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Don't Be a Stiff
A Review Article on the Management of Tetanus

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ABSTRACT
Vaccine-preventable diseases, such as tetanus, are oftentimes a thought of the past in countries that only see a handful of cases per year. In recent years, though, there has been more controversy around vaccinations and fewer individuals getting vaccinated. This movement has resulted in vaccine-preventable diseases resurfacing (e.g., measles). Tetanus is one of the diseases that health care providers should continue to be familiar with in regard to its clinical presentation and the treatments that are available to manage the corresponding signs and symptoms. Because tetanus is an acute, toxin-mediated illness that can be fatal, prevention and treatment are critical. This article briefly summarizes tetanus and the therapies considered to be first line in its management.
Key words: muscle spasm, prevention, tetanus, tetanus immunoglobulin, tetanus toxoid booster, vaccination, wound care

GIVEN THE CONTROVERSIES and debates surrounding vaccines in the United States, the topic of vaccine-preventable diseases such as tetanus has resurfaced as health care providers may encounter more of these cases than they have in previous years. The incidence of tetanus is low in the United States, but the occurrence in low- and middle-income countries remains a problem. The mortality in these areas remains high as data from Africa revealed a 43% mortality risk (Loan et al., 2018). It is challenging to estimate the number of tetanus cases worldwide as most cases occur in countries where surveillance tools are scarce. Despite the fact that it is preventable, tetanus is an acute and often fatal disease secondary to the neurotoxin associated with *Clostridium tetani.* The neurotoxin is responsible for muscle spasms; these can be generalized or localized, as well as responsible for dysfunction of the autonomic nervous system (Yen & Thwaites, 2019). This article provides a review of tetanus as well as nonpharmacological and pharmacological options for treatment.

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TETANUS

Tetanus is the name used for the disease caused by the bacterium *Clostridium tetani,* which was discovered in 1884 by Carle and Rattone. *Clostridium tetani* is a gram-positive anaerobic rod. The bacterium is spore-forming and produces potent neurotoxins. Of the two exotoxins it produces, tetanolysin and tetanospasmin, the tetanospasmin is the one that is known to produce the clinical manifestation of tetanus. This is one of the most potent toxins known to man, with a minimum lethal human dose of 2.5 ng/kg of body weight. Although the bacterium is sensitive to heat, the spores are able to withstand autoclave temperatures of 121 °C for up to 15 min. In addition, the spores are not affected by antiseptics, phenol, or other chemical cleaning agents (Centers for Disease Control and Prevention, 2015).

When the bacterium is introduced, whether through a wound, abrasion, or the umbilical stump in neonates, under anaerobic conditions, it will produce vegetative bacteria that release the tetanospasmin and cause the disease we know as tetanus. Tetanus is characterized by nervous system dysfunction and muscle spasms. Many may recognize it by the common presentation of "lockjaw," where the jaw and neck muscles become paralyzed and the affected person is no longer able to move his or her mouth.

Although tetanus is vaccine preventable, it is impossible to eradicate due to the widespread presence of *C. tetani* in our natural environment. It can be found in almost every corner of the earth in our soil and is present in the digestive tract of many domesticated animals. In areas where agriculture is the primary means of subsistence, many humans will even harbor the organism. Because tetanus infection cannot be transmitted from person to person, it is the only noninfectious vaccine-preventable illness (Centers for Disease Control and Prevention, 2015).

Epidemiology

Tetanus cases in the United States have declined by more than 95% since it became a nationally reportable disease in 1947. Deaths secondary to tetanus from 1947 to 2017 were reduced by more than 99%. This is largely due to the introduction of the tetanus toxoid vaccine in the 1920s. However, its first widespread use was throughout military forces during World War II for soldiers, as well as an addition to routine childhood immunizations in the same time period. The average number of cases in the United States is now around 29 per year (Centers for Disease Control and Prevention, 2017).

Tetanus is more common in countries where access to vaccination is limited. Particularly, mothers who are unvaccinated put newborns at risk for fatal tetanus infections in more rural areas where births may generally take place at home. The World Health Organization (WHO) only reported seven countries in 2019 with vaccination rates of less than 50%, but there are still 13 countries that have not reached the goal of less than 1 case per 1,000 births of neonatal tetanus infection (WHO, 2019a, 2019b).

