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# Management and Prevention of Tetanus

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**ABSTRACT:** The World Health Organization was committed to eliminating neonatal tetanus by 1995. Three years after this date, the infection killed over 400,000 babies a year, even though a safe, effective vaccine had been available for most of this century. The frequency of tetanus in the developing world epitomizes the healthcare disparity between the developed and the developing world. Consequently, the priority of the medical profession must be prevention, with the development of simpler immunization schedules with longer protection. Consequently, the purpose of this collective review is to provide an overview to the management of tetanus as well as to review the immunization strategy that will prevent this potentially deadly illness.

Tetanus is caused by *Cloistridium tetani,* which is an obligate anaerobic, gram-positive rod that is motile and readily forms endospores. Although *C. tetani* is located everywhere, the disease is encountered largely in underdeveloped, overcrowded, and economically disadvantaged countries. *C. tetani* is widespread in the feces of domestic animals and humans, while spores of *C. tetani* are abundant in soil and in the environment surrounding the habitation of humans and animals. Tetanus usually follows deep penetrating wounds where anaerobic bacterial growth is facilitated. Three basic forms of tetanus may be distinguished: local, cephalic, and generalized. At least 80% of the cases are the generalized form. In the adult patient, the most characteristic sign of generalized tetanus is lockjaw, or trismus. The diagnosis of tetanus is most frequently made on clinical manifestations, rather than on bacteriologic findings. The three objectives of management of tetanus are: (1) to provide supportive care until the tetanospasmin that is fixed in tissue has been metabolized; (2) to neutralize circulating toxin; and (3) to remove the source of tetanospasmin. Because there is essentially no immunity to tetanus toxoid, the only effective way to control tetanus is by prophylactic immunization.

**KEYWORDS:** *Cloistridium tetani*, tetanospasmin, endospores, trismus, deep penetrating wounds, penicillin, metronidazole, neuromuscular blocking agents, magnesium sulphate, tetanus immune globulin, tetanus toxoid, acellular pertussis vaccine, diphtheria toxoid, Vaccine Information Statements, vaccine immunization record

## I. INTRODUCTION

Tetanus was first described in Egypt over 3000 years ago and was evident throughout the ancient world. Tetanus is caused by the action of a potent neurotoxin, tetanospasmin, which is produced during the growth of *Clostridium tetani.* The disease, which is frequently fatal, can be prevented by immunization with tetanus toxoid. Since the introduction of vaccination with tetanus toxoid in the 1940s, tetanus has become a rare disease in the United States.[1] The overall incidence of tetanus has declined from 0.4 per 100,000 population in 1947 to 0.02 during the latter half of the 1990s. In addition, the case-fatality ratio has declined from 91% to 11% during this same period. Between 1989 and 1997, the majority of tetanus cases reported occurred in individuals who had not completed a three-dose primary tetanus toxoid vaccination series or for whom vaccination histories were uncertain. No tetanus deaths occurred in individuals who received primary tetanus immunization.[2,3] Because tetanus occurs where facilities for ventilation are limited, there is an urgent need for new treatments that reduce the necessity for ventilation, and improve cardiovascular stability in an effort to reduce mortality.[4]

## II. PATHOGEN

Tetanus is caused by *C. tetani,* which is an obligate anaerobic, gram-positive rod that is motile and readily forms endospores.[5] They are widely distributed in the environment and have been identified in the intestinal flora of domestic animals, horses, chickens, and humans. In gram stain preparations, these bacteria can occur singly, in pairs, or in long chains. Spore-bearing bacilli usually contain a single, spherical, terminal endospore that swells the end of the organism and produces a characteristic clubbed appearance resembling a drumstick. The organism grows well on blood agar at 37 °C under anaerobic conditions. Slight hemolysis is readily apparent on blood agar. Because the bacteria tend to swarm, isolated colonies are rare. *C. tetani* is relatively inert biochemically, with no fermentation of carbohydrates and no proteolytic activity.

Ten distinct serological types of *C. tetani* have been described based on their flagellar antigen. All these types have one or more common somatic antigens. Two exotoxins are produced by this bacteria. One, a hemolysin, is relatively unimportant. The other tetanus neurotoxin, also termed tetanospasmin, is responsible for the clinical manifestations of the disease. Some strains of *C. tetani* apparently do not yield the tetanospasmin. Most of the toxin is produced at the end of the germination phase, which occurs under strictly anaerobic conditions. Although the vegetative forms of this organism can be inactivated by heat and disinfectants, spores of *C. tetani* are relatively resistant to desiccation and disinfectants. They are able to survive exposure to phenol, merbromin, and many other chemicals effective in disinfection. The spores are extremely stable, although immersion in boiling water for 15 minutes kills most spores. There is no form of life that survives exposure to saturated steam under 15 lbs. of pressure for 15–20 minutes at 121 °C. Sterilization by dry heat is slower than by moist heat (1–3 h at 160 °C), but it is also effective against spores. Ethylene oxide sterilization is also sporocidal.

In clinical practice, most attempts to culture *C. tetani* are unsuccessful, because it is difficult to culture this organism. In addition, finding this organism in culture does not indicate whether the bacteria contains the toxin-producing plasmid. Moreover, *C. tetani* will not cause a fatal disease in patients with protective immunity. There is little present information on the antimicrobial sensitivity of this organism.

## III. EPIDEMIOLOGY

Although *C. tetani* is located everywhere, the disease is encountered largely in underdeveloped, overcrowded, and economically disadvantaged countries.[6] Because immunization is totally effective in preventing tetanus, it is most frequently noted in countries or in ethnic groups in which effective immunization is less likely to be achieved. In the United States, tetanus is encountered more frequently in blacks in the rural South, where a combination of more extensive exposure to spores and incomplete immunity are predisposing factors.

In the United States, the incidence and mortality of tetanus have decreased approximately 10-fold in the last 25 years. While the incidence of tetanus has diminished dramatically with the routine use of tetanus toxoid, the number of reported cases has remained relatively constant in the last decade (approximately 100 cases annually). About three-fourths of all cases occur from April through September. Incidence and mortality rates are substantially higher for neonates and persons over 50 years of age than for any other age group.

