



Tetanus: A review of the literature

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Abstract: This review work was conducted from august 2016 to march in 2017 in Ethiopia. Tetanus is caused by an infection with the bacterium *Clostridium tetani* which is commonly found in soil, saliva, dust, and manure. Tetanus, also known as lockjaw, is an infection characterized by muscle spasms. In the most common type, the spasms begin in the jaw and then progress to the rest of the body. These spasms usually last a few minutes each time and occur frequently for three to four weeks. Tetanus is now a rare disease in the developed world. However, it remains an important cause of death worldwide and is associated with a high case mortality, particularly in the developing world. Modern intensive care management should prevent death from acute respiratory failure, but cardiovascular complications as a result of autonomic instability and other causes of death remain problematic. In this article, I review the epidemiology, pathophysiology, clinical features, and current management of tetanus. [Gashaw, E. **Tetanus: A review of the literature**, *Biomedicine and Nursing* 2023;9(1):61-72]. ISSN 2379-8211 (print); ISSN 2379-8203 (online). <http://www.nbmedicine.org>. 09. doi:[10.7537/marsbnj090123.09](https://doi.org/10.7537/marsbnj090123.09).

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INTRODUCTION

Tetanus is caused by an infection with the bacterium *Clostridium tetani* (which is commonly found in soil, saliva, dust, and manure). The bacteria generally enter through a break in the skin such as a cut or puncture wound by a contaminated object. They produce toxins that interfere with muscle contractions, resulting in the typical symptoms (Vandalare *et al.*, 2003). Diagnosis is based on the presenting signs and symptoms. The disease does not spread between people. Tetanus, also known as lockjaw, is an infection characterized by muscle spasms. In the most common type, the spasms begin in the jaw and then progress to the rest of the body. These spasms usually last a few minutes each time and occur frequently for three to four weeks (Atkinson and William, 2012). Spasms may be so severe that bone fractures may occur. Other symptoms may include fever, sweating, headache, trouble swallowing, high blood pressure, and a fast heart rate. Onset of symptoms is typically three to twenty-one days following infection. It may take months to recover. About 10% of those infected die (Atkinson and William, 2012).

Infection can be prevented by proper immunization with the tetanus vaccine. In those who have a significant wound and less than three doses of the vaccine both immunization and tetanus immune globulin are recommended. The wound should be cleaned and any dead tissue should be removed. In those who are infected tetanus immune globulin or, if it is not available, intravenous immunoglobulin (IVIG) is used. (Atkinson and William, 2012). Muscle relaxants may be used to control spasms. Mechanical ventilation may be required if a person's

breathing is affected.

Tetanus occurs in all parts of the world but is most frequent in hot and wet climates where the soil contains a lot of organic matter.[1] In 2015 there were about 209,000 infections and about 59,000 deaths. This is down from 356,000 deaths in 1990 (Brauner *et al.*, 2002). Description of the disease by Hippocrates exists from at least as far back as the 5th century BC. The cause of the disease was determined in 1884 by Antonio Carle and Giorgio Rattone at the University of Turin, with a vaccine being developed in 1924 (Atkinson and William, 2012).

Cause

Clostridium tetani is strongly durable due to its endospores. Pictured is the bacterium alone, with a spore being produced, and the spore alone. Tetanus is caused by the tetanus bacterium *Clostridium tetani* (Wells and Wikin, 1996). Tetanus is often associated with rust, especially rusty nails. Although rust itself does not cause tetanus, objects that accumulate rust are often found outdoors or in places that harbor anaerobic bacteria. Additionally, the rough surface of rusty metal provides a prime habitat for *C. tetani* endospores to reside in (due to its high surface area), while a nail affords a means to puncture skin and deliver endospores deep within the body at the site of the wound (Astend Karnad, 1995).

