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Best Practices for Tetanus Vaccination and Treatment

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Introduction

Tetanus is an acute, morbid, and potentially fatal disease caused by tetanospasmin, a toxin produced by the bacterium *Clostridium tetani*.[1] Infection with *C. tetani* usually occurs when spores enter the body through a wound and transform to active bacteria in an anaerobic environment.[1] Worldwide, tetanus is responsible for approximately 56,700 deaths per year; 10% to 20% of patients with active tetanus infection will die even with modern medical care,[2,3] and those who survive often suffer from permanent neurologic issues.[4] Antibiotics have limited efficacy against *C. tetani* and cannot reverse the effects of bound tetanus toxin; therefore, treatment for tetanus is limited to proper wound management, supportive care to mitigate the effect of tetanic spasms, and administration of tetanus immune globulin (TIG).[1] For this reason, prevention of tetanus is paramount.

In addition, the cost of medical treatment for active tetanus is significantly higher than routine and regular immunization.[5] One study estimated the cost of treating tetanus in unvaccinated adults to be approximately $14,400 per patient, not including the costs due to loss of productivity.[5] A more recent study of tetanus among unvaccinated children in Pennsylvania found much higher costs for treatment, including a median hospital charge of $50,122.[6] The high cost of tetanus treatment, the ubiquity of *C. tetani*, and the lack of effective therapies warrant routine preventive vaccination for all children and adults in the United States.[1,4]

Vaccination Programs

Vaccination programs implemented among military personnel during World War II illustrate how dramatically the efficacy of tetanus vaccines reduces incidence and mortality. Before vaccine availability, tetanus rates among US military personnel during World War I were 13.4 per 100,000 wounded soldiers. In contrast, tetanus rates among vaccinated soldiers in World War II were 0.44 per 100,000 soldiers.[1,7] Similarly, few vaccinated

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British troops developed tetanus, whereas unvaccinated German troops suffered high rates of infection.[8]

Before the introduction of tetanus toxoid vaccines in the 1940s, between 500 and 600 cases of tetanus occurred in the United States each year.[1] After the adoption of tetanus vaccination as a main component of routine childhood immunization schedules, the number of tetanus cases dropped significantly (Figure 1).[4] Overall, 197 tetanus cases were reported in the United States from 2009 through 2015, with 16 deaths. Of these, 25% (49 cases) occurred in individuals older than 65 years of age, and 63% (124 cases) occurred in those between the ages of 20 and 64 years. Individuals younger than 20 years of age accounted for 12%, including 2 neonatal cases.[9] Deaths associated with tetanus occurred among persons older than the age of 55.[9] Twenty-nine cases were reported in the United States in 2015, and many occurred in older patients experiencing declining immunity or who had not been vaccinated.[3,4,10] Humans rarely develop immunologic memory in response to *C. tetani* infection; therefore, the development of an effective vaccine was instrumental in protecting against the disease and reducing tetanus morbidity and mortality.[3,4]

Tetanus Vaccination Development

Tetanospasmin blocks neurotransmitters, leading to muscle rigidity, uncontrolled muscle spasms, and seizures; it is primarily responsible for the morbidity and mortality associated with tetanus infection.[1] The incubation period is approximately 3 to 21 days, with symptoms most commonly appearing at 8 days; it is therefore critical that patients seek treatment without delay.[1]

The first tetanus vaccine became available in 1938.[4] This single-antigen vaccine was used until multicomponent vaccines were developed in the late 1950s.[4] Since then, tetanus vaccine has been administered almost exclusively as a multicomponent vaccine formulation to protect against numerous infectious diseases while limiting the number of vaccinations needed for protection and improving compliance.[11,12] Although the formulation of tetanus vaccine has undergone many changes in the past 80 years, it is administered most frequently with diphtheria toxoid and pertussis vaccine (Table 1).[4]

Unlike exposure to tetanus bacteria or tetanus toxin alone, the tetanus vaccine induces a strong antigen-specific T- and B-cell response. Repeat doses strengthen this response and

