investigation for the treatment of autonomic dysfunction in tetanus.

Magnesium is a vasodilator, both by a direct action and by inhibition of hormone induced vasoconstriction [70]. It also reduces the release of catecholamines from the adrenal medulla [71,72] and adrenergic nerve endings [73]. These properties have been used successfully in clinical practice by James in the control of SOA of phaeochromocytoma [74] and severe tetanus [75]. Lipmann also used magnesium sulfate in severe tetanus and demonstrated a concurrent reduction of catecholamine levels [47]. However, the regimen used by both James and Lipmann was complicated as the dose had to be titrated to serum magnesium levels which had to be measured four hourly to establish the required concentrations.

Supportive therapy

Quality intensive care is essential to prevent complications in a patient who is heavily sedated, paralyzed and ventilated for periods of 3 to 5 weeks. Deaths are often due to complications of this treatment which include ventilator associated pneumonia, deep vein thrombosis, pressure sores, pulmonary embolism, atelectasis, paralytic ileus and weight loss.

The effects of drug therapy are compounded by increased bronchial secretions and restriction of the chest due to rigidity. Tracheostomy and meticulous lung care, which includes chest physiotherapy, frequent tracheal suction and good mouth care, are essential to minimize pulmonary complications. Regular limb physiotherapy, skin care and thromboprophylaxis are necessary to minimize pressure sores, deep vein thrombosis and pulmonary embolism.

Early enteral feeding in adequate amounts is of paramount importance but it is often difficult to satisfy the nutritional needs. Requirements are high due to the increased metabolic rate from muscle activity, pyrexia and critical illness. Oral feeding is not possible due to trismus and dysphagia and gastrointestinal dysfunction is common both due to the SOA and the side effects of drugs used.

The management of tetanus is summarized in BOX 1.

New options

Tetanus has been aptly described as a third world disease, that requires first world technology to treat [76]. In the developing world, facilities for ventilation and quality intensive care are limited. Despite the introduction of new drugs, deaths due to cardiovascular instability have not been significantly reduced and even in the best centers, complications of therapy itself contribute to significant mortality. Therefore there is a continuing search for a drug, which will be effective in controlling spasms and SOA without the need for heavy sedation or artificial ventilation. Any regimen for tetanus should be effective and also practical in the setting that the disease is found.

Box 1. Management of tetanus.

- Early diagnosis by clinical features and spatula test
- HTIg 500 units im. (or ATS if not available)
- Tetanus toxoid vaccination
- Metronidazole iv. 500 mg every 8 h for 10 days
- Transfer to HDU/ICU
- Under general anaesthesia:
  - Wound debridement
  - Tracheotomy (if dysphagia or generalized rigidity is present)
  - Naso-gastric tube for feeding
- Control of spasms
- Control of autonomic dysfunction
- Nutrition, general nursing, mouth and tracheotomy care

HDU: High dependency unit; HTIg: Human tetanus immunoglobulin;
ICU: Intensive care unit; im.: Intramuscularly; iv.: Intravenously.

Dantrolene (Dantrium®, Procter and Gamble Pharmaceuticals, UK) produces skeletal muscle relaxation by a direct action on excitation contraction coupling, presumably by decreasing the amount of calcium released from the sarcoplasmic reticulum of skeletal muscle. This indirectly prevents the activation of myosin ATPase and muscle contraction. Its use in the control of spasms in tetanus without the need for artificial ventilation has been reported [77] and would be a better option than NMBAs for the few centers that can afford the cost. It has no effect on sympathetic overactivity and liver enzymes must be monitored due to the danger of hepatic damage with long-term use.

Baclofen (Lioresal®, Novartis, Switzerland) is a GABA$_B$ agonist and possesses many of the theoretical requirements of an ideal drug for tetanus. It reduces poly- and monosynaptic tendon reflexes and is accompanied by a dose-dependent muscular hypotonia. However, baclofen does not cross the blood–brain barrier and has to be administered intrathecally. Muller, using a continuous intrathecal infusion, was able to control spasms of tetanus in two patients without causing sedation or ventilatory depression [78]. The drawback to the use of baclofen is the risk of infection with external infusion devices, which are less costly, and the high cost of the implantable device. Due to these constraints, Saissy administered baclofen as intermittent intrathecal injections in ten patients but failed to avoid sedation and ventilatory depression [79]. He was unable to confirm the ability of baclofen to control cardiovascular instability, which was demonstrated by Muller.