An endospore is a non-metabolizing survival structure that begins to metabolize and cause infection once in an adequate environment. Because *C. tetani* is an anaerobic bacterium, it and its endospores thrive in environments that lack oxygen. Hence, stepping on a nail

(rusty or not) may result in a tetanus infection, as the low-oxygen (anaerobic) environment is caused by the oxidization of the same object that causes a puncture wound, delivering endospores to a suitable environment for growth (Dobop, 1998).

Tetanus is an international health problem, as *C. tetani* spores are ubiquitous. The disease occurs almost exclusively in persons unvaccinated or inadequately immunized (CDC, 2010). It is more common in hot, damp climates with soil rich in organic matter. This is particularly true with manure-treated soils, as the spores are widely distributed in the intestines and feces of many animals such as horses, sheep, cattle, dogs, cats, rats, guinea pigs, and chickens. Spores can be introduced into the body through puncture wounds. In agricultural areas, a significant number of human adults may harbor the organism. The spores can also be found on skin surfaces and in contaminated heroin. Heroin users, particularly those that inject the drug subcutaneously, appear to be at high risk of contracting tetanus (Handel and McCallum, 1995). Rarely, tetanus can be contracted through surgical procedures, intramuscular injections, compound fractures, and dental infections.

Types of tetanus

Generalized tetanus

Generalized tetanus is the most common type of tetanus, representing about 80% of cases. The generalized form usually presents with a descending pattern. The first sign is trismus, or lockjaw, and the facial spasms called risus sardonicus, followed by stiffness of the neck, difficulty in swallowing, and rigidity of pectoral and calf muscles (Demoraespin *et al.*, 1996). Other symptoms include elevated temperature, sweating, elevated blood pressure, and episodic rapid heart rate. Spasms may occur frequently and last for several minutes with the body shaped into a characteristic form called opisthotonos. Spasms continue for up to four weeks, and complete recovery may take months. [citation needed] Sympathetic overactivity (SOA) is common in severe tetanus and manifests as labile hypertension, tachycardia, dysrhythmia, peripheral vasculature constriction, profuse sweating, fever, increased carbon dioxide output, increased catecholamine excretion and late development of hypotension (Attygalle and Rodrigo, 1997). Death can occur within four days.

Neonatal tetanus

Neonatal tetanus is a form of generalized tetanus that occurs in newborns, usually those born to mothers who themselves have not been vaccinated. If the mother has been vaccinated against tetanus, the infants acquire passive immunity and are thus protected (Doshie *et al.*, 2014). It usually occurs

through infection of the unhealed umbilical stump, particularly when the stump is cut with a non-sterile instrument. As of 1998 neonatal tetanus was common in many developing countries and was responsible for about 14% (215,000) of all neonatal deaths. In 2010 the worldwide death toll was 58,000 newborns. As the result of a public health campaign, the death toll from neonatal tetanus was reduced by 90% between 1990 and 2010, and by 2013 the disease had been largely eliminated from all but 25 countries (Porter *et al.*, 1992). Neonatal tetanus is rare in developed countries.

Local tetanus

Local tetanus is an uncommon form of the disease, in which patients have persistent contraction of muscles in the same anatomic area as the injury. The contractions may persist for many weeks before gradually subsiding. Local tetanus is generally milder; only about 1% of cases are fatal, but it may precede the onset of generalized tetanus (Adelve *et al.*, 2012).

Cephalic tetanus

Cephalic tetanus is the rarest form of the disease (0.9–3% of cases) (Pinder, 1997) and is limited to muscles and nerves in the head. It usually occurs after trauma to the head area, including skull fracture, laceration eye injury, dental extraction, and otitis media, [(Buccafulla *et al.*, 1995). But it has been observed from injuries to other parts of the body. Paralysis of the facial nerve is most frequently implicated, which may cause lockjaw, facial palsy, or ptosis, but other cranial nerves can also be affected. Cephalic tetanus may progress to a more generalized form of the disease. Due to its rarity, clinicians may be unfamiliar with the clinical presentation and may not suspect tetanus as the illness. Treatment can be complicated as symptoms may be concurrent with the initial injury that caused the infection (Mayy clinic staff, 2013). Cephalic tetanus is more likely than other forms of tetanus to be fatal, with the progression to generalized tetanus carrying a 15–30% case fatality rate.

