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Tetanus Tetanus is a preventable disease manifested by skeletal muscle spasms and autonomic nervous system disturbance. It is caused by a powerful neurotoxin produced by the bacterium Clostridium tetani, which is found globally. Tetanus commonly occurs in areas with low vaccination coverage. In developed countries, the disease is seen occasionally in individuals who are incompletely vaccinated. Even though the mortal ity rate has decreased significantly over the past two decades, the dis ease causes around 50,000 deaths annually worldwide. The mortality rate of tetanus varies depending on staff skills, clinical practices, and equipment capacity. PART 5 Infectious Diseases ■ ■DEFINITION Tetanus diagnosis is based on clinical manifestations with limited sup portive laboratory confirmation. Case definitions are often used to facilitate clinical and epidemiologic assessments. The Centers for Dis ease Control and Prevention (CDC) defines probable tetanus as “in the absence of a more likely diagnosis, an acute illness with muscle spasms or hypertonia, and diagnosis of tetanus by a health care provider.” Neonatal tetanus is defined by the World Health Organization (WHO) as “an illness occurring in a child who has the normal ability to suck and cry in the first 2 days of life but who loses this ability between days 3 and 28 of life and becomes rigid and has spasms.” Given the unique presentation of neonatal tetanus, the history generally permits accurate classification of the illness with a high degree of probability. Maternal tetanus is defined by the WHO as “tetanus during pregnancy or within 6 weeks after the end of pregnancy (whether with birth, miscarriage, or abortion).” ■ ■ETIOLOGY C. tetani is an anaerobic, gram-positive, spore-forming rod whose spores are highly resilient and can survive readily in the environment throughout the world. The spores resist boiling and many disinfectants. C. tetani spores and bacilli survive in the intestinal systems of many animals, and fecal carriage is common. The spores or bacteria enter the body through abrasions, wounds, or the umbilical stump (in the case of neonates). Once in a suitable anaerobic environment, the organisms grow, multiply, and release tetanus toxin that enters the nervous system and causes disease. Approximately 20–30% tetanus cases have unclear entry wounds. Superficial abrasions to the limbs are the most common entry sites in adults. Deeper injuries or infections (e.g., open fractures, drug injec tion) are associated with more severe clinical presentations. Home delivery with unhygienic umbilical cutting and inadequate umbilicalcord care are the main causes of

neonatal tetanus. Circumcision or ear-piercing also can result in neonatal tetanus. Tetanus occurs when immunity is lacking. Unvaccinated individuals or those with incomplete vaccination history are at increased risk of developing tetanus.

■ ■EPIDEMIOLOGY The incidence of tetanus has decreased gradually over the past few decades as vaccine coverage has increased. This disease is rare in devel oped countries. In 2022, 28 tetanus cases were reported in the United States. Most tetanus cases occur in individuals who have not received recommended tetanus vaccinations and booster shots every 10 years. In the United States between 2009 and 2017, tetanus cases occurred primarily in those between the ages of 20 and 64 (64%), with only 13% of cases occurring in those younger than 20. Three cases of neonatal tetanus were reported in this period. Diabetes and intravenous drug use were associated with increased tetanus risk. The global incidence of neonatal tetanus has reduced significantly following a concerted elimination program by WHO partnering with the United Nations Children's Fund (UNICEF) and the United Nations Population Fund (UNFPA); however, approximately 25,000 neonates with tetanus died in 2018. The incidence of tetanus among older children and adults (who have a high risk of tetanus due to the deterioration of immunity and lack of booster shots) is unknown. As few countries have good surveillance systems, in 2015, there were esti mated to be between 30,000 and 62,000 deaths from tetanus in older children and adults. ■ ■PATHOGENESIS Genome sequencing of C. tetani has allowed identification of several exotoxins and virulence factors. Only those bacteria producing tetanus toxin can cause tetanus. Tetanus toxin undergoes retrograde transport into the central nervous system (CNS) and thus produces clinical effects. Tetanus toxin is intra-axonally transported to motor nuclei of the cranial nerves or ventral horns of the spinal cord. This toxin is pro duced as a single 150-kDa protein that is cleaved to produce heavy (100-kDa) and light (50-kDa) chains linked by a disulfide bond and noncovalent forces. The carboxy terminal of the heavy chain binds to specific membrane components in presynaptic α-motor nerve ter minals; evidence suggests binding to both polysialogangliosides and membrane proteins. This binding results in toxin internalization and uptake into the nerves. Once inside the neuron, the toxin enters a retrograde transport pathway, whereby it is carried proximally to the motor neuron body. It is known that tetanus toxin exhibits several dif ferent pH-dependent conformations and therefore can interact with a variety of different receptors. During its passage from the periphery to the central nervous system, tetanus toxin can access neuronal traffick ing systems and evade degradation. Following retrograde transport in the motor neuron, the tetanus toxin undergoes translocation across the synapse to the GABA-ergic presynaptic inhibitory interneuron terminals. Here the light chain, which is a zinc-dependent endopeptidase, cleaves vesicle-associated membrane protein 2 (VAMP2, also known as synaptobrevin). This mol ecule is necessary for presynaptic binding and release of neurotrans mitter; thus, tetanus toxin prevents transmitter release and effectively blocks inhibitory interneuron discharge. The result is unregulated activity in the motor nervous system. Similar activity in the autonomic system accounts for the characteristic features of skeletal muscle spasm and autonomic system disturbance. The increased circulating cat echolamine levels in severe tetanus are associated with cardiovascular complications. Relatively little is known about the processes of recovery from tetanus. Recovery can take several weeks. Peripheral nerve sprouting is involved in recovery from botulism, and similar CNS sprouting may occur in tetanus. Other evidence suggests toxin degradation as a mechanism of recovery. APPROACH TO THE PATIENT Tetanus The clinical manifestations of tetanus occur only after tetanus toxin has reached presynaptic inhibitory nerves. Treatment should not be delayed once the diagnosis of tetanus is confirmed. Management

