INVITED ARTICLE

Intensive Care Management of Severe Tetanus

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Abstract

- Tetanus is caused by an exotoxin, tetanospasmin, produced by *Clostridium tetani*, an anaerobic gram-positive bacillus.
- Tetanospasmin prevents the release of inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the spinal cord, brainstem motor nuclei, and the brain, producing muscle rigidity and tonic spasms.
- Trismus (lockjaw), dysphagia, laryngeal spasms, rigidity of limbs and paraspinal muscles, and opisthotonic posture are common.
- Frequent severe spasms triggered by touch, pain, bright light, or sounds may produce apnea and rhabdomyolysis.
- Autonomic overactivity occurs in severe tetanus causing labile hypertension, tachycardia, increased secretions, sweating, and urinary retention. Dysautonomia is difficult to manage and is a common cause of mortality; magnesium sulfate infusion is often used.
- Antibiotics (penicillin or metronidazole) and wound care reduce toxin production and human tetanus immune globulin neutralizes the circulating toxin.
- Nasogastric tube placement for feeding and medications is needed.
- Early elective tracheostomy is performed in moderate or severe tetanus to prevent aspiration and laryngeal stridor.
- Benzodiazepines help reduce rigidity, spasms, and autonomic dysfunction. Large doses of diazepam (0.2–1 mg/kg/h) are administered via nasogastric tube.
- Neuromuscular blocking agents and mechanical ventilation are used for refractory spasms.
- Mortality ranges from 5% to 50%.

Keywords: Autonomic dysfunction, Benzodiazepine, Immunization, Intensive care unit, Laryngospasm, Muscle spasm, Rhabdomyolysis, Severe tetanus,Tracheostomy, Tropical infections.

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Introduction

Tetanus is caused by a neurotoxin produced by the spore-forming bacterium *Clostridium tetani*.[1–3] Though a vaccine-preventable disease, 14,751 cases of tetanus were reported to the World Health Organization (WHO) in 2019 of which 7071 were from India;[4,5] it is still frequently seen in developing countries and carries a high mortality.

Tetanus is characterized by muscle rigidity, paroxysmal muscle spasms, respiratory distress, and autonomic dysfunction which may last for 4–6 weeks and requires prolonged intensive care.[1–3] Tetanus is often seen in children and adults in developing countries, but mortality in these age groups is generally less than in neonates.[5–7] Neonatal tetanus occurs as a result of *C. tetani* infection of the umbilicus in newborn children born to non-immunized womenand is a public health problem in many countries. Neonatal tetanus can be prevented by administration of tetanus toxoid to pregnant mothers in mid-pregnancy. WHO launched the global maternal–neonatal tetanus elimination program in 1989 to reduce neonatal tetanus <1 case per 1000 live births in all countries. In April 2018, there were still 14 countries that had not achieved this goal and despite an estimated 85% decline in deaths due to neonatal tetanus, it is estimated that 25,000 neonatal deaths occurred due to tetanus worldwide.[7] This review mainly focuses on intensive care management of non-neonatal tetanus.

Etiology

C. tetani, the organism that causes tetanus, is an anaerobic spore-forming gram-positive bacillus. Its spores are found in soil and surfaces worldwide, and also in the feces of some mammals.[1–3] The spores remain viable for several months and are destroyed by autoclaving at 120°C for 15 min.[2] Although *C. tetani* spores frequently enter the body through wounds, minor abrasions, animal bites, and infected injection needles in drug abusers, they may remain dormant in the wound for weeks, and germinate to form vegetative bacteria only when suitable local anaerobic conditions are present.[1–3] The bacteria produce a potent metalloprotease toxin called tetanospasmin, which is responsible for the disease. The gene for tetanospasmin production is located on a plasmid and not all *C. tetani* produce toxin.[1] Presence of protective neutralizing antibodies as a result of prior immunization can prevent the toxin from causing tetanus.[1–3] As a result, tetanus is extremely rare in developed countries, while it is still seen in many developing

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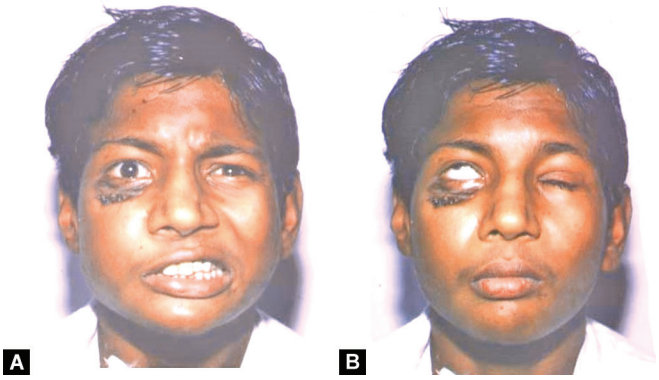