Those most at risk for tetanus infection are unvaccinated individuals. With the rise of the anti-vaccine movement, only around 80% of children complete the tetanus vaccine series (Hill, Elam-Evans, Yankey, Singleton, & Kang, 2018). Unvaccinated or undervaccinated children account for a few of the highly publicized cases of tetanus each year. However, the majority of cases are in adults who either are unvaccinated or have skipped the recommended booster doses that should be administered every 10 years (Hassel, 2013). In addition, diabetes, immunosuppression, and intravenous drug abuse may be independent risk factors for tetanus infection. Based on demographic data from 2009 to 2017, intravenous drug users represented 7% of all tetanus cases and diabetic patients accounted for 13% of all cases as well as 25% of all tetanus-related deaths (Hassel, 2013).

Pathogenesis of Tetanus

As stated, spores most commonly enter the body through a wound (Hassel, 2013). Tetanus spores require anaerobic conditions

to germinate and begin producing the potent neurotoxin, tetanospasmin (Centers for Disease Control and Prevention, 2015). Tetanus toxin will disseminate throughout the body through the bloodstream and the lymphatic system. It will then act on the central nervous system, affecting motor end plates in the brain and the spinal cord. It has effects on both the sympathetic and autonomic nervous systems. Tetanospasmin interferes with the release of neurotransmitters and blocks inhibitor impulses, resulting in unopposed muscle spasm and contraction that may lead to seizure activity (Bae & Bourgate, 2019).

The average incubation period is around 10 days from spore entry to symptom presentation. The farther the wound is from the central nervous system, the longer the incubation period, which can take up to 21 days. Shorter incubation periods are associated with higher mortality. The average onset for neonatal tetanus is around 7 days (Centers for Disease Control and Prevention, 2015).

Clinical Presentation

There are four recognized clinical forms of tetanus: generalized, localized, neonatal, and cephalic. Generalized tetanus is the most common and recognizable form and accounts for greater than 80% of cases. It most often presents as "lockjaw." Localized tetanus is unusual and presents as muscle spasms only around the site of the injury. It is associated with infection in people with at least partial immunity but can progress to generalized tetanus. Neonatal tetanus occurs due to exposure through the umbilical cord, and cephalic tetanus is incredibly rare and is attributed to lesions of the head or otitis media. It has the shortest incubation period of only 1–2 days. Patients with cephalic tetanus present with flaccid cranial nerve palsies, but these symptoms can progress to those more commonly associated with generalized tetanus (Centers for Disease Control and Prevention, 2015).

The most recognizable symptom of tetanus is painful muscular contractions. These contractions are primarily in the masseter and neck muscles, resulting in trismus or "lockjaw." A grimaced facial expression known as *risus sardonicus*, drooling, and uncontrolled urination and defecation may also occur. Abdominal rigidity is a common first sign of infection in adults and older children. Generalized muscle spasms can also occur and can frequently be induced by sensory stimuli. As the symptoms progress, maintaining a patent airway may become difficult as the muscles required for respiration become involved. The back-arching spasm known as opisthotonos can lead to respiratory distress. Intubation and mechanical ventilation combined with sedation and muscle relaxants may become necessary for treatment (Bae & Bourgate, 2019).

Tetanus can also cause autonomic instability. In these cases, patients may have fever, dysrhythmias, labile blood pressure and heart rate, and respiratory difficulty. Early death is associated with presentation of these symptoms (Yen & Thwaites, 2019).

There are no confirmatory laboratory tests for tetanus and even in the presence of wound cultures organisms are only recovered in approximately 30% of cases (Yen & Thwaites, 2019). Some infections may have no apparent portal of entry because the wound or abrasion may have been unnoticeably minor and healed prior to symptom onset. Based on this, tetanus is diagnosed on the basis of clinical presentation. The key markers for diagnosis are acute onset of symptoms, muscle contractions, and generalized spasms in the absence of any other medical cause. On physical examination, there have been reports of the "spatula test" showing accuracy in diagnosis of tetanus. This examination is performed by using a soft-tipped instrument to touch the posterior pharyngeal wall. If the normal gag reflex is elicited, the test is negative for tetanus. If the stimulation results in involuntary jaw contraction, it may be considered positive for tetanus (Yen & Thwaites, 2019).