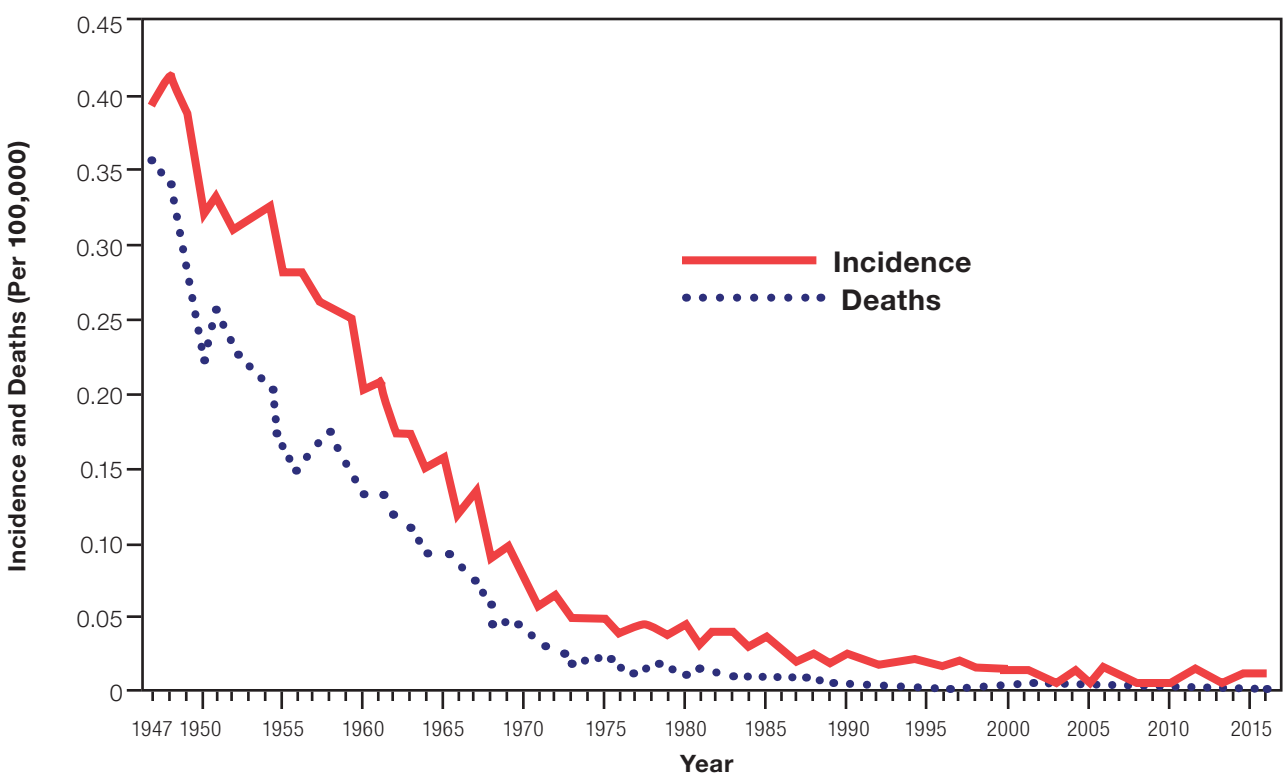

Figure 1. The effect of tetanus vaccine on incidence and deaths in the United States.

Based on reference 4.

facilitate the development of immunologic memory.[3,13,14] The longevity of immunologic memory in response to tetanus is nonetheless unclear. Studies have shown that a 3- or 4-dose primary series provides protective antibody levels for more than 25 years.[15,16] However, susceptibility to tetanus increases every year after vaccination, with the majority of tetanus deaths occurring in elderly patients.[3,14] The CDC recommends repeat routine tetanus immunization every 10 years for this reason.[4]

Current Formulations

Tetanus vaccination is accomplished primarily via formulations containing[4]:

- tetanus toxoid, diphtheria toxoid, and acellular pertussis (ie, DTaP, Tdap); and
- tetanus toxoid and diphtheria toxoid only (ie, DT, Td) (Table 1).