strategies aim to neutralize remaining unbound toxin, support vital functions, treat symptoms, and control complications until the effects of the toxin have worn off. Patients usually recover after 4–6 weeks (see “Treatment,” below). ■ ■CLINICAL MANIFESTATIONS Clinical presentations of tetanus are diverse and are divided into the following categories: generalized, localized, cephalic, and neonatal teta nus. In the mild form of local tetanus, only isolated areas of the body are affected and only small areas of local muscle spasm may be appar ent. Localized tetanus can progress to generalized tetanus. If the cranial nerves are involved in localized cephalic tetanus, the pharyngeal or laryngeal muscles may spasm, with consequent aspiration, respiratory failure, or airway obstruction. Generalized tetanus is the most com mon form of clinical presentation, characterized by muscle rigidity and generalized spasms. Neonates with tetanus typically present with an inability to suck, poor feeding, and generalized spasms. The most common initial symptoms are trismus (lockjaw), which progresses to neck and body muscle rigidity, difficulty swallowing, and pharyngeal and laryngeal spasms. As the disease progresses, generalized muscle spasms develop and cause pain. Laryngeal spasm can cause respi ratory failure or apnea and is a life-threatening event; without immediate respiratory support, this is the most common cause of death in tetanus. Autonomic nervous system disturbance (ANSD) occurs during the second week of severe tetanus, and death due to cardiovascular events becomes the major risk. Clinical symptoms of ANSD include fluctuated heart rate (tachycardia or bradycardia) accompanied by a fluctuation in blood pressure (hypertension or hypotension) resulting from alteration in the activities of the sympathetic or parasympathetic nervous systems. Autonomic involvement is evidenced by gastrointes tinal stasis, sweating, and increased tracheal secretions. The Ablett score classifications of the clinical presentation of tetanus are outlined in Table 157-1. ■ ■DIAGNOSIS The diagnosis of tetanus is based on clinical findings. Confirma tory laboratory tests are limited. Positive culture of C. tetani from wounds cannot confirm a diagnosis of tetanus. Serum antitetanus immunoglobulin G may also be measured in a sample taken before the administration of antitoxin or immunoglobulin; levels >0.1 IU/mL

(measured by standard enzyme-linked immunosorbent assay) are deemed protective and do not support the diagnosis of tetanus. If levels are below this threshold, a bioassay for serum tetanus toxin may be helpful, but a negative result does not exclude the diagnosis, and these levels are not generally performed. Polymerase chain reaction and recombinase polymerase amplification have been developed to detect the tetanus neurotoxin gene; these techniques have proven promising in recent years. A diagnosis of tetanus requires differentiation from other diseases. The few conditions that mimic generalized tetanus include strychnine poisoning, dystonic reactions to antidopaminergic drugs, somatic symptom disorder, stiff person syndrome, and neuroleptic malignant syndrome. Abdominal muscle rigidity is characteristically continu ous in tetanus and should be differentiated from peritonitis or acute abdominal emergency. Cephalic tetanus can be confused with trismus TABLE 157-1 Ablett Classification of Severity of Tetanus GRADE SEVERITY SYMPTOMS I Mild Mild trismus, general spasticity, no respiratory compromise, no spasms, no dysphagia II Moderate Moderate trismus, rigidity, short spasms, mild dysphagia, moderate respiratory involvement, respiratory rate >30 breaths/min III Severe Severe trismus, generalized rigidity, prolonged spasms, severe dysphagia, apneic spells, pulse >120 beats/min, respiratory rate >40 breaths/min IV Very severe Grade 3 with autonomic dysfunction

of other etiologies, such as oropharyngeal infection, cranial nerve diseases, intracranial hemorrhage, submaxillary lymphadenitis, or peritonsillar infections. Hypocalcemia and

meningoencephalitis are included in the differential diagnosis of neonatal tetanus.