Complications

Tetanus can lead to many complications secondary to the sustained convulsions and contractions that occur in the muscles throughout the body. Laryngospasms, spasms of the muscles used for respiration, can lead to difficulty breathing and maintaining a patent airway. The need for hospitalization and intubation can result in a nosocomial infection or a pulmonary embolism. In addition, prolonged convulsions and contractions in the muscles surrounding the spine and long bones can lead to fractures. Tetanus also affects the autonomic nervous system and can lead to abnormal heart rhythms or hypertension. The most serious potential complication of tetanus is death, and the mortality rate of tetanus has most recently been estimated at 11% of all cases reported (Centers for Disease Control and Prevention, 2015).

PREVENTION

As discussed previously, wounds are the primary entry point for infection. In the event wounds are exposed to soil bacteria, it is important to clean the wound(s) and seek medical attention in the setting of vaccination absence or have not had a tetanus booster shot within the last 10 years. Although tetanus is difficult to avoid due to its widespread presence in our natural environment, it is entirely preventable through vaccination (Centers for Disease Control and Prevention, 2015).

Vaccination

The tetanus vaccine is an intramuscular injection into the deltoid muscle. It was added to the childhood vaccination series in 1938 and was combined with the pertussis and diphtheria vaccines in 1948 to create the diphtheria-tetanus-pertussis (DTP) combination vaccine. If children begin the vaccine series before 1 year of age, they will receive four total doses given at 2 months, 4 months, 6 months, and between 15 and 18 months of age. If a child is older than 1 year when the series is started, he or she will only need three doses. The first two doses should be spaced at least 4 weeks apart, and the third and final dose should be given 6 months after the second dose. If, by chance, a patient reaches adulthood without vaccination, the primary series is three doses. The first two doses in this series should be at least 4 weeks apart, with the third and final dose following by 6–12 months after dose two. The current vaccine schedule recommends a booster dose before entering elementary school at 4–6 years of age, then again at 11–12 years of age, and then every 10 years thereafter. The booster doses are needed to maintain protective antitoxin titers and are discussed more in the "Treatment" section. With adequate initial vaccination and booster doses, immunity to tetanus infection is virtually 100% (Centers for Disease Control and Prevention, 2015).

The vaccine is available only as a combination product with other vaccines. It is most commonly combined with diphtheria and pertussis vaccinations. The vaccine needs to be stored in refrigerated temperatures prior to use (i.e., between 35° and 46 °F) and should not be stored in the freezer (Centers for Disease Control and Prevention, 2015).

Local reactions to the vaccine are common, with redness, pain, and minor swelling at the injection site being the most frequently reported adverse events. Severe allergic reactions including hives and anaphylaxis are rare but possible, especially if the individual has had a previous reaction to the vaccine or its components. There have been some reports of Guillain–Barré syndrome and peripheral neuropathy after vaccination, but there is no evidence to support or reject a causal relationship (Centers for Disease Control and Prevention, 2015).

TREATMENT

Supportive Care

With the majority of tetanus cases occurring in countries with limited resources, mechanical ventilation may or may not be available.

When it is available, it is associated with better patient outcomes as aggressive sedative and neuromuscular blocking agents can then be used in the management of the patient's spasms. For those patients who have laryngeal spasms at their initial presentation, tracheostomy may be necessary as endotracheal intubation may not be feasible depending on the extent of the patient's laryngeal spasms. Tracheostomy is also preferred as these patients may require mechanical ventilation for 3–5 weeks and during that time tracheal stenosis may occur but occurs less frequently in those who undergo tracheostomy (Yen & Thwaites, 2019). An observational study of patients with tetanus on the ventilator demonstrated that mechanical ventilation was not associated with an increased mortality rate from ventilator-associated respiratory infections; however, intensive care unit (ICU) and hospital lengths of stay were higher (Phu et al., 2017).

Human Tetanus Immunoglobulin

Tetanus immunoglobulin (TIG) has been available since the early 1900s, but the first formulation available was derived from equine. Human TIG is now available in most countries, but the data are minimal when it comes to which of these two products is better. Potential advantages of human TIG include its longer half-life and less hypersensitivity reactions. The success of TIG is associated with its mechanism of action as it can assist with the removal of unbound toxin. Dosing and the route of administration vary from country to country, but lower doses of approximately 500 units and intramuscular preparations are currently recommended in the United States. Tetanus immunoglobulin is recommended to be given as a deep intramuscular injection into either the deltoid muscle or the lateral thigh muscle. Intramuscular injection into the gluteal area, however, is not recommended secondary to the risk of sciatic nerve damage (HyperTET; Grifols Therapeutics Inc., 2012). Intrathecal administration of TIG can be considered as it has been associated with decreased mortality, but the primary literature has to be reviewed cautiously as bias and other confounding factors were limitations in many of the earlier trials from the 1970s and 1980s (Yen & Thwaites, 2019).