The standard vaccine against tetanus in all formulations comprises a manufactured tetanus toxoid precipitated onto an aluminum salt adjuvant.[4] Aluminum salts stimulate a strong immune response against the tetanus toxoid with minimal and transient local or general reactions.[17,18] Pediatric formulations of tetanus vaccines contain 5 to 10 limit of flocculation (Lf) units of antigen, whereas adolescent and adult formulations contain 2 to 5 Lf units of antigen.[1,19] Tetanus toxoid is usually administered in combination with diphtheria toxoid.[1] Adult formulations of tetanus-diphtheria vaccines (ie, Tdap, Td) have less diphtheria toxoid (2-2.5 Lf units) than pediatric formulations (ie, DTaP, DT), which have 3 to 4 times more diphtheria toxoid (6.7-25 Lf units).[1] A single dose of vaccine is insufficient to elicit immunologic memory; thus, vaccination is administered in a series, followed by boosters.[4]

Generally, vaccines that include pertussis antigens are indicated for initial immunization in children or adults who did not receive childhood immunization, whereas tetanus and diphtheria vaccines without pertussis are used for routine boosters for adolescents and adults who have completed a prior vaccination series. The exceptions include a one-time Tdap dose for all adolescents and adults, and 1 dose administered with every pregnancy.[4] Current acellular pertussis vaccines differ from the original formulation (DTP), which included a whole-cell pertussis component.[4] Whole-cell pertussis vaccine was associated with a number of adverse events (AEs), including injection site reactions, fever, convulsions, and hypotonic–hyporesponsive episodes.[20] Therefore, DTP was discontinued in the 1990s and replaced with acellular pertussis formulations (ie, DTaP, Tdap).[4] The number and combination of pertussis antigens in acellular pertussis vaccines vary by manufacturer, but may include filamentous haemagglutinin, pertactin, pertussis toxin, and fimbriae types 2 and 3.[4]

Safety

Adult and pediatric tetanus vaccines are safe, with a low risk for serious AEs.[4,21] Postlicensure safety evaluations of

Table 1. Current and Former Tetanus Vaccine Formulations Used in the United States

Vaccine	Formulation	Use
TT	Monovalent tetanus toxoid	• Before the development of combined vaccines • No longer available
DTP	Diphtheria and tetanus toxoids, whole-cell pertussis	• Before the development of DTaP • Discontinued due to safety concerns
DTaP	Diphtheria and tetanus toxoids, acellular pertussis	• Primary immunization series in pediatric patients • Replaced DTP
Tdap	Tetanus toxoid, reduced diphtheria toxoid, acellular pertussis	• Adolescents and adults who have not been vaccinated • Adolescents and adults who otherwise require pertussis vaccination
Td	Tetanus toxoid and reduced diphtheria toxoid	• Booster immunization for adolescents and adults
DT	Diphtheria toxoid and tetanus toxoid	• Primary immunization in children with contraindications to pertussis vaccine

Based on reference 4.

currently approved vaccines have shown a high correlation between clinical trial data and real-world safety, as reported in AE surveillance systems (ie, the Vaccine Adverse Event Reporting System, Vaccine Safety Datalink).[4] Furthermore, research has not revealed any causal association between vaccination and rare AEs, including Guillain-Barré syndrome, seizures, encephalopathy, paralytic syndromes, and cranial nerve disorders.[22,23] Local reactions, such as pain, redness, or swelling are the most common AEs associated with immunization.[4] Mild systemic reactions, such as fever, also may occur.[23] These less common AEs are self-limiting and manageable with symptomatic treatment.[1]