Epidemiology

Tetanus cases reported worldwide (1990-2004). Ranging from some (in dark red) to very few (in light yellow) (grey, no data). In 2013 it caused about 59,000 deaths – down from 356,000 in 1990 (Brauner *et al.*, 2002). Tetanus – in particular, the neonatal form – remains a significant public health problem in non-industrialized countries with 59,000 newborns worldwide dying in 2008 as a result of neonatal tetanus.[35][36] In the United States, from 2000 through 2007 an average of 31 cases were

reported per year.[8] Nearly all of the cases in the United States occur in unimmunized individuals or individuals who have allowed their inoculations to lapse (Borgeat *et al.*, 1991).

In spite of the World Health Organization's intention to eradicate tetanus by the year 1995, it remains endemic in the developing world and WHO estimated approximately 1000 000 deaths from tetanus worldwide in 1992. This included 580 000 deaths from neonatal tetanus, with 210 000 in South East Asia and 152000 in Africa. The disease is uncommon in developed countries. In South Africa approximately 300 cases occur each year, approximately 12±15 cases are reported each year in Britain and between 50 and 70 in the USA (Farrar *et al.*, 2000).

Mortality and outcome

Case fatality rates and causes of death vary dramatically according to the facilities available. Trujillo and colleagues reported a reduction in mortality from 44 to 15% after the introduction of intensive care treatment. In developing countries, without facilities for prolonged intensive care and ventilatory support, deaths from severe tetanus exceed 50% with airway obstruction, respiratory failure, and renal failure as prominent causes. A mortality of 10% has been suggested as an acceptable goal in developed countries (Ahmadsyan and Salin, 1995). Modern intensive care should prevent death from acute respiratory failure but as a result, in severe cases, autonomic disturbance becomes more apparent. Trujillo reported that 40% of deaths after introduction of ICU care were a result of sudden cardiac death and 15% a result of respiratory complications (Reid *et al.*, 1996). Before ICU was established, 80% of historical controls died as a result of early acute respiratory failure. Important complications of ICU care include nosocomial infections, particularly ventilator-associated pneumonia, generalized sepsis, thromboembolism, and gastrointestinal haemorrhage. Mortality varies with patient age. In the USA, mortality in adults below 30 yr. may approach zero, but in those over 60 yr. is 52%. In Portugal, between 1986 and 1990 all age mortality varied between 32 and 59% (Reis *et al.*, 1994). In Africa, mortality from neonatal tetanus without artificial ventilation was reported as 82% in 1960 and 63±79% in 1991. With artificial ventilation available this may be as low as 11% but other authors report rates close to 40%. Severe cases of tetanus generally require ICU admission for approximately 3±5 weeks. Recovery can be expected to be complete, with return to normal function. However, in one of the few follow up studies in survivors of tetanus, persisting physical and psychological problems were frequent (Rocke *et al.*, 1996).

Incubation period

The incubation period of tetanus may be up to several months, but is usually about ten days (Simonjen, 1989). In general, the farther the injury site is from the central nervous system, the longer the incubation period. The shorter the incubation period, the more severe the symptoms. In neonatal tetanus, symptoms usually appear from 4 to 14 days after birth, averaging about 7 days. On the basis of clinical findings, four different forms of tetanus have been described (Witlin and Sabai, 1998).