Magnesium therapy has the advantage of blocking both neuromuscular transmission and SOA. At the neuromuscular junction high concentrations of magnesium compete with calcium ions for prejunctional sites and inhibit the release of acetylcholine. The significant dose-dependant correlation between the depression of neuromuscular transmission and serum magnesium concentrations makes it more controllable. Electromyographic studies have concluded that magnesium tends to spare the respiratory muscles, which is a marked advantage [80].

These characteristics ensured its widespread use in the prevention and treatment of seizures in eclampsia, the dose being titrated to the exaggerated patellar reflex.

In 1996, a similar regimen used in eight patients with severe tetanus showed that spasms and autonomic dysfunction could be controlled without supplementary sedatives and muscle relaxants. [81]. This was followed by a prospective study of 40 patients with a wider range in terms of age (16 out of 40 patients were >60 years) and severity [82].

The results indicated that magnesium, as the sole agent, was effective in the control of spasms and rigidity without the need for ventilatory support in 57% of patients. Support was required for respiratory complications, pre-existing lung disease and high dose magnesium therapy. Supplementary NMBAs were required in very severe cases.

Magnesium therapy was also effective in the prevention of hypertension and tachycardia without supplementary drugs in all patients once spasms were controlled. There was no evidence of SOA even in those predicted to develop very severe tetanus (incubation periods <7 days and onset times <24 h) and there were no deaths due to cardiovascular instability.

Supportive treatment was simplified to a great extent since patients were conscious and cooperative, mobilization being possible in the majority of patients in the second or third week.

Tolerance to enteral feeding via nasogastric tube is especially advantageous in the tetanus patient whose metabolic rate is increased considerably and weight loss is a common feature. ICU stay was significantly reduced (average 23.1 days) and mortality (12% overall and 32% in the elderly) compared favorably with conventional treatment.

The studies concluded that magnesium titrated to clinical end points should be used as a first-line therapy in the routine management of tetanus.

Protocol for magnesium in tetanus

Since tetanus and eclampsia are very different diseases, the magnesium therapy protocol recommended for tetanus differs from that for eclampsia in the following aspects.

The rate of infusion of magnesium

The rate of infusion of magnesium (after the loading dose of 5 g bolus over 20 min) should be titrated not only to the control of spasms but also to muscle rigidity. Rigidity should be reduced to a level acceptable to the patient which allows swallowing of saliva, mouth care and limb physiotherapy. The hourly dose required may be as high as 4–5 g/h, which is far greater than used in eclampsia. Total abolition of rigidity is not required and may lead to muscle hypotonia.

The patellar reflex cannot be used as a valid indicator of serum magnesium concentrations in all patients, as the reflex is sometimes masked by rigidity and tends to be lost early in the elderly patients. Depression of ventilation should therefore be monitored for.

Severe tetanus

In severe tetanus, the dose required to control spasms may lead to ventilatory inadequacy and ventilatory support should be provided. The dose needs to be reduced only if hypotension or bradycardia occurs, then falling back on NMBAs to control spasms.

The elderly

In the elderly:

- The dose required is significantly less, though the serum levels attained are similar
- The safe limit is reduced as ventilatory inadequacy and cardiac depression occurs before the 4 mmol/l limit is reached

Minimizing ventilatory support

To minimize ventilatory support stringent protocols, which include early tracheotomy, frequent suction clearance and lung physiotherapy are mandatory. Stand by ventilatory facilities are needed to ensure safety.

Pharmacoeconomics

The cost of drugs in tetanus has to take into account the large doses required and the long duration of the disease. In conventional therapy, however, drug costs are only a fraction of the cost of hi-tech intensive care required. The cost of managing a tetanus patient with conventional treatment in an intensive care unit in the UK was estimated 10 years ago to be approximately £30,000 [JC STODDART, PERS. COMM.]. Any drug which reduces the degree of support therapy and ICU stay can significantly reduce the overall cost of treatment. Thus, propofol and midazolam though more expensive may be cost effective in the long-term if ICU stay can be reduced.

The cost of magnesium sulfate is approximately US$10–15 a day, whilst support therapy is minimal since magnesium avoids sedation, reduces the need for artificial ventilation and period of stay in the ICU. The total cost of managing a tetanus patient on magnesium therapy would therefore be considerably less than that of conventional therapy even with inexpensive drugs like diazepam, pancuronium and morphine. Titration of the dose to clinical end points ensures the safety of magnesium therapy without measurement of serum levels, which is often too expensive for hospitals in the developing world.