TREATMENT Tetanus If possible, the entry wound should be identified, cleaned, and debrided of necrotic material in order to remove anaerobic foci of infection and prevent further toxin production. Wound care should be performed several hours after anti-toxin administration. Fail ure to remove devitalized tissue and treat infection may result in recurrent or prolonged tetanus. Metronidazole (400 mg rectally or 500 mg IV every 6 h for 7 days) is preferred for antibiotic therapy. Although not a first choice for therapy, an alternative is penicillin (100,000–200,000 IU/kg per day); this drug theoretically may exac erbate spasms due to its ability to bind to the GABA receptor and, in one study, was associated with increased mortality. Antitoxin should be given early in an attempt to deactivate any circulating tetanus toxin and prevent its uptake into the nervous system. Two preparations are available: human tetanus immuno globulin (HTIG) and equine antitoxin. HTIG is the preparation of choice, as it is less likely to be associated with anaphylactoid reac tions. A single IM dose (500–5000 IU) is given. Equine-derived antitoxin is available widely and is used in low- and middle-income countries; after hypersensitivity testing, 10,000–20,000 U is admin istered IM. According to a recent randomized controlled trial in Vietnam, there were no significant differences in the outcome and complications between groups using either intramuscular equine antitoxin or HTIG. Additional intrathecal antitoxin (HTIG) showed no benefit. CHAPTER 157 Benzodiazepines are commonly used to control spasms, and patients can tolerate them in high doses. The use of intermittent or continuous sedation depends on the severity of spasms and the availability of appropriate resources, e.g., mechanical ventilators. High-dose diazepam may cause hyperosmolarity and lactic acido sis. Midazolam is another option for controlling spasms in tetanus; it has fewer side effects and can be used continuously. Infusions of propofol can be used to control spasms and provide sedation; how ever, consideration should be given to the likely long duration of therapy. Sedatives should be reduced in the elderly and patients who have liver diseases due to drug accumulation and slow excretion. Tetanus When sedatives alone cannot control spasms, a combination of neuromuscular blocking agents is recommended. Nondepolarizing neuromuscular blockers are used in clinical practice, depending upon availability. IV magnesium sulfate has been used as a muscle relaxant. Patients who are using these agents require mechani cal ventilation support. In those settings with limited availability of mechanical ventilators, controlling spasms while maintaining adequate ventilation is problematic. Patients may require ventilator support for several weeks. It is important to establish a secure airway early in severe teta nus. Ideally, patients should be nursed in calm, quiet environments because light and noise can trigger spasms. Dysphagia due to pharyngeal involvement combined with hyperactivity of laryngeal muscles makes endotracheal intubation difficult. Tracheostomy is the better option for securing the airway in severe tetanus. Magnesium sulfate has been used in autonomic nervous system dysfunction to control high blood pressure and tachycardia; main taining a plasma concentration of 2–4 mmol/L is recommended. If magnesium alone cannot control tachycardia, short-acting betablockers (labetalol, propranolol, esmolol) or calcium antagonists can be used with strict monitoring. When the parasympathetic nervous system predominates—resulting in prolonged low blood pressure and bradycardia—vasopressors are required. A complication arising from treatment with diazepam injection is thrombophlebitis. Long-term hospitalization with high-dose sedation

creates a high risk of hospital-acquired infections (ventilator-associated pneumonia, bloodstream infection, urinary tract infection, sepsis), deep vein thrombosis, pneumonia emboli,

myocardiopathy, myo cardial infarction, stress ulcers, muscle weakness, and pressure sores. Many of these patients require long-term rehabilitation.