Pathophysiology

Tetanus affects skeletal muscle, a type of striated muscle used in voluntary movement. The other type of striated muscle, cardiac, or heart muscle, cannot be tetanized because of its intrinsic electrical properties. The tetanus toxin initially binds to peripheral nerve terminals. It is transported within the axon and across synaptic junctions until it reaches the central nervous system (Fischer and Baer, 1996). There it becomes rapidly fixed to gangliosides at the presynaptic inhibitory motor nerve endings, and is taken up into the axon by endocytosis. The effect of the toxin is to block the release of inhibitory neurotransmitters glycine and gamma-aminobutyric acid (GABA) across the synaptic cleft, which is required to check the nervous impulse. If nervous impulses cannot be checked by normal inhibitory mechanisms, the generalized muscular spasms characteristic of tetanus are produced. The toxin appears to act by selective cleavage of a protein component of synaptic vesicles, synaptobrevin II, and this prevents the release of neurotransmitters by the cells (Ajayi and Obimakindales, 2011).

Under anaerobic conditions found in necrotic or infected tissue, the tetanus bacillus secretes two toxins: tetanospasmin and tetanolysin. Tetanolysin is capable of locally damaging otherwise viable tissue surrounding the infection and optimizing the conditions for bacterial multiplication. Tetanospasmin leads to the clinical syndrome of tetanus (Dutta *et al.*, 1994). This toxin may constitute more than 5% of the weight of the organism. It is a two-chain polypeptide of 150 000 Da which is initially inactive. The heavy chain (100 000 Da) and the light chain (50 000 Da) are linked by a protease sensitive loop that is cleaved by tissue proteases leaving a disulphide bridge linking the two chains. The carboxyl terminus of the heavy chain binds to neural membrane and the amino terminus facilitates cell entry (Borgata *et al.*, 1994).

The light chain acts pre-synaptically to prevent neurotransmitter release from affected neurons. Released tetanospasmin spreads to underlying

tissue and binds to gangliosides GD1b and GT1b on the membranes of local nerve terminals. If toxin load is high, **some may enter the blood stream** from where it diffuses to bind to nerve terminals throughout the body. The toxin is then internalized and transported intraxonally and retrogradely to **the cell body** (Alaska and Gas, 1995). Transport occurs first in motor and later in sensory and **autonomic nerves**. Once **in the cell body** the toxin can diffuse out so affecting and **entering nearby** neurons. When spinal inhibitory **interneurons are affected**, symptoms **occur**. Further retrograde intraneural transport occurs with toxin spreading to **the brain stem** and midbrain. This passage includes **retrograde transfer** across synaptic **clefts** by a mechanism that is unclear. After internalization into inhibitory neurons the disulphide bonds linking the light and heavy chains are reduced, liberating the light chain (Brooks and Asanuma, 1994).

The effects of the toxin result from prevention of the release of neurotransmitters. Synaptobrevin is a membrane protein necessary for the export of intracellular **vesicles** containing neurotransmitter. The tetanospasmin **light chain** is a zinc metalloprotease, **which cleaves** synaptobrevin at a single point, thereby preventing neurotransmitter release. The toxin has a predominant effect **on** inhibitory neurons, inhibiting release of glycine and gamma-aminobutyric acid (GABA) (Gyasi, 1993).

Interneurons **inhibiting** alpha motor neurones are first affected and the **motor neurones** lose inhibitory **control**. Later (because of the longer path) **preganglionic** sympathetic neurones in the lateral horns and the parasympathetic centers are also affected. Motor neurones are similarly affected and the release of acetyl choline into the neuromuscular cleft is reduced (Brown *et al.*, 1994). This effect is similar to the action of **the** closely related botulinum toxin, which produces a \bar{c} paralysis. However, **in tetanus** the disinhibitory effect on the motor neuron overwhelms any diminution of function at the neuromuscular junction. Medullary and hypothalamic centers may also be affected. Tetanospasmin has a cortical convulsant effect in animal studies. Whether these mechanisms contribute to intermittent spasm and autonomic storms is unclear (Enters and Bate, 1991). The pre junctional effect on the neuromuscular junction may lead to considerable weakness between spasms and might account for **both the paralysis of cranial nerves observed** in cephalic tetanus and myopathies observed after recovery (Myers *et al.*, 1982).