Neonatal tetanus (occurring in the first 28 days of life) is a serious and frequently fatal form of tetanus in developing countries but has been found infrequently in recent years in the United States. The typical neonate with tetanus is born outside of the hospital to a nonimmunized mother and is delivered by a midwife who has used unsterile techniques in managing the umbilical cord, which acts as the portal of entry.

## IV. PATHOGENESIS

*C. tetani* are widespread in the feces of domestic animals and humans, while spores of *C. tetani* are abundant in soil and in the environment surrounding the habitation of humans and animals. They have been isolated from soil, house, operating theater, dust, fresh and salt water, and gun wads. These spores are usually introduced into the body through wounds, cuts, or burns. The incubation period for tetanus is variable, ranging from a few days to 3 weeks between the inoculation of spores and the initial clinical manifestations. Because the spores cannot germinate until oxygen is depleted, such focal anaerobic conditions are most likely to occur in wounds with tissue necrosis and foreign bodies. The presence of other organisms enhances the reversion of spores to their vegetative forms. The longer incubation periods are usually related to injury sites further away from the central nervous system, while centrally located cephalic wounds may produce symptoms after shorter periods. The length of the time between the injury that introduces clostridial spores into the body and the onset of symptoms is another determinant of severity. Those cases with clinical manifestations occurring 1 week or less after injury are frequently more severe and have higher case/fatality ratios.

*C. tetani* is a relatively noninvasive pathogen whose presence is rarely demonstrated in the wound. On rare occasions, it has been cultured from the bloodstream. It elicits minimal local reaction in the wound, usually without suppuration. Its principal role in the pathogenesis of tetanus is limited to the elaboration of the soluble toxin, tetanospasmin, which produces tetanus. The toxin is produced initially as a single polypeptide chain, with a molecular weight of approximately 150,000 d.[7] This toxin is cleaved into two subunits with molecular weights of approximately 107,000 and 43,000 d by the action of endogenous proteases. The genetic factor controlling the production of tetanospasmin is on a plasmid.

The tetanospasmin is formed by the germinated growing cells and is transported from the infected site to the axon terminals of the peripheral nerves. After its uptake into the nerve terminals, it reaches the cell somata of the respective neurons by fast intraxonal transport. This process is enhanced by increased neuronal activity. To exert its toxic action, tetanospasmin has to reach interneurons by trans-synaptic migration. Trans-synaptic transmission of toxin has been demonstrated not only from motoneurons into presynaptic terminals of interneurons, but also from postsynaptic into presynaptic neurons of the sympathetic system. The main action of the toxin is a blockage of transmitter release from presynaptic terminals. Generally, tetanus toxin seems to impair inhibitory synapses more strongly than synapses mediating excitation. The reason for this empirical finding is unknown. The ultimate receptor for tetanus toxin and the sequence of reactions leading to impairment of transmitter release are largely unknown. Disialogangliosides have been considered not only as the fixation site, but also as the ultimate receptor. The physiological action of tetanospasmin is similar to that of strychnine.

## V. CLINICAL MANIFESTATIONS

Tetanus usually follows deep penetrating wounds where anaerobic bacterial growth is facilitated. The most common sites of infection are wounds of the lower limbs, postpartum or postabortion infections of the uterus, nonsterile intramuscular injections, and compound fractures. However, it is important to emphasize that even minor trauma can lead to this disease. In as many as 30% of patients, no portal of entry is apparent.[8] Tetanus has been identified after a wide variety of injuries, including intravenous and intramuscular injection, acupuncture, ear piercing, and even toothpick punctures. It can occur following chronic infection, such as otitis media,[9] and has been noted after a decubitus ulcer.[10] Tetanus following an intramuscular injection with quinine is associated with a higher mortality than other modes of acquisition.[11]

Three basic forms of tetanus may be distinguished: local, cephalic, and generalized.

## V.A. Generalized Tetanus

At least 80% of cases are the generalized form. In the adult patient, the most characteristic sign of generalized tetanus is lockjaw, or trismus, the inability to open the mouth because of spasm of the masseter muscles. This may be accompanied by stiffness of the neck, difficulty in swallowing, rigidity of abdominal muscles, and temperature elevation of 2–4 °C above normal. As tetanus progresses in severe cases, there is spasm of the facial muscles resulting in a grotesque grinning expression called *risus sardonicus*. Spasms of the somatic musculature may be widespread, resulting in opisthotonos and board-like rigidity of the abdomen. Acute, paroxysmal, uncoordinated, widespread muscle spasms are characteristic of generalized tetanus. Such toxic convulsions occur intermittently, irregularly, and unpredictably and last from several seconds to several minutes. While they are usually mild initially and separated by periods of relaxation, paroxysms tend to become painful and exhausting as they continue. They may either occur spontaneously or be precipitated by a variety of external or internal stimuli. A distended bowel or bladder or mucous plugs in the bronchus can elicit paroxysms. Drafts of cold air, noise, lights, movement of the patient, as well as the patient's attempts to drink, may precipitate paroxysmal spasms. The frequency and severity of generalized spasms are related to the severity of involvement. Cyanosis and even sudden death may result from these spasms.

Occasionally, patients with generalized tetanus display autonomic manifestations that complicate patient care and may prove life-threatening. Sympathetic nervous system overactivity has been more frequently encountered in elderly patients or narcotic addicts with tetanus. Autonomic overactivity may result in wide fluctuations in blood pressure that vary from hypertension to hypotension, as well as tachycardia, sweating, hyperthermia, and cardiac arrhythmias.

Almost all neonatal tetanus is the general form. The first sign is difficulty sucking, beginning 3–10 days after birth and progressing to total inability to suck.

## V.B. Local Tetanus

Patients with local tetanus have spasm and increased muscle tone, confined to muscles near a wound without systemic signs. These contractions may persist for many weeks before gradually subsiding. Local tetanus may precede the onset of generalized tetanus, but is usually milder and much less likely to be fatal, having a mortality of approximately 1%.