Figs. 1 A and B: A case of cephalic tetanus. Note the injury below the right eyelid that was the source of tetanus. A high dose of toxin reaching the facial nerve nucleus from the site of injury has resulted in a lower motor neuron pattern of the weakness of the facial muscles with a decreased furrowing of the forehead and nasolabial fold (panel A) and eye closure weakness with Bell's phenomenon (panel B) on the side of the injury. Overactivity of facial muscles on the opposite side is also seen

countries where universal immunization coverage is poor.[7] Tetanus-prone wounds include wounds with deep penetrating injury, abscesses, presence of foreign bodies in wounds, ulcerating malignant tumors, intravenous drug abuse, and middle ear infection in children (otogenic tetanus).[2,8,9]

Pathogenesis

Tetanospasmin is transported from the site of production to the central nervous system along motor nerves and also via circulation.[1–3] Circulating toxin attaches to motor nerve endings of alpha motor neurons and gains access to the central nervous system by retrograde axonal transport.[1–3] It finally reaches inhibitory interneurons in the spinal cord and brainstem where it binds to synaptobrevin, a protein that is required for neuroexocytosis, a process that results in the release of neurotransmitters at nerve endings.[1–3] Its selectivity for inhibitory interneurons that produce gamma-aminobutyric acid (GABA) and glycine results in loss of inhibition and spontaneous excessive discharge of motor and autonomic nerve impulses as well as exaggerated responses to stimuli manifesting as tonic muscle contraction, intermittent muscle spasms, and autonomic overactivity.[1,3] Since tetanospasmin reaches the motor nuclei of the shortest motor axons first by retrograde axonal transport, muscles innervated by motor cranial nerves are affected first,followed by trunk muscles, and finally limb muscles.[2]

Clinical Features

The incubation period (interval between injury and onset of symptoms) ranges from 3 to 21 days but may sometimes be as long as a few weeks. A short incubation period suggests a greater likelihood of developing severe tetanus but a long incubation period does not necessarily indicatea milder disease.[1–3] A short "period of onset", defined as the interval between the first symptom and first paroxysmal muscle spasm, is a better predictor of disease severity.[1–3] In some cases there is no obvious history of injury or the injury may be so trivial as to be forgotten.[2,3]

Tetanus can be present in the following forms:[1–3]

Localized tetanus, where muscle rigidity is restricted to the limb with the wound that is infected with *C. tetani*; this is extremely rare.[2]

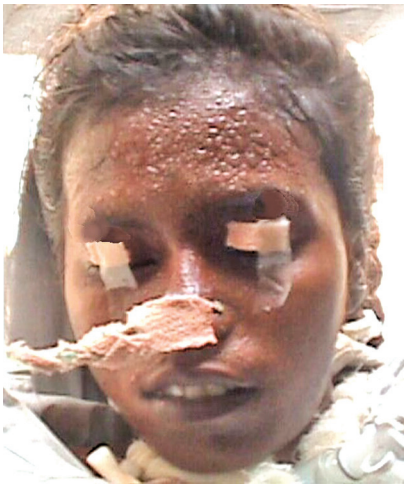


Fig. 2: Profuse sweating on the forehead in a patient with severe tetanus with autonomic dysfunction. This patient also had episodes of hypertension and tachycardia along with sweating

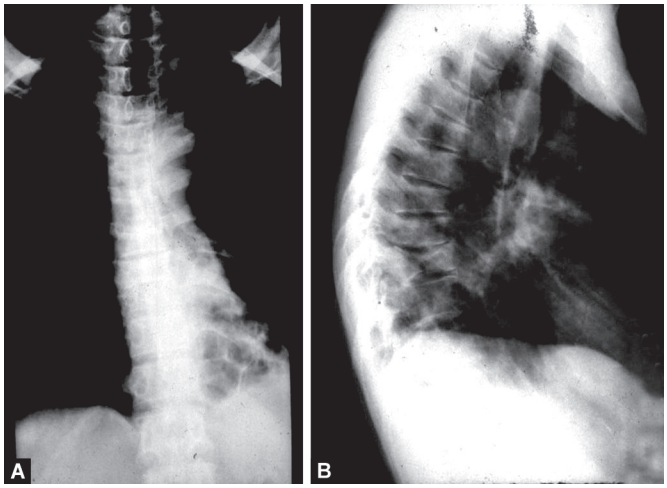
Cephalic tetanus is seen when the infected wound is on the face. The facial muscles on the affected side are paralyzed while the facial muscles of the opposite side and other muscles of the body are overactive (Fig. 1).[1–3]