Immunoglobulin Intravenous

In the event that equine or human TIG is not available, immunoglobulin intravenous (IVIG) is an option for patients being treated for tetanus as it contains tetanus antitoxin. This treatment option would increase the patient's endogenous levels of serum immunoglobulin G and assist the patient in mounting an immune-mediated response. The dose for tetanus is not specifically known, so it would be left to the provider's discretion (Hemming, 2001; Hill et al., 2018). Doses of 200–400 mg/kg have been recommended, but it is important to note that this is not approved by the Food and Drug Administration (Kimberlin, Brady, Jackson, & Long, 2018).

Tetanus Toxoid Booster

All tetanus toxoids are prepared using the toxin itself that is created from virulent tetanus bacilli (*C. tetani*). Formaldehyde is used to alter the toxin so that it no longer carries its toxic effects but preserves its capability to act as an antigen and produce active immunity (Adacel package insert; Aventis Pasteur Limited, 2005). There are currently two forms of the toxoid available on the market today: adsorbed toxoid, containing precipitated aluminum salts, and fluid toxoid. Of the two, the adsorbed toxoid is preferred over the fluid toxoid secondary to a better antitoxin response and longer duration of protection (Centers for Disease Control and Prevention, 2015). The diphtheria toxoid, adsorbed (Td) booster doses should be provided every 10 years after completion of the original immunization schedule (Adacel package insert; Aventis Pasteur Limited, 2005). There is one exception to the 10-year rule, and this is for those who have

endured a wound that is considered to be something other than clean and minor. Patients meeting this description should receive their booster if more than 5 years have passed since their last tetanus vaccine (Centers for Disease Control and Prevention, 2015).

Contraindications for the tetanus toxoid are similar to other preventive vaccines/boosters. These include if a patient is currently febrile or experiencing an acute infection at the time of vaccination request, a history of an allergic reaction to a previously given tetanus vaccine/booster, and hypersensitivity to any element of the vaccine, including the thimerosal component (Adacel package insert; Aventis Pasteur Limited, 2005).

Agents to Control Muscle Spasms

Increased muscle spasms are one of the most familiar signs of tetanus. The muscle spasms usually present as "locked jaw" and progressively spread down the extremities and to the abdominal area over the course of a few days. Complications of these muscle spasms can contribute significantly to the increased mortality rate in patients with tetanus if not promptly treated (Rodrigo, Fernando, & Rajapakse, 2014).

A literature search on the treatment of muscle spasms secondary to tetanus revealed diazepam as one of the most preferred drugs as there were articles dating back to the 1960s and 1970s (Bacon, 1968; Bennett, 1971; Femi-Pearse, 1966). Despite the amount of time that has passed, benzodiazepines are still standard of care today and are thought to be effective as they have added benefits such as anticonvulsant properties as well as their sedative/anxiolytic effects all while being able to adequately control muscle spasms. This class has also been noted to cause less respiratory depression than barbiturates, which have also been used in the treatment of muscles spasms. Diazepam is cost-effective and is available in almost all settings. Diazepam's mechanism of action allows it to boost the action of γ-amino butyric acid (GABA) Type A receptor antagonism. This action opens membrane channels and allows for the entry of chloride ions, which leads to cellular depolarization (Valium package insert; Roche Products Inc. Pharmaceuticals, 2008). It can be given via several different routes of administration (i.e., orally, intravenously, and rectally), making it a good option for most situations. A Cochrane review concluded that in most of the early studies diazepam alone compared with phenobarbitone and chlorpromazine (with or without the addition of diazepam) resulted in fewer deaths and in most of the studies had statistically significant results (Okoromah & Lesi, 2004). Although the benzodiazepines, specifically diazepam, have been shown to cause less respiratory depression than previously used methods to control muscle spasms, patients with tetanus are generally still placed on mechanical ventilation for a significant portion of their treatment. More recently, there have been other drugs studied in hopes of reducing the amount of time these patients are on mechanical ventilation.