## V.C. Cephalic Tetanus

Cephalic tetanus is an unusual form of the disease, occasionally occurring with otitis media or following injuries of the head. Isolated or combined dysfunction of any of the cranial nerves may occur, but involvement of the seventh cranial nerve is most common. Cephalic tetanus may progress into generalized tetanus or remain localized.

## V.D. Severity

Tetanus can be classified into three gradations of severity, based on symptoms and signs. Mild tetanus usually has an incubation period of at least 2 weeks. Initially, there is local rigidity of the muscles near the wound, which progresses to general rigidity. Stiffness of the neck and jaws develops slowly and results in mild trismus. True dysphagia and paroxysmal spasm are usually not present. Gradual and complete recovery occurs during the 2-4 weeks following the onset of symptoms.

Moderately severe tetanus has a shorter incubation period, usually 7–10 days. It is characterized by severe trismus, dysphagia caused by pharyngeal muscular spasm, and general muscle rigidity. Paroxysmal spasms are mild and short, but they progress slowly for several days, becoming frequent, painful, and violent. They are not associated with dyspnea or cyanosis.

Severe tetanus is always characterized by a short incubation period, typically less than 72 hours. Muscular hypertonicitiy is so pronounced that interference with breathing, opisthotonos, and board-like abdominal rigidity are present. The paroxysmal spasms are frequent, prolonged, violent, and asphyxial. Patients surviving longer than 1 week exhibit a gradual reduction in the intensity and frequency of spasms. A decrease in general rigidity and in residual stiffness occurs later. Complete recovery takes place in 2–5 weeks.

Some clinicians have devised scoring systems to assess prognosis—for example, the Phillips score and the Dakar score.[12,13] Both scoring systems are relatively straightforward approaches that take in to account the incubation period and the period of onset as well as neurological and cardiac manifestations. The Phillips score also considers the state of immune protection. Udwadia[14] has devised a more clinical grading system that is also useful.

## VI. DIAGNOSIS

The diagnosis of tetanus is most frequently made on clinical manifestations, rather than on bacteriologic findings. The diagnosis of tetanus is relatively easy in areas where tetanus is seen often but is delayed in the developed world, where cases are seen infrequently.[15] In addition to trismus, physical examination may reveal marked hypertonicity of the muscles, hyperactive deep tendon reflexes, clear mentation, low-grade fever, and absence of sensory involvement. Local or general paroxysmal spasms may be observed. The vast majority of these patients have evidence of a wound that occurred within the last 2 weeks. Such patients commonly have no clear history of previous tetanus toxoid immunization.

Bacteriologic studies can confirm the presence of *C. tetani* in only about one-third of all patients who have clinical evidence of the disease. It must also be remembered that isolation of *C. tetani* from contaminated wounds does not mean that the patient will contract or has contracted tetanus. The frequency of isolation of *C. tetani* from wounds of patients with clinical tetanus may be improved by heating one set of specimens to 80 °C for 15 minutes to destroy vegetative forms of non-sporulating competing microorganisms before culture media are inoculated.

Laboratory studies show a moderate leukocytosis. The cerebrospinal fluid is normal in patients with tetanus, but the pressure may be elevated by muscular contractions. The results of electromyography and electroencephalography are usually normal and not helpful in the diagnosis. Occasionally, if cardiac involvement is present, the electrocardiogram may show T-wave inversion. A sinus tachycardia is also common.

One must be cautious in diagnosing tetanus in patients having verified histories of receiving two or more injections of tetanus toxoid in the past. Serum specimens should be obtained by assaying antitoxin by hemagglutination and, preferably, mouse neutralizing tests. The presence of 0.01 IU of antitoxin/mL of serum is generally considered protective.

The differential diagnosis of tetanus includes a number of conditions that can simulate one or more of the clinical findings of tetanus and are sometimes designated "pseudotetanus." The early symptoms of tetanus may be mimicked by either strychnine poisoning or a dystonic reaction to phenothiazines. Phenothiazine reactions can cause trismus, but the associated tremors, athetoid movements, and torticollis should make one suspect this drug reaction. In strychnine poisoning, the possibility of homicide or suicide may be evident from the history. Moreover, trismus tends to appear late, and symptoms and signs develop much more rapidly than in tetanus.

The most common local condition that results in trismus is an alveolar abscess. A careful history and physical examination complemented by radiographic studies should identify the abscess. Purulent meningitis can be excluded by examination of the cerebrospinal fluid. Encephalitis is occasionally associated with trismus and muscular spasms, but the patient's sensorium is usually clouded. Rabies must also be considered in the differential diagnosis even though trismus is not present. Muscle spasms occur early in the course of rabies and involve the muscles of respiration and deglutition. In children less than two years of age, hypocalcemic tetany must be considered. However, the typical posturing of the hands and feet, the absence of trismus, and a low serum calcium level will confirm the diagnosis of hypocalcemic tetany.

## VII. TREATMENT

The three objectives of management of tetanus are: (1) to provide supportive care until the tetanospasmin that is fixed in tissue has been metabolized; (2) to neutralize circulating toxin; and (3) to remove the source of tetanospasmin. All patients should be admitted to a medical or neurological intensive care unit where they can be monitored and observed continuously. Some hospitals in which tetanus is frequently encountered have specially constructed, quiet, dark rooms to minimize extrinsic stimuli that might trigger paroxysmal spasms. Patients must be allowed to rest quietly to limit peripheral stimuli, and they must be positioned carefully to prevent aspiration pneumonia. Intravenous fluids should be instituted, and electrolytes and blood gases are essential to guide therapy.

Penicillin is the standard therapy for tetanus in most parts of the world, although antibiotics for *C. tetani* probably play a relatively minor role in the specific treatment of this disease. The recommended dose is 100,000–200,000 IU/day intramuscularly or intravenously for 7–10 days. In 1945, Johnson and Walker[16] were the first to note that intravenous administration of penicillin could produce convulsions. They went on to show in animal models that penicillin caused myoclonic convulsions when applied directly to the cortex. Penicillin became the standard model for producing experimental focal epilepsy.

