

TETANUS: REVIEW 1998

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SUMMARY

Tetanus is uncommon in developed countries, with most cases occurring in older adults. The majority of cases occur in developing countries, with 50% of those cases occurring in neonates. Mortality is estimated in 30-50% even with optimal treatment. Prevention remains the best therapy. In addition, some advocate more liberal use of human tetanus immunoglobulin and suggest that all wounds be considered tetanus prone. The present review describes the up to date epidemiology, physiopathology, diagnosis and treatment.

INTRODUCTION

Tetanus is a devastating disease of muscle spasm and autonomic instability with a high mortality. Despite being easily preventable a highly effective vaccine, tetanus remains a significant source of morbidity and mortality worldwide. In the US, the incidence of tetanus has significantly decreased since the 1940's when immunization programs were enacted; however, the incidence has remained relatively stable for the last 10 years¹. Studies have shown that the population that accounts for the majority of cases in the US are inadequately immunized older adults.

EPIDEMIOLOGY AND ETIOLOGY

The true incidence of tetanus is not known, but is estimated to be between 500,000 to one million cases per year worldwide^{2,3}. The majority of cases occur in developing countries, with 50% of those cases occurring in neonates. In contrast, tetanus is uncommon in developed countries, with most cases occurring in older adults^{1,4,5}. In the US, there were 201 cases of tetanus reported between 1991 and 1994. The average incidence was 40-60 cases per year, or 0.02 cases per 100,000 population annually¹. This rate has remained relatively stable since the late 1980s.

An acute injury precedes most cases of tetanus¹ (Table 1). The most common injuries are puncture wounds and lacerations. Recent surgery also accounts for several cases. Non-acute etiologies include chronic wounds, IV drug use, and complications of diabetes. Case reports have implicated other less obvious etiologies, including otitis media, intranasal foreign bodies, corneal abrasions/ulcers/foreign bodies, dental procedures, injections, abortion, childbirth and burns⁶⁻¹⁰. On 6-8% of cases, there is no obvious etiology^{1,7,11}.

Table 1
Etiologies of Tetanus

Source	Incidence (%)
Acute injury	77
Puncture	49
Laceration	20
Abrasion	12

Animal bite	3
Misc.	16
Non-acute*	12.0
Recent surgery	3.6
Not reported	7.3
a Chronic wound, IV drug use, diabetes	
From CDC ¹	

Lack of immunization is the greatest risk factor for contracting tetanus. Among victims of tetanus whose immunization histories are known, 74% never completed a primary immunization series¹ (Figure 1). The groups identified as having the lowest rates of immunization in the US include older persons, females, Hispanics, those with poverty income levels, and those without military service^{12,13}. Of these risk groups, older age is the most significant. Serologic surveys show that only 28-50% of those over 65-70 years old are adequately immunized, compared to greater than 80% of those 6-39 years old^{12,14}. This lack of immunity results in a higher incidence of tetanus in older adults. Fifty four percent of victims are more than 60 year old, an additional 19% are between 40-60 years old, and only 5% are less than 20 years old¹ (Figure 2).

FIGURES 1,2

Even with optimal treatment, the mortality, of tetanus is very high. The global fatality rate is estimated to be 30-50%^{15,16}. In the US, the overall fatality rate is 25%¹. Eighty 2% of the fatalities are in persons more than 60 years of age. The age-related death rate is 9% of those less than 60 years old and 39% of those greater than 60 years old¹. Besides age, the fatality rate also varies with the clinical forms of tetanus.

PHYSIOPATHOLOGY

Clostridium tetani is a spore-forming, Gram positive bacillus. While the bacillus is an obligate anaerobe, its spores remain viable at ambient oxygen concentrations. The spores are highly resistant to extremes in temperature and humidity, and can survive indefinitely. Spores are ubiquitous in soil and in the feces of many animals² and of humans⁷. Carried into wounds along with soil, spores may not germinate immediately due to unfavorable tissue conditions. They may activate well after the wound has healed, which may account for the cases of tetanus that have no identifiable source. When conditions such as gross contamination or tissue injury favor anaerobic proliferation, the spores germinate into mature bacilli, which then form the toxins tetanolysin and tetanospasmin. Tetanolysin has an uncertain role in clinical tetanus; it may contribute to an anaerobic environment by damaging viable tissue².