Generalized tetanus is the commonest presentation accounting for nearly 95% of all the cases. Sometimes the disease may start as localized or cephalic tetanus but become generalized in 2 or 3 days. Lockjaw or trismus, characterized bytonic contractions of masseter muscles, is usually the first and commonest clinical feature.Spasm of the facial muscles produces a characteristic facial expression—risus sardonicus (snarling smile) consisting of raised eyebrows, tight closure of the eyelids, wrinkling of the forehead, and extension of the corners of the mouth laterally.[1–3] The rigidity then progresses to all muscle groups. Intermittent painful muscle spasms are seen in moderately severe cases, affecting the trunk, limbs, respiratory and bulbar muscles. Spasms are usually precipitated by physical stimuli like noise, bright light, touch, suction, and injections.[1–3] Hence it is important to keep the patient in a calm and quiet environment. Laryngeal spasms can cause complete airway obstruction and can be precipitated by attempts to swallow food or saliva or during nasogastric tube insertion or oral suction.[2,3] Untreated patients may develop characteristic opisthotonus or bow-like posture as a result of sustained powerful spasms of extensor muscle of the spine. The body remains rigid between spasms too and board-like rigidity of the abdomen.[1,2]

Autonomic dysfunction is commonly seen in severe tetanus.[1–3,8–10] Most patients have persistent tachycardia and hypertension.[1–3] Fluctuations in blood pressure and heart rates are also encountered, especially during spasms.[2] Profuse sweating (Fig. 2), increased respiratory secretions and altered bowel function and urinary retention are also common.[1–3,8,10] Sometimes excessive vagal overactivity can cause episodes of sudden bradycardia and hypotension.[2,8]

Complications

Severe muscle spasms may cause fractures (Fig. 3), tendon avulsions, hyperpyrexia, rhabdomyolysis, and acute kidney injury.[1–3,9] Hemodynamic disturbances and cardiac arrhythmias may occur due to autonomic overactivity.[1–3,8,10] Patients require long-term treatment in an intensive care unit (ICU), as recovery



Figs. 3 A and B: X-ray of the thoracic spine, anteroposterior (panel A), and lateral (panel B) views done after recovery showing compression fractures of vertebrae due to rigidity and spasms of the paraspinal muscles in an elderly patient with severe tetanus

requires degradation of the toxin and also the growth of new axonal terminals.[1] Ventilator-associated pneumonia and other complications of prolonged ventilation, catheter-associated urinary tract infection, pulmonary thromboembolism, critical illness neuropathy,and pressure ulcers can complicate long-term ICU stay.

Diagnosis

The diagnosis of tetanus is mainly clinical and is obvious in most cases based on typical clinical signs.The spatula test is a useful test that can help confirm the diagnosis.[2,11] Touching the posterior pharyngeal wall with a spatula normally leads to a gag reflex and expulsion of the spatula. In tetanus, it evokes spasms of the masseter muscles and the patient bites the spatula making it difficult to remove it.[11] Laboratory diagnosis has a limited role. *C. tetani* can be cultured from the wound in less than 30% of cases.[2,3] Concentrations of protective antibody in serum (antibody titer ≥0.1 IU/mL by ELISA test) indicate protective levels and make a diagnosis of tetanus unlikely.[1]

Differential diagnosis of tetanus includes muscle rigidity and spasms due to strychnine poisoning and dystonia secondary to antidopaminergic drugs.[1–3,11] The rare stiff-person syndrome too may mimic generalized tetanus and prompt response to diazepam injection in both conditions can further confound the diagnosis.[1–3] Abdominal rigidity may mimic acute abdominal conditions. Trismus can also be seen in oropharyngeal and mandibular pathologies.[2,11] Neck rigidity may mimic meningitis or encephalitis with seizures. However, headache is absent in tetanus, and patients with tetanus are never unconscious on presentation.[2]

Management of Tetanus

The first step is to assess the severity of the disease and risk of progression to severe tetanus over the next few days. An incubation period of fewer than 7 days and a period of onset less than 48 h predict rapid progression to severe disease. These patients should be managed in a hospital with good intensive care facilities including invasive hemodynamic monitoring, mechanical ventilation, and good infection control practices. The severity of the disease can be assessed by using Ablett classification (Table 1).[1,2]