Metronidazole (Galderma Laboratories, Fort Worth, Texas) is now considered the first line of therapy and is a safe alternative to penicillin. Rectal administration of metronidazole is rapidly bioavailable and produces fewer spasms than repeated intravenous or intramuscular injections. In 1985, Ahmadsyah and Salim[17] were the first to compare metronidazole and penicillin and showed a reduction in mortality in the metronidazole group. A randomized clinical study reported by Yen et al.[18] demonstrated that there was no significant difference in mortality between the penicillin and metronidazole group. However, the 533 patients in the metronidazole group required fewer muscle relaxants and sedatives compared with the 572 patients randomized to penicillin. Consequently, metronidazole is considered as the drug of choice in the treatment of tetanus. The dose is 400 mg rectally or 500 mg intravenously every 6 hours for 7–10 days.

Vigorous and aggressive management of muscle spasms is a cornerstone of therapy. There appears to be divergent therapeutic approaches to the control of severe muscle spasms in tetanus between those who rely on central nervous system depressants that produce muscle relaxation and those who employ neuromuscular blocking agents. The objective of the first approach is to mildly sedate the patient without affecting respiratory function. The sedated patient is less affected by peripheral stimuli and less likely to develop muscle spasms. The short-acting barbiturates such as secobarbital and phenobarbital are useful in sedating patients with mild tetanus. Initial doses of 1.5–2.5 mg/kg for children or 100–150 mg intramuscularly for adults may be used. Because maintenance doses required for optimal sedation vary widely, they usually have to be titrated. When spasms become severe and/or more frequent, the use of both diazepam and barbiturates, administered intravenously, may be justified. Phenobarbital may be given in a dose of 120–200 mg intravenously, and diazepam may be added in divided doses up to 120 mg/day. Diazepam may prevent or control seizures. Chloropromazine, given every 4–8 hours in doses from 4–12 mg in the infant to 50–150 mg in the adult, may be effective in controlling tetanic convulsions. Mechanical ventilatory support is often required to counteract the drug-induced ventilatory depression that becomes apparent in the intervals between spasms.

In the other therapeutic approach, muscle spasms may be controlled primarily by neuromuscular blocking agents, such as d-tubocurarine chloride or pancuronium bromide, while sedation is induced with smaller doses of the central depressant drugs. Because the paralyzed patient risks asphyxia, mechanical ventilatory support is mandatory. The judicious use of tracheostomies may be important in maintaining adequate ventilation among the patients with opisthotonos and involvement of back and thoracic muscles. In addition, tracheostomy enhances the maintenance of good bronchopulmonary toilet.

Deaths from pulmonary dysfunction in tetanus have not been convincingly reduced by these various regimens of sedation. This problem has been exemplified in the series reported by Edmondson and Flowers[19] in which six out of ten of their patients with tetanus died from respiratory complications. Consequently, there has been a continuing search for drugs that can control spasms and autonomic dysfunction of tetanus without the need for heavy sedation or artificial ventilation. The role of magnesium in the management of tetanus has been suggested by many. Magnesium is a physiological calcium antagonist in which there is a significant correlation between the depression of neuromuscular transmission and serum magnesium concentrations. In 1997, Attygalle and Rodrigo[20] investigated the efficacy and safety of intravenous magnesium sulphate in controlling the spasms of severe tetanus without the need for sedation and ventilatory support. The infusion rate of magnesium sulphate was increased to control spasms, while retaining the patella tendon reflex, which proved a valuable guide to prevent overdose. Spontaneous ventilation was adequate with this treatment in four of their eight patients. Ventilatory support was necessary in four of their patients for the management of lung pathology. In a report by Thwaites and Farrar,[21] they expressed concern about the use of magnesium sulphate as a first-line therapy in the management of tetanus. While they agreed that magnesium was a potential treatment for tetanus, they warned that magnesium could cause more harm than the conventional therapy. They recommended that a carefully designed double-blind randomized controlled clinical trial of sufficient sample size be initiated to confirm the safety of magnesium sulphate in the management of tetanus.

Various cardiovascular disturbances have been described in tetanus and are a frequent cause of death. Although the exact mechanism of these disturbances is still obscure, autonomic dysfunction appears to be involved in the majority of problems. The signs of sympathetic overactivity often appear a few days after the onset of muscle spasms, probably a result of the longer and more complex route that the toxin must take to reach the lateral horns of the spinal cord compared with the relatively more direct approach to the anterior horn. The signs of sympathetic overactivity are most evident in younger patients (<55 years) and are characterized by fluctuating tachycardia, hypertension sometimes followed by hypotension, peripheral pallor, and sweating.

The extreme hypertension and tachycardia and the elevated systemic vascular resistance that have been recorded in some paralyzed and sedated patients indicate that sympathetic overactivity may result in an increase in both $\alpha$ and $\beta$ adrenergic activity. Under such conditions, the heart may depend on $\beta$ stimulation to enable it to maintain an adequate blood flow through a constricting vascular bed. The inhibition of this stimulation by the use of $\beta$ adrenergic blocking agents, such as propanolol, may precipitate cardiovascular failure by decreasing cardiac output and inducing a further decrease in systemic vascular resistance by blocking $\beta$ mediated vasodilation in the muscle.

The incidence of sympathetic overactivity appears to be lessened in tetanus patients who have been treated with large doses of drugs that depress the level of activity of the central nervous system. However, cardiovascular instability may still occur in such patients. Although cardiac function does not appear to be impaired by large doses of diazepam and phenobarbital alone, several fatal accidents have occurred when $\beta$ blockers were administered to heavily sedated tetanus patients. Because of the possibility of interaction between drugs, it is probably safer to control the sympathetic overactivity by further damping central nervous system activity, rather than by initiating peripheral autonomic blockade.