Tetanospasmin is primarily responsible for the clinical manifestations of tetanus. It enters peripheral nerves and travels via the axonal retrograde transport system to the central nervous system. Tetanospasmin then enters presynaptic neurons and disables neurotransmitter release, most importantly, the inhibitory neurotransmitters gamma-aminobutyric acid (GABA) and glycine. This results in a disinhibition of end-organ neurons, such as motor neurons and those of the autonomic nervous system. This accounts for the muscle spasms characteristic of tetanus and for the autonomic instability seen with severe tetanus. Seventy three percent of patients develop their first symptom between 4-14 days after an injury; the median incubation period is 7 days¹. The rapidity of incubation and onset correlates with the severity of disease (Table 2). Currently, it is thought that recovery involves synthesis of new presynaptic components and their transport to the distal axon². This accounts for the typical 2-3 week period before clinical improvement begins.

Table 2
Classifying the Severity of Tetanus

Severity	Incubation ^a (days)	Onset ^b (days)	Associated findings
Mild	= 10	4-7	Local rigidity, mild trismus
Moderate	7-10	3-6	Severe trismus, dysphagia, spasms
Severe	< 7	< 3	Severe spasms, diffuse rigidity, autonomic dysfunction

a Time from injury to first symptom.

b Time from first symptom to generalized spasm

From Bleck⁵⁸

CLINICAL PRESENTATION

There are four clinical forms of tetanus representing the extent and location of neurons involved: generalized, local, cephalic, and neonatal. In the US and other developed countries, generalized tetanus is the most common form, occurring in 81% of cases¹. The initial symptom is trismus “lockjaw” secondary to masseter muscle spasm in 50-75% of cases¹⁷. Risus sardonicus, the “ironical smile of tetanus”, can occur due to facial muscle contraction. Nuchal rigidity and dysphagia may also be initial complaints. As the disease spreads, generalized muscle spasms occur, either spontaneously or to minor stimuli such as touch or noise. Opisthotonus, a tonic contraction very similar to decorticate posturing, is classically described with tetanus. Severe spasms can result in vertebral fractures, long bone fractures, and detachment of tendons from their insertions^{9,10}. Unfortunately for the patient, mental status is not affected and spasms are felt with severe pain⁹.

In the acute phase, death results from acute respiratory failure due to diaphragmatic paralysis and/or laryngeal spasms^{2,18}. With intensive medical intervention, including paralysis and mechanical ventilation, such deaths can be averted. However, with patients surviving beyond the acute phase, autonomic instability becomes the major cause of death, with a fatality rate of 11-28%^{16,19}. Autonomic instability occurs several days after the onset of generalized spasms and manifests most importantly as labile hypertension, tachycardia, and pyrexia. Arrhythmias and myocardial infarction are the most common fatal events¹⁶. The exact mechanism of this syndrome is unclear but likely involves disinhibitions of the sympathetic nervous system. Case reports have documented elevated levels of catecholamines in patients with autonomic instability; levels fall as patients are successfully treated²⁰⁻²³.

Local tetanus presents as persistent muscle rigidity close to the site of injury. The rigidity may linger for weeks to months and often self-resolves without sequelae². A caveat is that what appears to be localized tetanus may instead be the first symptom of generalized tetanus. The incidence is 13%¹, and the fatality rate is about 1%²⁴.