Best Practices for Tetanus Vaccination

Although tetanus vaccination is essential to public health, adult immunization rates are generally poor.[4,24] In addition, guidelines continue to change as the science evolves on the effect of vaccination on immunologic memory.[25] In April 2018, the CDC Advisory Committee on Immunization Practices published a compilation of recommendations for the administration of tetanus vaccine, including treatment schedules, appropriate populations for the various tetanus vaccine formulations, and strategies for preventing and treating tetanus in the clinic.[4] A comprehensive understanding of these guidelines can improve compliance to vaccination protocols and increase tetanus immunity in the United States.[4]

Schedule and Dosing

Several formulations of DTaP, Tdap, Td, and DT are approved in the United States, and the CDC has published updated recommendations for tetanus vaccine schedules (Table 2).[4] Initial vaccination in infants and children from 2 months to 6 years of age is typically accomplished by a 3- or 4-dose series of DTaP. Six DTaP and DTaP combination vaccines are licensed in the United States; when possible, the same product should be administered for all doses of the initial series. Subsequently, the CDC recommends a DTaP booster in children aged 4 to 6 years. If pertussis vaccination is contraindicated, the CDC recommends DT with the same vaccination schedule for initial immunization. The use of DT vaccine is limited to children aged 7 years and younger.[4]

The CDC recommends a one-time dose of Tdap for all individuals aged 11 years or older with the exception of an additional dose to women during each pregnancy, followed by Td boosters at 10-year intervals. For adolescents and adults over the age of 7 years who have completed the primary course of immunization with DTaP, an additional booster dose is recommended at 11 to 12 years of age if they are otherwise fully vaccinated, or 13 to 18 years of age if they have not been vaccinated previously with Tdap. The CDC recommends a Td vaccine with every 10-year booster, unless wound management warrants more frequent administration. A pertussis-containing vaccine (ie, Tdap) is available for adolescents and adults when pertussis vaccination is indicated. For adults who did not complete a childhood vaccination series, the CDC recommends 1 dose of Tdap, followed by 2 doses of Td.[4]

Contraindications

Although currently approved tetanus vaccines are safe,[4,21] the CDC advises providers to assess for contraindications (ie, conditions that increase the risk for serious adverse reactions), and withhold vaccine administration when a contraindication is present.[4] Contraindications include[4]:

- a history of severe allergic reaction to a previous dose or to any vaccine component; and
- encephalopathy (eg, coma, decreased level of consciousness, or prolonged seizures) within 7 days of a prior dose of DTaP and not attributable to another cause.

Precautions

The CDC recommends that vaccinations be deferred in the presence of certain conditions unless the perceived benefit of protection from the vaccine outweighs the risk for an adverse reaction.[4] Precautionary conditions include[4]:

- Arthus reaction after tetanus or diphtheria immunization (patients should not receive additional Td doses for at least 10 years);
- Guillain-Barré syndrome occurring within 6 weeks of a tetanus-containing vaccine;
- moderate or severe (vs minor) illness with or without fever; and
- uncontrolled seizures, progressive or unstable neurologic disorder, or progressive encephalopathy until the establishment of a treatment regimen and stabilization of the condition (for pertussis components).

Pertussis vaccination may be associated with a slightly increased risk for neurologic AEs.[22] Encephalopathy of unknown origin occurring within 7 days of a pertussis-containing vaccine is a contraindication to future immunization.[4] In addition, caution should be exercised for patients who have experienced adverse reactions to previous pertussis vaccination, including temperatures of 105°F or higher; a hypotonic–hyporesponsive episode; and persistent, or inconsolable, crying for 3 hours or longer.[4]

Pertussis-Containing Vaccines in Adults

The CDC recommends a routine Td booster every 10 years in adult patients who have completed a primary vaccination series and have a verifiable vaccine history; pertussis-containing vaccines should be limited to children, adults who have not previously been vaccinated, a one-time pertussis-containing Td booster, and pregnant women (Table 2).[4]