Table 1: Ablett classification of tetanus based on the severity of illness

Grade of tetanus	*Defining features*
Grade 1: mild	Mild to moderate trismus Generalized spasticity No respiratory compromise No spasms Little or no dysphagia
Grade 2: moderate	Moderate trismus Marked rigidity Mild to moderate but short spasms Moderate respiratory compromise (>30 breaths/min) Mild dysphagia
Grade 3: severe	Severe trismus Generalized spasticity Reflex prolonged spasms Increased respiratory rate (>40 breaths/min) Apneic spells Severe dysphagia Tachycardia (>120 beats/min)
Grade 4: very severe	Clinical features of grade 3 tetanus plus violent autonomic disturbances involving the cardiovascular system—severe hypertension and tachycardia alternating with relative hypotension and bradycardia

Patients with tetanus should be treated in the ICU in consultation with a critical care specialist.[1–3,12] The key principles in the management of patients are shown in Table 2. Patients should receive immediate sedation with intravenous diazepam to prevent life-threatening muscle spasms, before antibiotics or other treatment measures are started.[2,12,13]

Antibiotics

Intravenous metronidazole 500 mg every 6 h or benzyl penicillin G 100,000–200,000 units/kg body weight in 4 divided doses intravenously for 7 days are the anti-clostridial antimicrobial agents of choice. Some authors favor metronidazole because of possible inhibition of the GABA receptor by penicillin. Ganesh Kumar et al. randomized 161 patients with tetanus to receive benzathine penicillin (1.2 million units as a single dose intramuscularly; $n = 56$), intravenous benzyl penicillin (2 million units every 4 h for 10 days; $n = 50$), and oral metronidazole (600 mg every 6 h for 10 days; $n = 55$).[14] Although the three antibiotic regimens investigated appear equally effective, benzathine penicillin offers the convenience of a single intramuscular injection.[14]

Early debridement of infected wounds, including removal of dirt, foreign bodies, and devitalized tissues, and drainage of abscesses is probably more effective in halting toxin production than antibiotics alone.[1–3]

Neutralizing Circulating Toxin

Equine anti-tetanus serum 10,000–20,000 units given intravenously after skin sensitivity testing or human tetanus hyperimmune globulin (TIG) 3000–6000 units by intramuscular injection should be given as soon as possible to neutralize the circulating toxin.[1–3,13] These drugs do not neutralize intracellular toxin that has already entered

Table 2: Principles of treatment of severe tetanus

1) Stopping production of tetanus toxin
a) Antibiotics—benzyl penicillin G, metronidazole
b) Wound debridement—removal of foreign bodies, dirt, devitalized tissue
2) Neutralizing circulation toxin
a) Equine anti-tetanus serum—10,000 units IV after hypersensitivity skin testing
b) Human tetanus immune globulin—3000–6000 units by intramuscular injection
c) Intrathecal human tetanus immune globulin is of debatable value
3) Treatment of muscle rigidity and spasms
a) Keep in a quiet dark room
b) Avoid oral suction (can induce severe laryngeal spasm)
c) Benzodiazepines—diazepam, lorazepam, midazolam
d) Phenobarbital with chlorpromazine in some patients
e) Dexmedetomidine infusion
f) Neuromuscular blocking drugs + mechanical ventilation
4) Supportive treatment
a) Nasogastric tube insertion after adequate sedation
b) Enteral nutrition—high caloric needs due to muscle rigidity, spasms
c) Tracheostomy—for laryngeal spasms, clearing respiratory secretions
d) Management of fever
e) Mechanical ventilation—after neuromuscular blockade for refractory spasms
5) Management of autonomic dysfunction
a) Benzodiazepines
b) Magnesium sulfate
c) Clonidine, labetalol
6) General critical care—thromboprophylaxis, stress ulcer prophylaxis, nosocomial infection prevention bundles
7) Tetanus immunization—3 doses of tetanus toxoid as the disease itself does not result in a protective immune response

motor neurons and the disease may progress despite antibiotics and immune globulin administration as the intracytoplasmic toxin reaches the central nervous system.[2] Intrathecal injection of TIG is not recommended in many guidelines.[1,12]