There remain other cardiovascular disturbances that can cause death in the tetanus patient. Hypertension accompanied by tachycardia, peripheral circulatory failure, and hyperpyrexia may develop, despite thera-

**TABLE 1.**

| Abbreviations | Tetanus toxoid vaccines |
|---|---|
| DT | Diphtheria and tetanus toxoids vaccine (for children) |
| DTaP | Diphtheria and tetanus toxoids and acellular pertussis vaccine |
| DTaP-Hib | Diphtheria and tetanus toxoids and acellular pertussis anden Haemophilus influenzae type b |
| DTP | Diphtheria and tetanus toxoids and pertussis vaccine (unspecified pertussis antigens) |
| DTP-Hib | Diphtheria and tetanus toxoids and pertussis and *Haemophilus influenzae* type b Vaccine (unspecified pertussis antigens) |
| DTwP | Diphtheria and tetanus toxoids and whole-cell pertussis vaccine |
| DTwP-Hib | Diphtheria and tetanus toxoids and whole-cell pertussis and *Haemophilus influenzae* type b |
| PRP-T Hib | Polyribosylribitol phosphate polysaccharide conjugated to tetanus toxoid and *Haemophilus influenzae* type b |
| Td | Tetanus and diphtheria toxoids vaccine (for adolescents and adults) |
| TT | Tetanus toxoid vaccine |

peutic intervention. These cardiovascular disturbances may be due to massive tetanus intoxication.

Because tetanus is associated with clinical and biochemical evidence of sympathetic overdischarge and protein catabolism, maintenance of nutritional support is essential. From nitrogen balance studies, it was demonstrated that conventional enteral-feeding techniques were unable to maintain nutrient homeostasis in the majority of patients with severe tetanus. Consequently, the resulting loss of body weight encountered must reflect a diminution of lean body cell mass. The consequent protein depletion will result in reduced host defenses and may thereby worsen prognosis. This loss of lean body cell mass is inevitable in such patients unless the metabolic response can be suppressed by the use of more aggressive

**TABLE 2. Recommended and Minimum Ages and Intervals Between Vaccine Doses[a]**

| Vaccine and dose number | Recommended age for this dose | Minimum age for this dose | Recommended interval to next dose | Minimum interval to next dose |
|---|---|---|---|---|
| Diphtheria and tetanus toxoids and acellular Pertussis (DTaP)1 | 2 mos | 6 wks | 2 mos | 4 wks |
| DTaP2 | 4 mos | 10 wks | 2 mos | 4 wks |
| DTaP3 | 6 mos | 14 wks | 6–12 mos | 6 mos[ab] |
| DTaP4 | 15–18 mos | 12 mos | 3 yrs | 6 mos[b] |
| DTaP5 | 4–6 yrs | 4 yrs | | |

[a] Combination vaccines are available. Using licensed combination vaccines is preferred over separate injections of their equivalent component vaccines. When administering combination vaccines, the minimum age for administration is the oldest age for any of the individual components: the minimum interval between doses is equal to the greatest interval of any of the individual antigens.

[b] Calendar months

forms of nutritional support. A rational approach to achieving metabolic control would be the use of adrenergic blocking agents, although it remains to be seen whether such therapy can suppress the hypermetabolic state. The other therapeutic alternative for such patients is to match the increased metabolic losses by parenteral feeding. Total parenteral nutrition containing hypertonic glucose and insulin, in sufficient quantities to control blood sugar, can suppress this protein catabolism. The use of amino acid formulations containing increased branched chain amino acid concentrations is another helpful approach to limit protein catabolism. Physical therapy should be started early in the convalescent period of the disease. If neuromuscular blocking agents are used in treatment, passive movements of the patient's arms and legs should be instituted.

After the initial evaluation, human tetanus immune globulin (TIG) (Bayer Pharmaceutical Division, Elkhart, Indiana) should be injected intramuscularly in a total dose of 3000 units, injected in three equal portions into three separate sites. Because the half-life of TIG is 25–30 days, only a single treatment is required. The earlier the treatment is rendered, the more efficacious it is. Antiserum does not neutralize tetanospasmin already fixed in the nervous system, nor does it have any special effect when administered locally in the wound. Hypersensitivity reactions to TIG have not been documented, and pretreatment testing is not needed. A patient who gets tetanus is not immune against a subsequent attack because tetanospasmin is so potent that toxicity can be expressed without adequate concentrations to immunize. Consequently, active immunization should be instituted concomitantly with the passive immunization. The combined active and passive prophylaxis of tetanus does not decrease the subsequent development of antibodies from tetanus toxoid.

The wound should be cleansed thoroughly and debrided. Abscesses should be drained, and foreign bodies and necrotic tissue should be removed. While antibiotics are effective against the toxin-producing vegetative forms of *C. tetani,* the effects of antibiotic therapy alone on the prevention of clinical tetanus are minimal. The deficiency of antibiotics alone was found when tetanus-prone injuries were treated without antitoxin in patients with hypersensitivity to the antitoxin. Nevertheless, antimicrobial agents are given as previously recommended.

Because pulmonary embolism has been a common cause of death in tetanus patients, many employ anticoagulants routinely during treatment. Although subcutaneous heparin has been used to anticoagulate these patients, complete protection against thromboembolism has not always been obtained, and the risks of hemorrhage are always present. Other complications of tetanus include atelectasis, aspiration pneumonia, pulmonary emboli, acute gastric ulcers, fecal impaction, urinary retention, urinary tract infection, and decubitus. The intensity of the paroxysmal spasm is sometimes sufficient to result in spontaneous rupture of muscles and intramuscular hematoma. Compression fractures or subluxation of vertebrae may occur, usually affecting thoracic vertebrae.

## VIII. PREVENTION

Because there is essentially no natural immunity to tetanus toxin, the only effective way to control tetanus is by prophylactic immunization. Thus, universal primary immunization with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters is necessary to protect all age groups.

In the past, the diphtheria-tetanus-whole-cell pertussis (DTwP) vaccine had been the primary means of prophylaxis for children (Table 1). More recently, there has been a growing concern about the adverse effects of this vaccine, which were related primarily to the use of whole-cell-pertussis vaccine.[22] With the advent of the acellular pertussis vaccine, the annual incidence of serious adverse reactions to this vaccination has declined.