The CDC recommends that all pregnant women routinely receive a Tdap vaccination between 27 and 36 weeks of pregnancy, with each pregnancy, regardless of prior immunization history.[4] Although the risk for neonatal tetanus has decreased significantly over the past century, newborns are at a higher risk for death and complications from pertussis than the general population.[4] Because infants do not receive the initial round of DTaP vaccine until 2 to 6 months of age,[4] they are particularly vulnerable to pertussis infection during these early months when the immune system is underdeveloped and maternal antibodies are the only source of active immunity.[26,27] Immunization of women with Tdap during pregnancy significantly

increases levels of pertussis-neutralizing antibodies in newborns due to the transfer of maternal antibodies across the placenta.[28-30] Infants born to vaccinated mothers have reduced rates of pertussis infection, and experience less severe disease and fewer hospitalizations when infection occurs.[31,32] Anti–pertussis antibody levels decline rapidly within a year of immunization, so women should receive a dose of Tdap during each pregnancy.[33,34]

Although the CDC continues to recommend Tdap for all health care workers and adults who have not previously received Tdap, and who come into contact with infants,[4,35] "cocooning" (once thought to reduce the risk for pertussis in infants) has been called into question, and studies on its effectiveness have not definitively supported this approach.[4] Animal models indicate that pertussis vaccines protect against symptoms of disease, but do not prevent infection or transmission.[36,37] Therefore, both the CDC and the World Health Organization recommend maternal immunization as a more effective strategy for protecting infants from pertussis infection.[4,38]

Prevention and Treatment

Although prophylactic vaccination at guideline-recommended intervals is the most effective strategy for preventing tetanus infection, many patients remain at risk. Research shows that as many as 50% of adults in the United States lack protective immunity against tetanus by age 60, necessitating careful evaluation of patients with open wounds for risk for disease and vaccine history to inform treatment decisions.[24]

High-Risk Populations

Individuals who have not completed a primary immunization series with a tetanus toxoid–containing vaccine and who have not received a booster within 10 years are at risk for tetanus.[4] Specific populations, however, have an elevated risk and thus require more careful evaluation and, potentially, more aggressive treatment.

Poor compliance with tetanus booster vaccination protocols and declining immunity with age put older individuals at higher risk for tetanus.[4,24] Because universal tetanus vaccination was not implemented in the United States until the mid-1940s,[4] individuals born before this time may never have received a complete vaccination series.[4,39] Immigrants also represent another high-risk group. One study demonstrated that up to 86% of adult Korean American immigrants are not adequately protected against tetanus.[40]

Comorbidities can increase the risk for tetanus. Patients with compromised immune systems, for example, may be at risk regardless of vaccination history.[41,42] Due to the

Table 2. Recommended Pertussis, Diphtheria, and Tetanus Vaccination Schedule

Vaccine	Age Group/Indication	Recommended Schedule
DTaP	2 mo-6 y	Primary (3 doses) • 1 dose at ages 2, 4, and 6 mo First booster • 1 dose at age 15-18 mo Second booster • 1 dose at age 4-6 y
Tdap	7-10 y[a]	• Not routinely recommended[b]
	11-18 y	• 11-12 y, 1 dose • 13-18 y, 1 dose if not vaccinated previously with Tdap
	≥19 y	• 1 dose if not vaccinated previously with Tdap
	Pregnant women[c]	• 1 dose each pregnancy; preferred at 27-36 wk of gestation
Td	NA	Booster • 1 dose every 10 y

[a] Off-label use of Tdap in persons aged 7-9 years.

[b] Refer to "Persons With Incomplete or Unknown Vaccine History" in the updated CDC recommendations (reference 4).

[c] Off-label use of Tdap.