Control of Muscle Rigidity and Spasms

Treatment of the muscular rigidity and spasms in tetanus is of vital importance as they can cause respiratory failure, stridor, dysphagia, aspiration pneumonia, and generalized exhaustion.[1–3] Various agents are used for control of the spasms. Despite antibiotics and tetanus immune globulin, the spasms usually continue to worsen over the first 7–10 days as a toxin that has already entered the motor neurons, continues to reach the central nervous system. The severity of illness then plateaus for 7–14 days and recovery usually begins after 2–4 weeks.[1–3]

Benzodiazepines

Benzodiazepines are the mainstay of drug treatment of tetanus and act by enhancing the effect of GABA on the postsynaptic membrane.[1–3,13] However, since very little GABA is released from the inhibitory interneurons due to the effect of tetanospasmin, large doses of benzodiazepines are required to achieve adequate muscle relaxation and prevent spasms.[2] Diazepam may be administered intravenously (10–30 mg in 5 mg boluses every 5 min) or through a nasogastric tube (10–40 mg every 1–2 h).[1,2,13] Most patients with tetanus can tolerate large doses (sometimes up to 1000 mg/day) of diazepam without getting sedated.[2] Large dosesof intravenous diazepam as infusion or boluses should be avoided because propylene glycol that is used as a solvent may produce hyperosmolarity and lacticacidosis.[1] Hence the authors prefer administering diazepam in doses of 0.2–1 mg/kg (max dose 60 mg) every 1 h by the enteral route, along with few intermittent intravenous boluses of midazolam or diazepam to control spasms if needed. The maintenance dose should be titrated as per spasms and sedation. Once spasms are controlled, the maintenance dose of diazepam needs to be continued for 2–4 weeks and then tapered slowly over 2 weeks to avoid recurrence of spasms.[2] Lorazepam and midazolam have also been used.[12,13] It should be remembered that midazolam, when used as an infusion beyond 24–48 h, is no longer a short-acting benzodiazepine.

In about 10% of cases, patients with tetanus develop a paradoxical excitatory response with benzodiazepines. They become agitated, restless, and get increasing spasms and autonomic overactivity with tachycardia, hypertension, hypersalivation, and sweating. It is important to recognize this syndrome and discontinue the benzodiazepines. These patients respond well to the combination of a long-acting barbiturate like phenobarbital and chlorpromazine, a phenothiazine that also has a mild alpha-blocking and anticholinergic activity.

Neuromuscular Blocking Agents

When the maximum dose of benzodiazepines is not adequate to control spasms, patients are started on neuromuscular blocking drugs and mechanically ventilated.[1–3,12,13] Vecuronium or other cardiovascular inert neuromuscular blockers are preferred. The duration of neuromuscular blocker administration should be as short as possible. The use of protocols based on monitoring of the desired blockade can reduce the mechanical ventilation time, length of ICU stay, and cost.[1,12] It is important to continue benzodiazepines in the same dose as was being administered prior to starting muscle relaxants because benzodiazepines are required to prevent autonomic overactivity.[2,10]

Other Drugs

Baclofen which stimulates postsynaptic GABA beta receptors has been used in a few small studies. As it does not cross the blood–brain barrier and the preferred route is intrathecal. It may be given either in a bolus of 1000 µg or by continuous intrathecal infusion. However, due to increased rates of meningitis and possibly higher mortality rate, its routine use is not recommended.[1,12,13]

Other drugs like propofol, ketamine, dantrolene, botulism toxin have been tried for refractory spasm control.[12,13] In our experience, high doses of benzodiazepines along with neuromuscular blocking drugs and mechanical ventilation are the preferred strategy. Dexmedetomidine is a promising drug that may be added to benzodiazepines. It is given as a continuous infusion and titrated as per the response. It could reduce tachycardia and hypertension in severe tetanus. However, experience with infusions beyond a few days is very limited.[2,10]

Airway Protection and Mechanical Ventilation

Mild tetanus can be managed by nasogastric tube feeds and enteral administration of diazepam. Patients with moderate or severe tetanus have pooling of saliva and risk of aspiration are also

prone to sudden laryngeal spasms triggered by aspiration.[2,13] Early tracheostomy is advisable in these patients, often within a few hours of admission.[2,13] Besides preventing aspiration, tracheostomy also protects against asphyxia due to laryngeal spasms. The frequency and severity of spasms and the need for sedatives usually decrease after tracheostomy. In patients with a period of onset of fewer than 48 h, we often perform tracheostomy soon after admission. Mechanical ventilation is needed in severe tetanus forrefractory spasms or respiratory depression due to excessive sedation. Conventional mechanical ventilatory strategy is adequate in most patients with tetanus.