Cephalic tetanus is an uncommon variant of localized tetanus that involves the cranial nerves. It has an incidence of 6%¹. Cephalic tetanus uniquely results in nerve palsies as well as muscle spasms. The seventh cranial nerve is most often involved, followed by the 6th, 3rd, 4th, and 12th in decreasing order of frequency²⁵. Cephalic tetanus also presents with trismus, but in 42% of cases, cranial nerve deficits precede the onset of trismus²⁵. In such cases, cephalic tetanus is easily misdiagnosed. With its predilection for the 7th cranial nerve, it commonly mimics Bell’s Palsy. Head trauma and otitis media are commonly cited etiologies^{24,26}. About 2/3 of the patients progress to generalized tetanus, and the overall mortality is 15-30%²⁵.

Neonatal tetanus is generalized tetanus that occurs in the newborn around the first week of life. Symptoms begin with non-specific irritability and poor feeding, and rapidly progress to generalized spasms. The portal of entry is the freshly cut umbilical cord. The risk of contracting neonatal

tetanus is directly related to the cleanliness of delivery conditions and to maternal immunization, since passive transfer of maternal immunoglobulins is protective²⁷. Mortality is very high, 50-100%, due to the high load of toxin per body weight in neonates^{3,9,28}. The global fatality rate was 6.5‰ live births in 1993, resulting in an estimated 515,000 deaths³. Eighty percent of the cases occurred in 12 developing countries in Africa and Asia²⁹. Programs to immunize pregnant women in these high incidence areas have dramatically decreased the incidence and fatality rates of neonatal tetanus³. In the US and other developed countries, neonatal tetanus is very rare due to cleaner delivery conditions and a high rate of immunization among women of childbearing years. There were no reports of neonatal tetanus in the US between 1991-1994¹.

DIAGNOSIS

The diagnosis of tetanus is clinical. There are no laboratory tests which can diagnose or rule-out tetanus. A “protective” serum antitoxin level, commonly accepted as 0.01 U/ml *in vivo* or 0.15 U/ml *in vitro*, makes the diagnosis of tetanus very unlikely, but not impossible³⁰⁻³². Unfortunately, antitoxin levels are not likely to be available at the time when management decisions must be made. Fortunately, the presentation of tetanus is so characteristic that a presumptive diagnosis can be made in most cases.

The differential diagnosis are few. Trismus can be caused by peritonsillar or odontogenic abscesses and dystonic reactions. These can be ruled-out by history and exam. Strychnine poisoning can closely resemble generalized tetanus; strychnine disables glycine release like tetanospasmin, but does not affect GABA release. A strychnine level should be sent for all suspected cases of tetanus. Hypocalcemia causing tetany is another mimic, which can easily be ruled-out. Other entities that cause diffuse muscle spasms, such as seizures, toxidromes, and encephalopathies are accompanied by changes in mental status. Processes that affect muscles locally, such as myopathies or neuropathies, tend to cause weakness rather than spasm and rigidity. In addition, neuropathies are associated with sensory deficits, which is not a feature of tetanus. Cephalic tetanus without trismus can be easily mistaken for Bell’s Palsy, CNS tumor, or stroke; with the inevitable appearance of trismus and muscle spasm, the diagnosis becomes clear. Similarly, neonatal tetanus initially presents much like a host of other disorders, including infectious, toxic and metabolic etiologies. However, once generalized spasms begin, the diagnosis is obvious.

As an aid in clinical diagnosis, Apte and Karnad describe a bedside “spatula test” for tetanus. A spatula is inserted into the pharynx. If the patient gags and tries to expel the spatula, the test is negative for tetanus; if the patient bites the spatula due to reflex masseter spasm, the test is positive for tetanus. They reported 94% sensitivity and 100% specificity¹¹. Given the high incidence of tetanus in the authors’ referral center (in India), trismus can be equated to tetanus. In areas where tetanus is less common, such as the US, this association is weaker. It can still be a useful adjunct to diagnosis, especially in the unresponsive patient.