In clinical trials, acellular pertussis vaccines have been clearly demonstrated to be less dangerous than whole-cell vaccines.[23,24] Today, immunization in infants is achieved with the diphtheria-tetanus-acellular pertussis (DTaP) vaccine. In addition, combination childhood vaccines are also available, including diphtheria and tetanus toxoids and acellular pertussis with *Haemophilus influenza* type b vaccine (HTaP-Hib) as well as polyribosylribitol phosphate polysaccharide conjugated to tetanus toxoid and *H. influenza* type B (PRP-T Hib). The use of combination vaccines is a practical way to overcome the challenges of multiple injections, especially in children who are behind schedule in vaccinations. In addition, the use of combination vaccine might improve timely vaccination coverage. However, combination vaccines have some drawbacks, including chemical incompatibility or immunologic interference.[25] For adult immunization, the tetanus toxoid adsorbed (T) (Aventis Pasteur Inc., Swiftwater, Pennsylvania) as well as diphtheria and tetanus toxoids adsorbed (Td) are available.

The basic immunization schedule for tetanus prophylaxis varies with the patient's age.

## VIII.A. Recommended Active Immunization Schedules

### *1. Normal Infants and Children*

Immunization should begin in early infancy and requires four injections of DTaP administered at 2 months, 4 months, 6 months, and 15-18 months (Table 2).[26] A fifth dose is administered at 4–6 years of age. Ten years after the fifth dose (14–16 years of age), an injection of Td, which contains the same dose of tetanus toxoid as DTP and a reduced dose of diphtheria toxoid, should be administered and repeated every 10 years throughout the individual's life in the event that there have been no significant reactions to DTP or Td. Adsorbed preparations should be administered intramuscularly. Vaccine administration by jet injection may be associated with more frequent reactions.

### *2. Normal Infants and Children Up to Age 7 Not Immunized at Early Infancy*

DTP should be administered on the first visit and 2 and 4 months after the first injection. A fourth dose should be administered 6–12 months after the first injection. The fifth dose is administered between 4 and 6 years of age. Ten years after the fifth dose (14–16 years of age), an injection of Td should be administered and repeated every 10 years throughout the individual's life in the event that there have been no significant reactions to DTP or Td. The preschool dose is not necessary if the fourth dose of DTP is administered after the fourth birthday.

### *3. Persons Seven Years of Age or Older Who Have Not Been Immunized*

Immunization requires at least three injections of Td. These injections should be administered on the first visit, 4–8 weeks after the first Td, and 6–12 months after the second Td. An injection of Td should be repeated every 10 years throughout life in the event that there have been no significant reactions to Td.

### *4. Pregnant Women Who Have Not Been Immunized*

Neonatal tetanus is preventable by active immunization of the pregnant mother. A previously unimmunized pregnant woman who may deliver her child under unhygienic conditions should receive two properly spaced doses of Td before delivery, preferably during the last two trimesters, given 2 months apart. There is no evidence that tetanus and diphtheria toxoids are teratogenic. After the delivery, the mother should be given the third dose of Td 6 months after the second dose to complete the active immunization. An injection of Td should be repeated every 10 years throughout life in the event that there have been no significant reactions to Td. If a neonate is borne by a nonimmunized mother without obstetric care, the infant should receive 250 units of human TIG. Active and passive immunization of the mother should also be initiated.

TIG is a solution of gamma globulin prepared from the venous blood of humans, hyperimmunized with tetanus toxoid. This immune globulin has been found to be nonreactive for hepatitis B surface antigen, using the radioimmunoassay method of counterelectrophoresis. It is administered by a deep intramuscular injection in a different extremity from that receiving the intramuscular injection of vaccine. Historically, such passive immunization was provided by antitoxin, derived from either equine or bovine serum. However, the foreign proteins in these heterologous products often produced severe allergic manifestations, even in individuals who demonstrated negative skin and/or conjunctival tests prior to administrations (5–30%). Consequently, do not administer these heterologous products, except when the human antitoxin is not available, and only if the possibility of tetanus outweighs the potential reactions to these products.

### *5. Children under Seven with a Contraindication to Pertussis Vaccination*

DT (for pediatric use) should be used rather than DTaP. Unimmunized children under 1 year old receiving their first DT dose should receive a total of four doses of DT as the primary series, the first three doses at 4- to 8-week intervals and the fourth dose 6–12 months later. If further doses of pertussis vaccine become contraindicated after beginning a DTaP series in the first year of life, DT should be substituted for each of the remaining scheduled DTaP doses.

Unimmunized children one year old or above for whom DTaP is contraindicated should receive two doses of DT 4–8 weeks apart, followed by a third dose 6–12 months later to complete the primary series. Children one year old or above who have received 1–2 doses of DT or DTaP and for whom further pertussis vaccine is contraindicated should receive a total of three doses of DT, with the third dose administered 6–12 months after the second dose.

### *6. Contraindications to Preparations Containing the Pertussis Vaccine*

The contraindications to pertussis vaccine are:

1. a personal history of a prior convulsion
2. the presence of an evolving neurologic disorder (e.g., uncontrolled epilepsy, infantile spasm, progressive encephalopathy, etc.)
3. adverse reactions to DTaP or single antigen pertussis vaccination that include any of the following:
   a. allergic hypersensitivity
   b. fever of 40.5 °C (105 °F) or greater within 48 hours
   c. collapse or shock-like (hypotonic-hyporesponsive episode) within 48 hours
   d. persisting, inconsolable crying, lasting 3 hours or more, or an unusual high-pitched cry, occurring within 48 hours
   e. convulsion(s) with or without fever, occurring within three days (such seizures do not predispose to permanent brain damage)
   f. encephalopathy occurring within seven days, including severe alterations in consciousness with generalized or focal neurologic signs (the encephalopathy may lead to permanent neurologic deficit)

Although hemolytic anemia and thrombocytopenic purpura have previously been considered contraindications, the evidence of a causal link between these conditions and pertussis vaccination is not sufficient to retain them as contraindications.

### *7. Infants with, or Unimmunized Infants Suspected of Having, Underlying Neurologic Disease*

It is prudent to delay initiation of immunization with DTaP or DT until further observation and study have clarified the child's neurologic status. The effect of treatment, if any, can be assessed. The decision whether to commence immunization with DTaP or DT should be made no later than the child's first birthday. In making this decision, it should be remembered that children with severe neurologic disorders may be at enhanced risk of exposure to pertussis from institutionalization or from attendance at clinics and special schools in which many of the children may be unimmunized. In addition, because of neurologic disabilities, these children may be in greater jeopardy from complications of the disease.