Management of Autonomic Dysfunction

Autonomic dysfunction in tetanus patients is characterized by loss of inhibitionresulting in overactive autonomic reflexes, manifesting as hypertension with labile blood pressure, tachycardia, diaphoresis, and rarely refractory hypotension and cardiorespiratory arrest.[1–3,8–10] These are triggered by same stimuli that set muscle spasms including pooling of saliva, oral and tracheal suction, pain, intramuscular injections, loud noises, and rarely touch and physical examination.[1–3] Effective sedation reduces autonomic dysfunction in majority of patients; additional drug therapy maybe needed in some patients.[2,10,12,13]

Magnesium Sulfate

Magnesium sulfate has been suggested to decrease spasm, cause vasodilation, control hypertension, reduced heart rate, decrease systemic catecholamine levels, and decreased autonomic fluctuations.[10,12,13] In an observational prospective study involving 40 severe tetanus cases, Attygalle et al. showed that $MgSO_4$ reduced the use of sedatives and neuromuscular blockers and decreased ventilatory support requirements when administered for 7 days.[15] In a randomized placebo-controlled trial in 2006 in Vietnam, Thwaites et al. studied 246 adults with severe tetanus cases, randomized to receive continuous intravenous $MgSO_4$ infusion or the placebo for 7 days.[16] In this study, a loading dose of 40 mg/kg over 30 min was used followed by a 2 g/hinfusion. They found that magnesium infusion did not reduce the need for mechanical ventilation but reduced the requirement for other drugs to control muscle spasms and cardiovascular instability.[16]

Clonidine, an alpha-2-agonist with sedative properties, has also been shown to effectively control dysautonomia. Gregorakos et al. studied 27 patients with severe tetanus and blood pressure instability.[17] Clonidine was administered until blood pressure stability was fully restored and the dose was then gradually reduced. Five patients from the non-clonidine group and two from the clonidine group died.[17]

Dexmedetomidine, an α1 and α2 adrenergic blocker, has a mechanism of action similar to clonidine, but with a greater α2 receptor selectivity and a lesser hypotensive effect. Its use has been described in some case reports for sympathetic overactivity.[2,10] Labetalol (0.25–1 mg/min), because of its dual alpha- and beta-blocking properties, may be administered as an infusion.[10,12,13] Long-acting beta-blocking drugs should not be used because sympathetic overactivity may suddenly be followed by parasympathetic overactivity and result in hypotension, bradycardia, or sudden asystole.[1,2,12] Morphine sulfate (0.5–1 mg/kg/h by continuous intravenous infusion) is also used in a few cases to control autonomic dysfunction as well as to induce sedation.[1,12,13]

Supportive Care

Early enteral feeding either with nasogastric tube should be started. The caloric requirements of these patients are as high as 40–50 kcal/kg/day because of continuous muscle overactivity and spasms. Proton pump inhibitorsor histamine-2 receptor antagonists may be used to prevent stress ulcers and low molecular weight heparin to prevent deep vein thrombosis. Patients usually require 3–6 weeks to recover.

Tetanus Immunization

Infection does not confer natural immunity against tetanus.[1–3] Therefore patients require a full course of primary immunization. The first dose of tetanus toxoid is usually administered on the day of admission, but at a site away from that of antitoxin injection. A second dose is administered during the hospital stay at 4–6 weeks and the third dose at 6 months.

Prognosis

The prognosis in severe tetanus depends on the experience of the treating center and the availability of intensive care facilities.[18] Mortality due to non-neonatal tetanus in resource-limited countries ranges from 5% to 53%,[1–3,8,9,18] and is much lower in developed countries with better intensive care facilities.[1,2] Poor prognostic features include age >60 years, period of onset <48 h, incubation period <7 days, severe tetanus requiring neuromuscular blockade and mechanical ventilation, and severe autonomic dysfunction. Deaths are commonly due to nosocomial infections or severe autonomic dysfunction with cardiac arrhythmias.[2,8,9,18]

Conclusion

Tetanus is a vaccine-preventable disease. Although its incidence is decreasing with better immunization coverage in children even in developing countries, it is still encountered in the elderly in most countries of the world. Patients with tetanus usually require 4–6 weeks of intensive care. Careful monitoring and adherence to protocolized care help reduce mortality. Despite good intensive care, mortality ranges from 5% to 50%. Liberal use of benzodiazepines, neuromuscular blockade, and mechanical ventilation forms the mainstay of treatment. Most deaths occur due to nosocomial infections or due to autonomic dysfunction.

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