TREATMENT

Treatment involves neutralizing tetanospasmin, removing the source of the toxin, and providing supportive care for muscle spasms, respiration, and autonomic instability. Human tetanus immunoglobulin (HTIG) is given to neutralize circulating tetanospasmin. It cannot inactivate toxin already within neurons. Its half-life is 25 days; only a single dose is necessary. The optimal dose is not well defined. In a retrospective study, Blake et al.³³ found that a dose of 500 IU IM was as effective as the 3,000-10,000 IU doses that are commonly used. The smaller dose has the advantage of requiring fewer injections to deliver and thus precipitating fewer reflex spasms. In areas where HTIG is not available and equine antitoxin is used, the smaller dose lowers the chance of an adverse

reaction. Authorities now consider 500 IU the preferred dose^{2,15}. There is no advantage to injecting directly into the wound². HTIG is safe to give during pregnancy.

Intrathecal administration of immunoglobulin is theoretically attractive. By delivering immunoglobulin to the CNS, one hopes to bind the toxin as it crosses from postsynaptic to presynaptic neuron. Clinical trials have yielded conflicting results. A recent metanalysis by Abrutyn and Berlin³⁴ concluded that there was insufficient evidence to recommend intrathecal therapy. They noted that many of the studies were of poor design and cautioned against forming final conclusions regarding this therapy. However, they made special mention of a study by Vakil et al.³⁵ the only randomized and blinded trial, that showed no benefit to intrathecal immunoglobulin. To date, there are too few well-designed studies to definitively support or refute intrathecal therapy. Further trials are needed, and the risks of the procedure must be better defined.

To prevent on-going production of toxin, antibiotics are given to eliminate **C. tetani**. Metronidazole is the drug of choice^{2,15,36}. It is superior to penicillin, the former drug of choice, in terms of recovery time and mortality³⁶. Metronidazole penetrates vascularly compromised wounds and abscesses better than penicillin. Furthermore, penicillin has GABA-antagonist activity, which may potentiate the effects of tetanospasmin. In addition to antibiotics, obviously dirty wounds, abscesses, or devitalized tissue must be cleaned, drained, or excised to decrease the bacterial load.

Benzodiazepines are the drug of choice for muscle spasms because of their GABA-agonist and sedative properties. Very large doses may be necessary; there are case reports of 3,400 mg of diazepam and 1,440 mg of midazolam given over 24 hour^{22,37}. When benzodiazepines have failed, other treatments include dantrolene, an agent which acts at the sarcoplasmic reticulum^{28,38}, and intrathecal baclofen, which is also a GABA-agonist^{39,41}. Topically applied mephenesine, a centrally acting muscle relaxant, was used in one case to control facial contractions⁴². For severe cases, paralytics may be needed. Succinylcholine may be used for rapid, initial control. Vecuronium is an ideal agent for long-term control due to its minimal cardiovascular effects⁴³.

When paralytics are used, mechanical ventilation is needed. Orotracheal intubation can be performed initially, but the presence of an endotracheal tube may precipitate or exacerbate laryngeal spasms in lightly paralyzed patients. To avoid this and to facilitate long-term ventilatory support, tracheostomy is often performed early.

Treatment of autonomic instability has been problematic and is the subject of on-going research. No therapeutic regimen has proven to be universally effective. Alpha and beta-blockers are used but have disadvantages. Unopposed alpha blockade can result in reflex worsening of tachycardia; unopposed beta blockade can result in worsening hypertension and an increased risk of sudden death^{19,44}. Labetalol would seem ideal and is commonly recommended^{2,20}, but more recent experiences have questioned its efficacy^{19,45}.

Agents that modulate sympathetic output have also been tried. Clonidine has yielded variable success^{46,47}. Magnesium, which blunts catecholamine release, has also given mixed results^{37,46,48}. One case report suggests that magnesium is ineffective alone but efficacious when given with sedation³⁷. Morphine and fentanyl centrally decrease sympathetic outflow and generally produce good control of hypertension and tachycardia^{19,22}. They have the additional benefit of providing sedation. Fentanyl may be superior to morphine because it does not depress the myocardium nor induce histamine release. Finally, there are case reports of epidural anesthesia successfully controlling autonomic instability^{23,49}. This is felt to work by blocking preganglionic sympathetic neurons.