DTaP, diphtheria and tetanus toxoids, acellular pertussis; **Td,** diphtheria and tetanus toxoids; **Tdap,** tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; **NA,** not applicable

Adapted from reference 4.

increased occurrence of chronic wounds and ulcers, diabetes also increases the risk for tetanus,[43] with up to 15% of tetanus cases in the United States occurring in patients with diabetes.[1] Moreover, studies show an increased risk for tetanus exposure among IV and subcutaneous drug users.[1,44] On average, IV drug users account for 6% of cases of tetanus in the United States, although higher rates have been documented.[3,44] Frostbite wounds may be neglected and thus not treated for potential tetanus exposure.[45,46] Animal bites also should be evaluated for tetanus even when there is no risk for other infections.[3]

Natural disasters, such as hurricanes, floods, and tornadoes, raise the possibility of injury for survivors and cleanup crews, who should be evaluated for immunization history. For this reason, local health departments often explicitly recommend that recovery workers receive tetanus vaccination if due for a booster shot.[47,48] The CDC does not consider natural disasters a significantly higher risk factor for tetanus exposure, but recommends normal precautionary routine vaccination protocols and proper wound care.[3] People wounded during floods and flood cleanup may benefit from TIG administration as well, depending on their previous immunization history.[4]

Assessing Tetanus Risk in the Emergency Department

In the United States, at-risk individuals tend to present to the emergency department (ED) for care.[49] In 2011, the CDC reported that approximately one-third of individuals with acute wounds pursued medical care; however, less than 4% received appropriate tetanus toxoid vaccination or TIG prophylaxis.[50] Evaluation for tetanus risk is a critical component of ED wound treatment—even if the wound is secondary to the cause of ED presentation—and should include a thorough vaccine history to determine whether patients have completed an initial DTaP or Tdap series as a child or an adult, as well as the time elapsed since the last booster.[4] In the most recent reporting period, vaccination status was known for only 25% of the 197 cases of tetanus in the United States. Of those cases, receipt of 3 or more doses of tetanus toxoid vaccine as a primary series was reported in a mere 20%. Because the remaining patients either received fewer than