Patients must be given a full primary course of immunization as tetanus toxin is poorly immunogenic and the immune response following natural infection is inadequate. ■ ■PROGNOSIS Rapid development of tetanus is associated with more severe disease; it is important to note time of onset and length of incubation period. More sophisticated modeling has revealed other important predic tors of prognosis. In many adults, particularly in the elderly, surviv ing tetanus is associated with reduced long-term functional outcome measures. Studies of children and neonates have suggested a higher incidence of neurologic sequelae. Neonates may be at increased risk of learning disabilities, behavioral problems, cerebral palsy, and deafness. Tetanus has a high survival rate if complications can be controlled and interventions conducted promptly. In assessing prognosis, the incubation period (time from wound to first symptom) and the period of onset (time from first symptom to first generalized spasm or pharyngeal or laryngeal spasm) are of par ticular significance. The shorter these periods, the worse is the prog nosis. Among the three main scales available to predict the severity and outcome of tetanus, the Tetanus Severity Score (TSS) (Table 157-2) is superior to the Dakar and Philips scores, with a sensitivity of 66% and a specificity of 91%. PART 5 Infectious Diseases ■ ■PREVENTION Tetanus is prevented by good wound management and vaccination (Chap. 129). Safe delivery, hygienic umbilical-cord care, and maternal vaccination are recommended to prevent neonatal tetanus. Individuals sustaining wounds should undergo passive immunization (see “Treat ment of Tetanus,” above) if their vaccination status is incomplete or unknown or if their last booster was given >10 years earlier. Vaccina tion programs and recommended prevention measures vary somewhat according to individual countries. The rate of primary vaccination coverage in infancy (three doses of DTP [diphtheria, pertussis, and tetanus]) is 86%, but rates for the subsequent boosters necessary for long-term protection are unknown. WHO guidelines for tetanus vaccination consist of a primary course of three doses and should start at 6 weeks of age; the interval between doses is 4 weeks. The first booster is given from 12–23 months of age. The second and third boosters are at 4–7 and 9–15 years of age, respec tively. There should be at least 4 years between booster doses. In 2022, the CDC reported the rate of infants who had received a full primary vaccination course of three doses of the diphtheria, tetanus toxoid (DTP3), and pertussis vaccine was 94%. There is a lack of data about boosters in older children, adolescents, and adults in many coun tries. The CDC recommends five doses of tetanus vaccine for infants and children at 2 months, 4 months, 6 months, 15 through 18 months, and 4 through 6 years of age, an additional booster dose at 11–12 years of age, and every 10 years thereafter. For those with delayed primary vaccination, catch-up immunization schedules are recommended. There are separate schedules for children ages 4 months through 6 years of age and from ages 7 through 18 years of age. Complete maternal vaccination reduces the incidence of neona tal tetanus by an estimated 94%. WHO recommends that pregnant women who have not been vaccinated with the tetanus vaccine should receive at least two doses, with an interval of 4 weeks between doses. The second dose should be given at least 2 weeks before delivery. The third dose should be received at least 6 months later, with the fourth and fifth doses following an interval of 1 year or during subsequent pregnancies. A total of five doses can provide long-term immunity. The CDC provides a special schedule for those with partial vaccination. In high-risk areas, women of childbearing age should receive a primary course of vaccination and education on safe delivery and postnatal practices.

TABLE 157-2 Tetanus Severity Score (TSS) (Sensitivity 66%, Specificity 91%), Cutoff Point to Predict Death ≥8 VARIABLES SCORE Age (year) ≤70 71–80 >80

Time from first symptom to admission (days) ≤2 3–5 >5

–5 –6 Difficulty breathing on admission No Yes

Coexisting medical condition Fit and well Minor illness or injury Moderately severe illness Severe illness not immediately life threatening Immediately life-threatening illness

Entry sites Internal or injection Other (including unknown)

Highest systolic blood pressure recorded during first day in

hospital (mmHg) ≤130 131–140 >140

Highest heart rate recorded during first day in hospital (beats/min) ≤100 101–110 111–120 >120

Lowest heart rate recorded during first day in hospital (beats/min) ≤110 >110

–2 Highest temperature recorded during first day in hospital (oC) ≤38.5 38.6–39 39.1–40 >40

Since March 2022, 47 countries have achieved maternal and neo natal tetanus elimination. Despite this relative success, immunization programs need to be continued and promoted to maintain individual long-term protective immunity and to eliminate the incidence of tetanus gradually. Dedicated public health initiatives still need to be improved, and the continuing reports of sizable case series in the medi cal literature suggest that tetanus continues to pose a significant global health burden. Acknowledgment The authors wish to thank Dr. Lam Minh Yen for her contributions to this chapter in previous editions. ■ ■FURTHER READING Borrow R et al: The immunological basis for immunization series. Module 3: Tetanus update 2018. Edited by Vaccines and Biologicals Immunization. World Health Organization, 2018. Kyu HH et al: Mortality from tetanus between 1990 and 2015: Findings from the global burden of disease study 2015. BMC Public Health 17:179, 2017. Rodrigo C et al: Pharmacological management of tetanus: An evidencebased review. Crit Care 18:217, 2014.

Revision #1
Created 2026-01-06 16:33:05 UTC by Omar Ayman
Updated 2026-01-06 16:33:05 UTC by Omar Ayman