Experimental therapy includes the use of corticosteroids. Promising results have been achieved^{50,51}, but more work needs to be done to define the target patient, optimal dosing, and expected outcomes. The mechanism by which steroids might offer benefit is also unknown. At this time, there is insufficient data to include steroids as standard therapy.

Supportive care includes placing the patient in a quiet, dark environment, minimizing patient manipulation, and treatment for complications, most significantly rhabdomyolysis. Importantly, survivors must also receive a tetanus immunization series. The amount of tetanospasmin produced in clinical tetanus is small and partially sequestered in neurons; consequently, an immune response does not occur. Unimmunized survivors of tetanus have become victims a second time^{52,53}.

PREVENTION

Tetanus is preventable with proper immunization. Tetanus toxoid, which is an inactivated form of tetanospasmin, confers protective antibody levels in 81-95% of people after 2 doses and 100% of people after 3 doses⁵⁴. The vaccine is effective in HIV-infected individuals; however, the immunogenic response is somewhat blunted, and anti-toxin antibody levels may fall more quickly over time than in HIV-negative individuals⁵⁵. The immunization protocols below apply regardless of HIV status.

Recommendations for primary immunization depend on the age of the patient. If the patient is younger than 7 years old, a diphtheria, tetanus, and pertussis (DTP) vaccine should be given at 2, 4, 6 and 15 months of age, with a booster at 4 to 6 years of age. If the patient is more than 7 years old, immunization can be accomplished by three injections of tetanus and diphtheria (Td). The first two doses should be given at least 4 weeks apart with the third dose 6 months after the second dose. Primary immunization in the pregnant patient entails two injections of Td one month apart, preferably during the last two trimesters. Td boosters are generally avoided during the first trimester, although there is no evidence that they are harmful to the fetus²⁷.

In the setting of an acute injury, tetanus prophylaxis depends on the patient's immunization history and the wound characteristics (Tables 3, 4). HTIG is needed only for tetanus-prone wounds in patients who have never completed a primary immunization series. The dose is 500 IU IM. In all other cases, the only question is whether a tetanus booster is required. If the patient has not completed a primary immunization series, it will need to be initiated and/or completed. If the patient has, a booster is given if the last one was greater than 5 years ago in a tetanus-prone wound or greater than 10 years ago in a non-tetanus-prone wound²⁷.

Common adverse reactions to tetanus toxoid include erythema, swelling and tenderness at the injection site. These are minor and of no long-term consequence. Occasionally, fever and malaise can occur. These are more common with DTP than Td. Reactions tend to occur more often and more severely if boosters are given more frequently than the recommended schedule. More severe anaphylactic reactions and neuropathies are rare and constitute the only contraindications for giving toxoid²⁷.

CONCLUSION

Tetanus is uncommon in the US, yet when it occurs, it carries a significant mortality, even with state-of-the-art treatment. Prevention remains the best therapy. Thanks to laws mandating pediatric immunization, tetanus is a rare disease in children. In contrast, older adults are inadequately immunized and are the most frequent victims of tetanus in the US. This has prompted calls for routine tetanus immunization during adult ages, much like any other preventative health

measure^{12,15,56}. In addition, some advocate more liberal use of HTIG and suggest that all wounds be considered “tetanus prone”^{2,57}. Emergency care providers can contribute to the effort by screening and immunizing all who come to the emergency department, even those without wounds. The additional cost and morbidity would be minimal and the benefit potentially great. Tetanus can be made vanishingly rare in the US with meticulous immunization.

Resumen

El tétano es poco frecuente en países desarrollados, donde la mayor parte de los casos ocurren en ancianos. La mayoría de los casos de tétanos se producen en países en vías de desarrollo, donde la mayoría de los casos ocurren en neonatos. La mortalidad se estima en 30-50% aún con tratamiento óptimo. Por este motivo, mejor terapia es la prevención. Algunos sugieren un uso más liberal de la inmunoglobulina humana y sugieren considerar todas las heridas como riesgosas de tétanos. La presente revisión describe la epidemiología, fisiopatología, diagnóstico y tratamiento actualizados.

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