Magnesium sulfate therapy has been suggested as a probable treatment of tetanus as far back as the early 1900s. Its mechanism of action is that of a calcium antagonist through which it aids in the depression of the neuromuscular transmission of calcium, thereby increasing serum magnesium levels (Attygalle & Rodrigo, 1997). Magnesium has long been considered safe for the treatment of spasms related to eclampsia in pregnancy, and it has been hypothesized that it could provide the same anti-spasmodic effects to help with muscle spasm control in tetanus. The idea is that this could be accomplished without the use of mechanical ventilation in these patients. Despite this, magnesium should still be used with caution and close monitoring is warranted as its side effects can range from muscle weakness to paralysis.

In March 1996, a prospective study conducted in an ICU in Sri Lanka included eight patients with severe tetanus. These patients were originally treated with the antitoxin, surgical debridement of the area and

antibiotics, as well as diazepam. All eight patients subsequently underwent a tracheostomy secondary to spasms that were so severe they continued to have restrictions with respirations. Once ICU admission had occurred, the diazepam therapy was completed and magnesium therapy was initiated within 24 hr pending renal function. A loading dose of 5 g was administered over 20 min, followed by a continuous infusion of 2 g/hr. The infusion rate was increased every 8 hr, and this continued until ablation of muscle spasms occurred. Serum magnesium concentrations were measured throughout, as well as continued assessment of the patella reflex. After 2–3 hr, the intensity/frequency of the muscle spasms had decreased, and most patients saw complete cessation within 24 hr. The magnesium infusions were continued for a few days after the spasms had stopped, as it was difficult to wean the drip, and rigidity and tachycardia increased with weaning attempts in a few patients. The study concluded that magnesium sulfate can be used alone for the ablation of muscle spasms in severe tetanus as all eight patients saw cessation of spasms without the aid of ventilator support (Attygalle & Rodrigo, 1997).

Although Attygalle and Rodrigo (1997, 2002) demonstrated success with magnesium as the sole agent for muscle spasms in tetanus and reducing the need for mechanical ventilation, results vary throughout the literature. Another prospective study was conducted in a tertiary care teaching hospital from January 2006 to December 2007 and consisted of 33 patients (Mathew, Samra, & Wig, 2010). Similar to Attygalle et al.'s study, all patients received the tetanus toxoid, as well as immunoglobulin and antibiotics with surgical debridement of the injury site. A loading dose of 70 mg/kg over 30 min was given along with a follow-up infusion of 2 g/hr if the patient was 60 years or younger and 1 g/hr for those older than 60 years. The drip rate was increased every 6 hr based on response of muscle spasms and patellar reflex assessment. If spasms could not be controlled by magnesium alone, an infusion of diazepam was added at 2 mg/hr and titrated to effect. As a result, 18% of patients were controlled on magnesium sulfate alone without mechanical ventilation. However, the remaining 82% of patients required tracheostomy or mechanical ventilation. Of the patients requiring ventilation, 22% were not able to be controlled with the addition of the diazepam and therefore required essential neuromuscular paralysis with vecuronium. The overall mortality rate was 22.9%, and this included two of the patients who were maintained only on magnesium. On the basis of the results, the authors concluded that tetanus could not be managed with magnesium sulfate alone and that other agents were needed for complete ablation of muscle spasms.

A randomized, double-blind, placebo-controlled trial that included 256 patients was conducted in Vietnam (Thwaites et al., 2006). This study divided the patients into two groups, a magnesium sulfate group consisting of 97 patients and a placebo group with 98 patients. Patients receiving magnesium were given a loading dose of 40 mg/kg over 30 min, followed by a continuous infusion of 2 g/hr for patients who were heavier than 45 kg and 1.5 g/hr for those weighing less than 45 kg. Their conclusions were similar to that of Mathew et al. (2010) in that magnesium was not successful as a solo agent for the control of muscle spasms or for the decreased induction of mechanical ventilation. However, the authors did conclude that the addition of magnesium sulfate allowed for lower doses of midazolam and pipecuronium. It is notable that Thwaites et al. (2006) were not able to achieve the same magnesium levels as in other trials that showed some success.