### 8. Infants With Neurologic Events Temporarily Associated with DTaP Vaccination

Infants and children who experience a seizure within 3 days of receipt of DTaP or an encephalopathy within 7 days should not receive pertussis vaccine, even though cause and effect may not be established.

### 9. Incompletely Immunized Children with Neurologic Events Occurring Between Vaccination Doses

If the seizure or other disorder occurs before the first birthday and completion of the first three doses of the primary series of DTaP, deferral of further doses of DTaP or DT is recommended until the infant's status has been clarified. The decision whether to use the DTaP or DT to complete the series should be made no later than the child's first birthday and should take into consideration the nature of the child's problem and the benefits and risks of the vaccine. If the seizure or other disorder occurs after the first birthday, the child's neurologic status should be evaluated to ensure that the disorder is stable before a subsequent dose of DTaP is given.

### 10. Infants and Children with Stable Neurologic Conditions

Infants and children with stable neurologic conditions, including well-controlled seizures, may be vaccinated. The occurrence of single seizures (temporarily associated with DTaP) in infants and young children, while necessitating evaluation, need not contraindicate DTaP immunization, particularly if the seizures can be satisfactorily explained. Anticonvulsant prophylaxis should be considered when giving DTaP to such children. Parents of infants and children with histories of convulsions should be made aware of slightly increased chance of postimmunization seizures. A static neurologic condition, such as cerebral palsy or a family history of a neurologic disease or convulsions, is not a contraindication to giving vaccines containing pertussis antigen.

### 11. Children with Resolved or Corrected Neurologic Disorders

DTaP immunization is recommended for infants with certain neurologic problems that have clearly subsided without residue or have been corrected, such as neona-

**TABLE 3. Guide to Tetanus Prophylaxis**

| History of adsorbed tetanus toxoid (doses) | Tetanus-prone wounds Td[a] | Tetanus-prone wounds TIG[f] | Nontetanus-prone wounds Td[a] | Nontetanus-prone wounds TIG[b] |
|---|---|---|---|---|
| Uncertain or < 3 | Yes | Yes | Yes | No |
| 3 or more[c] | No[e] | No | No[d] | No |

[a] For children less than 7 years old, diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP) (diphtheria and tetanus toxoids adsorbed [DT], if pertussis vaccine is contraindicated) are preferred to tetanus toxoid alone. For persons 7 years old and older, Td is preferred to tetanus toxoid alone.

[b] When TIG and Td are given concurrently, separate syringes and separate sites should be used.

[c] If only 3 doses of toxoid have been received, a 4th dose of toxoid, preferably an adsorbed toxoid, should be given.

[d] Yes, if more than 10 years since last dose.

[e] Yes, if more than 5 years since last dose. (More frequent boosters are not needed and can accentuate side effects.)

[f] TIG: human tetanus immune globulin

tal hypocalcemic tetany or hydrocephalus (following placement of a shunt and without seizures).

### VIII.B. Contraindications to Preparations Containing the Diphtheria and Tetanus Toxoid

The only contraindication to tetanus and diphtheria toxoids is a history of neurologic or severe hypersensitivity reaction following a previous dose. Immunization with tetanus and diphtheria toxoids is not known to be associated with an increased risk of convulsions. Local side effects alone do not preclude continued use. Local reactions, generally erythema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria, tetanus, and acellular pertussis antigens. These reactions are most common following DTaP (40–70% of doses) and are usually self-limited and require no therapy. If an anaphylactic reaction to a previous dose of tetanus toxoid is suspected, intradermal skin testing with appropriately diluted tetanus toxoid may be useful before a decision is made to discontinue tetanus toxoid immunization. In one study, 95 persons giving histories of anaphylactic symptoms following a previous tetanus toxoid dose were nonreactive following intradermal testing and tolerated a further tetanus toxoid challenge without a reaction.[6] One person had immediate erythema and induration following skin testing but tolerated a full intramuscular dose without adverse effects.

Persons who experience Arthus-type hypersensitivity reactions or fever greater than 39.4 °C (103 °F) following a prior dose of tetanus toxoid usually have a high serum tetanus antitoxin level and should not be given even emergency doses of Td more frequently than every 10 years, even if they have tetanus-prone wounds.

If a contraindication to tetanus-containing preparations exists in a person who has not completed a primary immunizing course of tetanus toxoid and other than a tetanus-prone wound is sustained, only passive immunization should be given, using TIG.

The patient or responsible person should be informed of the risks of immunobiologics as well as the major benefits of preventing disease both in individuals and in the community. There should be ample opportunity to ask questions about immunization. As required under the National Childhood Vaccine Injury Act, all healthcare providers in the United States who administer any vaccine shall, prior to the administration of the vaccine, provide a copy of the Vaccine Information Statement (VIS) produced by the Centers for Disease Control and Prevention (CDC) to the parent or legal representative of any child to whom the provider intends to administer such vaccine, or any adult to whom the provider intends to administer such vaccine. The VIS must be supplemented with visual presentation or oral explanations, as appropriate. If there is not a single VIS statement for a combination vaccine (e.g., DTaP-Hib) use the VIS for both the DTaP and Hib component vaccine. Copies of the VIS are available from the CDC at cdc.gov/nip/publications/VIS. Copies are available in English as well as many other languages. While understanding the risks and benefits of these vaccines, the patient or responsible person must authorize that the appropriate vaccine has been administered. The responsible person or patient should sign a form indicating that he/she has read the VIS and has had a chance to ask questions to his/her satisfaction.

The adverse reactions to tetanus toxoid vaccines are outlined to the patient or guardian in clear, understandable language. The VIS also emphasizes that in the rare event that you or your child has a serious reaction to a vaccine, a federal program (the National Vaccine Injury Compensation Program) has been created to help the individual pay for care resulting from the adverse reaction. For details about the National Vaccine Injury Compensation Program call, 800-338-2382 or visit the website hrsa.gov/bhpr/vicp.