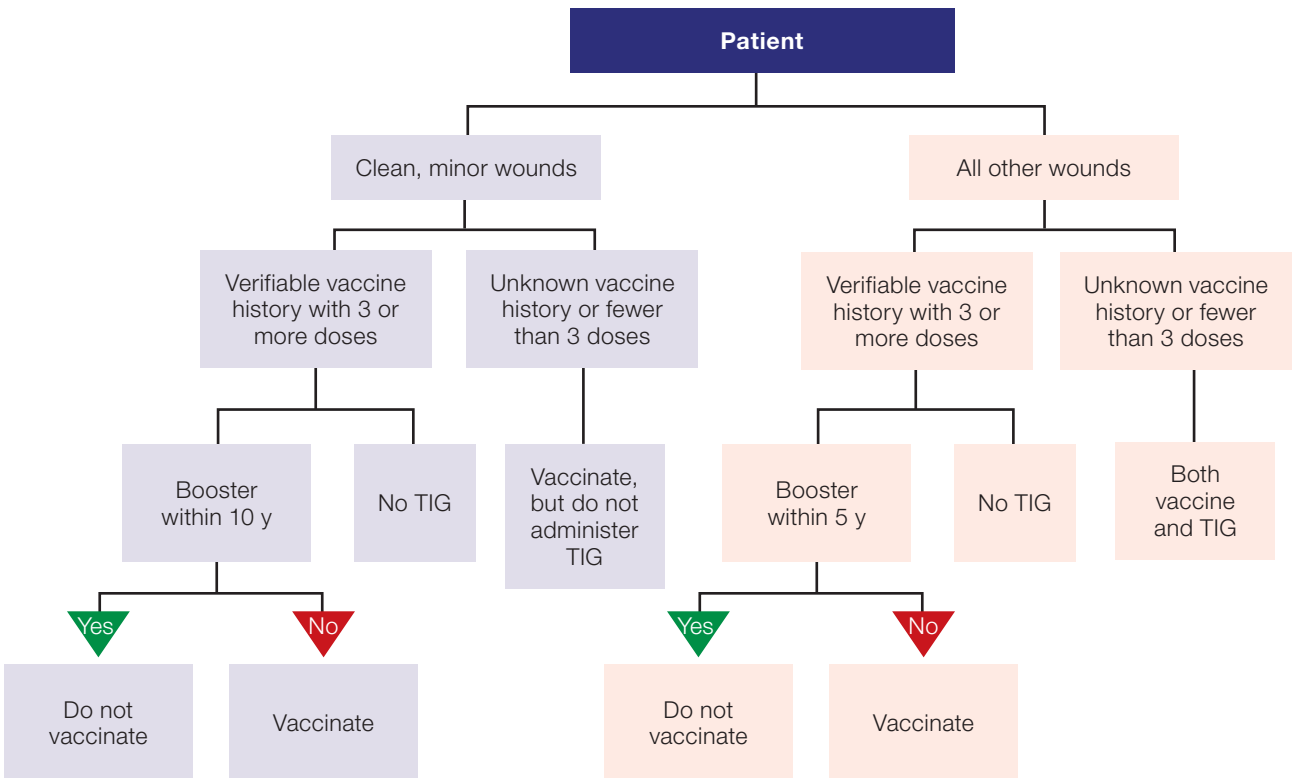

Figure 2. Tetanus treatment and prevention in wounded patients.

TIG, tetanus immune globulin

Based on reference 4.

3 doses of tetanus toxoid vaccine or were unvaccinated, they were not adequately immunized.[9] A vaccine history is also necessary to identify patients who should not receive immunization.[4] Repeat administration of tetanus toxoid–containing vaccines can lead to Arthus reactions, particularly when doses are given in close sequence.[1,51]

TIG, a specialized immune globulin product made from human plasma, is administered as a single intramuscular dose of 250 units,[52] and may mitigate many of the adverse effects associated with tetanus toxin exposure.[9] TIG is typically not required for patients with minor wounds, but vaccination is recommended if there is no prior tetanus immunization, unknown vaccine history, or a 10-year lapse since the last booster.[4] Conversely, unclean or serious wounds (eg, contaminated, punctures, avulsions, traumatic injuries) warrant the administration of TIG in patients with no prior tetanus immunization or unknown vaccine history, followed by a complete series of tetanus-containing vaccines to induce immunologic memory.[4] TIG is not required for individuals who have received a complete tetanus immunization series, but these patients are appropriate candidates for vaccination if 5 years have elapsed since the last booster (Figure 2).[4] TIG is used to treat active cases if the patient develops tetanus,[9] and regardless of immunization history, patients with contaminated wounds who have severe immunodeficiency or active HIV infection also should receive TIG.[4]

Conclusion

Tetanus is a serious illness that can result in significant morbidity, financial burden, and death, and prophylactic vaccination represents the most effective disease management strategy.[1,4,5] Underimmunization is a significant problem, and for this reason, older adults have a higher risk for acquiring tetanus.[9] Current CDC guidelines recommend tetanus-, diphtheria-, and pertussis-containing vaccines (DTaP or Tdap) for children 11 years of age and younger, pregnant women, and adults without a vaccination history.[4] Adults who have completed a vaccination series should receive regular boosters with a tetanus- and diphtheria-containing vaccine (Td) every 10 years.[4] Individuals who present with a tetanus-prone wound and who have not received a primary tetanus-diphtheria vaccine series should receive both tetanus vaccine and TIG. Careful risk evaluation, including a thorough vaccine history, is critical for assessing tetanus risk in the ED.[4]

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Disclosures: Dr Alagappan is a consultant to and serves on the speakers bureau for Grifols SA. Dr Poland chairs a Merck Research Laboratories safety evaluation committee for novel investigational vaccine trials, and is a consultant to Adjuvance, Alopexx, Avianax LLC, Emergent BioSolutions Inc, GlaxoSmithKline plc, Merck, and Sanofi Pasteur. Dr Poland holds 2 patents related to vaccinia and measles peptide research.

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