Based on this review of the literature, it can be concluded that the addition of magnesium does provide some benefit to patients being treated for tetanus, including severe tetanus. Magnesium is an acceptable option for adjunct therapy in the control of muscle spasms in tetanus but should not be used alone.

In the continued search for an alternative to the benzodiazepines and mechanical

ventilation, baclofen has become one of the top competitors to fill this position. Baclofen is a selective GABA Type B receptor antagonist. In its oral form, it has decreased ability to cross the blood–brain barrier and is therefore not an acceptable route of administration for the treatment of tetanus. Given this, studies have been successfully conducted using intrathecal baclofen as an alternative (Rodrigo et al., 2014; Yen & Thwaites, 2019).

A study conducted in Africa enrolled patients to receive multiple intrathecal injections of baclofen. All 10 patients received the standard tetanus toxoid, antibiotic therapy, and debridement of the wound. The doses were administered by the intrathecal route at the L3–L4 or L4–L5 area. For patients older than 55 years, the dose injected was 800 mcg. Patients who were between 16 and 55 years of age, received a dose of 1,000 mcg, whereas patients 16 years or younger received 500 mcg. Of the patients, 90% saw resolution of symptoms 1.5 hr after the first injection. Patients could be redosed when symptoms returned as long as it was more than 12 hr after the previous injection. Half of the patients progressed to mechanical ventilation and of those, 80% died. The other five patients were treated solely with intrathecal baclofen injections, and four of the five patients achieved "cure." The other patient in that group died of septic shock secondary to a urinary tract infection developed during treatment. As a result, the study demonstrated that multiple intrathecal doses of baclofen could play a significant role in the treatment of severe tetanus. However, given that 50% of their study group participants needed mechanical ventilation, more research is needed to prove its efficacy (Saissy et al., 1992).

A case report consisting of a single case of success, followed by additional data of 14 patients, was published in 1999. The single patient received an intrathecal catheter and received doses of baclofen as high as 1,750 mcg as a continuous infusion. By Day 18, the patient had developed a fever with cerebrospinal fluid and blood cultures positive for *Klebsiella pneumoniae.* At this time, his lines were pulled and his muscle spasms were then controlled with diazepam. The patient's cultures cleared, and he was discharged from the hospital on Day 24 without ever requiring mechanical ventilation (Engrand, Guerot, Rouamba, & Vilain, 1999). In the additional data report, an ICU looked at 14 patients with severe tetanus from May 1995 to August 1996. All the patients received standard of care, with tetanus toxoid, antibiotics, and debridement of the wound area being provided. Patients were given an initial baclofen dose of either 500 mcg or 1,000 mcg depending on their weight, less than 55 kg and more than 55 kg, respectively. After the initial bolus, the patients were given subsequent doses of baclofen via a continuous intrathecal infusion pump, with the dose being adjusted every 12 hr if necessary. During this time, if the intrathecal baclofen treatment failed, general sedation was resumed and the patients underwent mechanical ventilation. Overall, this case reported success as only two of the 14 patients required intubation (Engrand et al., 1999).

A retrospective study in Portugal looked at patients from 1998 to 2003 and included 22 patients treated with an initial bolus dose of baclofen ranging from 40 to 200 mcg, followed by a 20 mcg/hr continuous infusion. This infusion was titrated by 8 mcg every 4 hr until spasms were relieved or the patient reached a maximum daily dose of 2 mg. Only three of the 22 patients did not require mechanical ventilation for some portion of their hospital stay, and all but one of these patients survived and were discharged from the hospital. Santos et al. (2004) concluded that intrathecal baclofen is a "good option" for tetanus muscle spasms. The authors also concluded that administration by continuous infusion was superior to that of intermittent bolus doses (Santos et al., 2004).

Intrathecal baclofen remains a contender in the treatment of tetanus, especially in areas where mechanical ventilation may not be an easy option. However, this could also be a downfall as the preferred continuous infusion can be very expensive and in an area with

limited supplies could pose a significant problem. There are also some infection issues with the indwelling catheter and with it a risk for central nervous system infections as well as infections of the bloodstream (Rodrigo et al., 2014). It is therefore not recommended as a standard of care in the treatment of tetanus, but with more studies it could prove to be beneficial to our patients seeking treatment in more desolate areas.