Surveillance for vaccine associated with adverse events is an integral part of patient care in spite of the current record of safety of the tetanus toxoid vaccines. Any adverse events suspected to be associated with tetanus toxoid vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) at 800-822-7967. VAERS is a cooperative program for vaccine safety for the CDC and the Food and Drug Administration (FDA). VAERS is a postmarketing safety surveillance program that collects information about adverse events that occur after the administration of vaccines licensed in the United States. Its website, vaers.org, provides a nationwide mechanism by which adverse events following immunization may be reported, analyzed, and published. Its website provides a valuable vehicle for disseminating vaccine safety-related information to parents/guardians, healthcare providers, vaccine manufacturers, state vaccine programs or other institutions, and other facilities. A link on its website provides the VAERS form for reporting vaccine adverse events. The completed form can be either faxed to 877-721-0366 or sent by business mail (no postage is necessary).

Documentation of the date and type of immunization should be given to the responsible person or patient. Today, this information is usually recorded on wallet-sized cards. In the future, the immunization record will be an integral part of the patient's complete medical record in an optical memory card for optical data recording. Two megabytes of digital data can be recorded on this wallet-sized card, which is equivalent to 800 pages of typed information. These optical memory cards are designed for write/read applications, making them ideal for electronic publishing systems. Pertinent information about the manufacturer and lot number of the vaccine or TIG and the site of injection(s) should be included in the patient's medical record.

## VIII.C. Tetanus Prophylaxis of the Wounded Patient

Recommendations on tetanus prophylaxis are based on (1) condition of the wound and (2) the patient's immunization history. A wound with any of the following clinical features is a tetanus-prone wound: more than 6 hours old; stellate; avulsion; abrasion; greater than 1 cm deep; injury due to missile, crush, burn, or frostbite; signs of infection; devitalized tissue; contaminants; denervated and/or ischemic tissue.

A summary guide to tetanus prophylaxis of the wounded patient is outlined in Table 3. History of tetanus immunization should be verified from medical records so that appropriate tetanus prophylaxis can be accomplished. Patients with unknown or uncertain previous immunization histories should be considered to have no previous tetanus toxoid doses. Person who have performed military service since 1941 can be considered to have received at least one dose, although most may have completed a primary series of tetanus toxoid. However, this cannot be assumed for each individual.

Regardless of the active immunization status of the patient, meticulous surgical care using aseptic technique that includes removal of all devitalized tissue and foreign bodies should be provided immediately for all wounds. Such care is essential as part of the prophylaxis against tetanus.

Td is the preferred preparation for active tetanus immunization in wound management in the adult. This preparation immunizes the patient against tetanus, while enhancing diphtheria protection in a large proportion of the adult population who are susceptible to diphtheria. For routine wound management of children under 7 years of age, DTaP should be used instead of a single-antigen tetanus toxoid. If pertussis vaccine is contraindicated, DT may be used.

Passive immunization with TIG must be considered individually for each patient. The characteristics of the wound, the conditions under which it was incurred, the treatment, its age, and the previous active immunization status of the patient must be considered. When the wound is judged to be tetanus prone, TIG is indicated if the patient has received less than three doses of tetanus toxoid. The effectiveness of antibiotics for prophylaxis of tetanus is uncertain. Proper immunization plays the most important role in tetanus prophylaxis.

For every wounded patient, record in a permanent medical record pertinent information about the clinical features of the wound, previous active immunization status, history of a neurologic or severe hypersensitivity reaction, immunoprophylaxis (manufacturer, lot number, and site of injection), and plans for follow-up. An appropriate written record and VIS must be given to the patient describing treatment rendered, risks and benefits of immunization, immunization status (wallet-sized or optical memory card), and follow-up instructions that outline wound care and drug therapy, as well as referral to a designated physician who will provide comprehensive follow-up care, including completion of active immunization. The responsible person or patient should sign a consent form indicating that he or she has read the VIS about immunization and authorizes appropriate immunization.

Tetanus infection may not confer immunity; therefore, active immunization should be initiated at the time of recovery from the illness. Arrangements should be made to ensure that the remaining doses of a primary series are administered as early as possible.

### VIII.D. Tetanus in the Elderly

In the early 1980s, it was shown that a large percentage of older Americans did not have protective levels of tetanus antibodies. The Immunization Practices Advisory Committee (ACIP) of the CDC modified immunization guidelines for adults in 1995 to include a review of immunization status at age 50, with repeat immunization against tetanus every decade thereafter. Among geriatric patients, 50% to 70% have nonprotective tetanus antibody levels. In one study, geriatric patients without adequate antibody levels were given one tetanus toxoid immunization.[27] When tetanus antibody titers were obtained again, 86% were found to have protective antibody levels. Therefore, one tetanus toxoid injection may be sufficient to induce protective antibody levels in many geriatric patients.

Although older people frequently lack immunity to tetanus, appropriate immunization can promote an adequate antibody response in this population. All physicians must be aware of and adhere to the ACIP guidelines for adult immunization to ensure that this population is protected. Although primary care practitioners will have the most impact on immunity in older people, emergency physicians also play an important role when caring for injured adults.

## IX. CONCLUSIONS

Tetanus is caused by *Cloistridium tetani,* which is an obligate anaerobic, gram-positive rod that is motile and readily forms endospores. Although *C. tetani* is located everywhere, the disease is encountered largely in underdeveloped, overcrowded, and economically disadvantaged countries. *C. tetani* is wide spread in the feces of domestic animals and humans, while spores of *C. tetani* are abundant in soil and in the environment surrounding the habitation of humans and animals. Tetanus usually follows deep penetrating wounds where anaerobic bacterial growth is facilitated. Three basic forms of tetanus may be distinguished: local, cephalic, and generalized. At least 80% of the cases are the generalized form. In the adult patient, the most characteristic sign of generalized tetanus is lockjaw, or trismus. The diagnosis of tetanus is most frequently made on clinical manifestations, rather than on bacteriologic findings. The three objectives of management of tetanus are (1) to provide supportive care until the tetanospasmin that is fixed in tissue has been metabolized; (2) to neutralize circulating toxin; and (3) to remove the source of tetanospasmin. Because there is essentially no immunity to tetanus toxoid, the only effective way to control tetanus is by prophylactic immunization.

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