Conclusion & expert opinion

A treatment regimen for tetanus should be assessed by its impact on mortality and on the feasibility of its use in terms of costs and technology in the regions where it is prevalent.

The current regimen, although inappropriate, is being practiced by the developing world for want of an alternative. It is no wonder that deaths due to tetanus have not reduced worldwide over the last three decades. Therefore, there is a desperate need to introduce a suitable form of therapy, particularly for the developing world where resources and technology are minimal.

It is unfortunate that there is a paucity of research into drug therapy for the management of tetanus. The limited data available suggests that in today's context there is no better option than magnesium therapy, considering its advantages and despite its limitations. Controlled studies would be helpful in further defining the role of magnesium in preventing spasms and autonomic dysfunction.

The fact that magnesium can control spasms and SOA while patients remain conscious and cooperative and mobilized is a tremendous advantage contradicting all traditional axioms of treatment in tetanus and avoiding many of its problems. This enables simplified nursing care, which should contribute significantly to a better outcome, especially in the developing world.

Though the need for ventilatory support cannot be eliminated in the very severe cases and elderly patients with comorbid respiratory diseases, it can, however, be minimized. Respiratory complications can only be avoided if stringent protocols for lung care are observed even in the spontaneously breathing patient, for magnesium itself and muscle rigidity both contribute to a reduction of pulmonary reserves [83].

As such, magnesium as the sole therapy meets many of the requirements where conventional treatment fails. Young patients with moderate-to-severe tetanus can be managed without ventilatory support in a high dependency unit (HDU), with stand by ventilator facilities. The limited ventilator and ICU facilities are then available for the few who may need it. Resources would be maximized to meet the needs of the developing world.

Magnesium is already being used in a few centers in Asia and Africa and even in the UK [84] with a positive feed back, though anecdotal. A website has been established as a forum to discuss problems and also to provide details of protocols on request [101]. The way forward is to encourage more centers to adopt this technique to study its feasibility in terms of their own resources and its impact on mortality in their spectrum of disease severity. Multicenter trials are preferable to random controlled trials as age, severity and comorbid diseases cannot be matched in a single center due to the large numbers required and blinding is not possible.

Five-year view

Tetanus is essentially a prolonged disease affecting both respiratory and cardiovascular systems, symptomatic treatment will inevitably be associated with a high mortality, especially in the elderly. The fact that in tetanus, prevention is cheaper and far better than cure is incontrovertible. In the developed world, prevention is a feasible option as the population at risk has been identified. If the present immunization schemes were extended to target the high-risk category and include more boosters beyond the third decade, the incidence and mortality of the disease would be significantly reduced

The ideal treatment for tetanus would be to develop a drug, which can counteract the toxin bound to nervous tissue. GABA agonists, such as baclofen and sodium valproate, hold out some promise in this regard. If the pharmacokinetics of baclofen could be further investigated and modified to

achieve a simpler mode of administration, it could well prove to be the answer. Sodium valproate which inhibits GABA catabolism by blocking GABA aminotranseferase has been shown to prevent the clinical effects of tetanus toxin in animal studies [86]. If the drug is found to be effective in clinical studies, it may be the drug we are looking for.

In the developing world, tetanus will continue to be a clinical challenge for decades to come. It is likely that within the next 5 years, magnesium will be established as first line therapy for tetanus with a significant reduction in deaths worldwide. It would make a tremendous impact if it were successful in neonates without the need for ventilatory support.

Tetanus, even when it is almost forgotten by the developed world, will still remain a worldwide burden in the next decade. It is another one of those diseases which requires coordinated action between developing and the developed nations to improve its prevention and treatment. However, there is always a discrepancy between what man knows he should do and what he is willing to do.

Information resources
Review articles
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Key issues

• Prompt diagnosis is crucial and requires recognition of the high-risk group and the spatula test which is diagnostic with the first symptom (before spasms occur).

• Prevention of early complications consists of predicting severity, monitoring the patient for extending rigidity and early tracheotomy (before spasms occur).

• Conventional treatment (heavy sedation, paralysis and artificial ventilation) in the intensive care unit has not reduced mortality significantly and deaths still occur due to shortness of air and complications of treatment.

• Magnesium therapy meets a number of requirements where conventional treatment falls short. Spasms are controlled without supplementation except in the very severe disease. SOA is controlled and sedation avoided. Ventilatory support can be avoided except in the very severe disease and the elderly. It is a feasible regimen even in the developing countries and is recommended as first-line therapy for the control of spasms and shortness of air.

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