WOUND CARE

Antibiotics

Any wound has the potential to become infected if not properly cared for. Wounds are more likely to be "tetanus-prone" if they happen 6 hr or more before debridement of the wound can be achieved, or at any time past this while having one or more of following: puncture wound, large amount of devitalized flesh, evidence of sepsis, soil contamination, burns, frostbite, or a large penetrating muscle injury (WHO, 2019a).

For optimal wound care, it is recommended to wash the wound thoroughly with soap and water for 10 min. This should be followed by irrigation of the wound with normal saline. The next focus should be on debridement, whether that is simply removing any visible debris or a much more thorough debridement that is done in an operating room for removal of damaged/dead tissue. The wound should then be lightly packed with clean packing material. Packing material should be covered with a dry dressing. It is important to make sure the dressing is changed once a day at the very least and more frequently if called for (WHO, 2019a).

Antibiotics are also helpful when it comes to tetanus wound care as they are given for the prevention of spreading of the bacillus *C. tetani*. However, research from the *British Medical Journal* found that only 30%–60% of patients being treated for tetanus actually produce a positive culture result for *C. tetani* (Ahmadsyah & Salim, 1985). The antibiotics that are generally used are penicillin G, metronidazole, and doxycycline.

For the last several decades, penicillin has been the drug of choice for tetanus-related infections because of its widespread availability. Penicillin G exhibits bactericidal activity for the period of active multiplication of the bacteria. Adult dosing for clostridial infections, including tetanus, is 20 million units per day divided every 4–6 hr secondary to its short half-life (Bicillin package insert; Baxter Healthcare Corporation, 2016). Over time, penicillin has fallen out of favor as the drug of choice in tetanus infections as patients can have tolerability issues. In some instances, severe and sometimes fatal adverse events such as anaphylactic reactions can occur. Depending on patient presentation, it can sometimes be difficult to verify an allergy profile in these patients, especially if the patient is intubated prior to the time of antibiotic initiation.

Both penicillin and metronidazole are acceptable agents in the treatment of tetanus. However, there are those who claim that metronidazole is superior secondary to penicillin's inhibition of GABA receptors and the possibility of decreasing the seizure threshold (Rodrigo et al., 2014). According to Ahmadsyah and Salim (1985), metronidazole has surpassed penicillin as the drug of choice against *C. tetani*. Among their study of 173 patients, the metronidazole group was found to have a mortality rate that was significantly lower than the penicillin group, 7% versus 24%, respectively. During their study, they also found that the patients in the metronidazole group had fewer admission days (i.e., on average 5 fewer days).

Metronidazole's mechanism of action is described as a nitromidazole that works by way of passive diffusion into the cytoplasm of anaerobic bacteria. Once there, proteins transfer electrons to the nitro group on metronidazole and this, in turn, forms a nitroso free radical. This free radical then interacts with the intracellular DNA, causing a halt in DNA synthesis and ultimate cell death (Flagyl package insert; Pfizer, 2018). John's Hopkins Antibiotic Guide lists the dose of metronidazole for the treatment of tetanus to be 7.5 mg/kg intravenously or by mouth

every 6 hr with a maximum of 4 g per day (Bartlett, Auwaerter, Pham, & Jenh, 2000–2015). Metronidazole has been shown to be rapidly bactericidal against a myriad of anaerobic organisms in both in vitro and in vivo studies (Ahmadsyah & Salim, 1985).

Few studies exist describing the use of doxycycline in the treatment of tetanus. Doxycycline is described as a bacteriostatic antibiotic with a mechanism that works by inhibiting protein synthesis. The use of doxycycline becomes more prominent when penicillin is deemed contraindicated for infections such as those by the *Clostridium* species. This species includes the *C. tetani* species responsible for tetanus. The recommended dose of doxycycline is 100 mg intravenously every 12 hr for 7–10 days (Vibramycin package insert; Bedford Laboratories, 2013).

CONCLUSION

Even though the incidence of tetanus in the United States is low (i.e., approximately 29 cases per year), health care providers should continue to be familiar with the clinical presentation and treatment of this acute disease as it can be life-threatening. Mainstays in the management of tetanus include supportive care, with mechanical ventilation being an integral component, human TIG, and the tetanus toxoid booster. Management of muscle spasms and wound care are also important aspects in the care of these patients. The management of tetanus is costly and lengthy for patients, so prevention with the vaccination should be promoted by health care professionals when possible.

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