In other species, tetanus produces an illness characterized by placid paralysis. Uncontrolled disinhibited efferent discharge from motor neurones in the cord and brainstem **leads** to intense muscular rigidity **and spasm, which** may mimic convulsions. The reexhibiting of antagonist muscle groups is lost and agonist and antagonist muscles contract simultaneously (Midges, 1985). Muscle spasms are intensely painful and may lead to fractures and tendon rupture. Muscles of the jaw, face, and head are often involved first because of their shorter axonal pathways. The trunk and **limbs follow** but peripheral muscles in the hands and feet are relatively spared. Disinhibited autonomic discharge leads to disturbances in autonomic control, with sympathetic overactivity and excessive plasma catecholamine levels (Sassy *et al.*, 1992). Neuronal binding of toxin is **thought to be irreversible**. Recovery requires the growth of new nerve terminals which explains the prolonged duration of tetanus.

Clinical features

Tetanus often begins with mild spasms in the jaw muscles also known as lockjaw or trismus. The spasms can also affect the facial muscles resulting in an appearance called risus sardonicus. Chest, neck, back, abdominal muscles, and buttocks may be affected. Back muscle spasms often cause arching, called opisthotonos. Sometimes the spasms affect muscles that help with breathing, which can lead to breathing problems (Delpilar morals *et al.*, 2014).

Prolonged muscular action causes sudden, powerful, and painful contractions of muscle groups, which is called "tetany". These episodes can cause fractures and muscle tears. Other symptoms include drooling, excessive sweating, fever, hand or foot spasms, irritability, difficulty swallowing, suffocation, heart attack, breathing problems, irregular heartbeat, and uncontrolled urination or defecation (Wadia, 1994). Even with treatment, about 10% of people who contract tetanus die. The mortality rate is higher in unvaccinated people and people over 60 years of age (Sutton *et al.*, 1990).

Tetanus usually follows a recognized injury. Contamination of wounds with soil, manure, **or rusty metal** can lead to tetanus. It can complicate burns, ulcers, gangrene, necrotic snake bites, middle **ear infections**, septic abortions, childbirth, intramuscular injections, and surgery. Injuries may be toroviral and in up to 50% of cases the injury occurs indoors and/or is not considered serious enough to seek medical treatment (Abrutyn *et al.*, 1995). In 15±25% of patients, there is no evidence of a recent wound. There is a clinical triad of rigidity, muscle

spasms and, if severe, autonomic dysfunction. Neck stiffness, sore throat, and difficulty opening the mouth are **often** early symptoms. Masseter spasm causes **trismus** or 'lockjaw'. Spasm progressively extends to the facial muscles causing the typical facial expression, 'risus sardonius', and muscles of **swallowing** causing dysphagia (Sea *et al.*, 2012). Rigidity of the neck muscles leads to retraction of the head. Truncal rigidity may lead to opisthotonus and respiratory difficulty with decreased chest wall compliance. In addition to increased muscle tone, there are episodic muscular spasms. These tonic contractions have a convulsion-like appearance affecting agonist and antagonist muscle groups together. They may be spontaneous or triggered by touch, visual, auditory, or **emotional stimuli** (Ugwa and Okolugbo, 2012).

Spasms may vary in severity **and** frequency **but may be** strong enough to cause fractures **and tendon avulsions**. Spasms may be **almost** continual, **leading to** respiratory failure. Pharyngeal spasms are **often** followed by laryngeal spasms and are associated with **aspiration** and life-threatening acute airway obstruction. In the **commonest** form of tetanus, generalized tetanus, muscles throughout the body are affected. The muscles of the head and neck are usually affected **first** with progressive caudal spread of rigidity and spasm to affect the whole-body (James, 1998). The **differential** diagnosis includes **soro facial infection, dystonic drug reactions, hypo calcaemia, strychnine poisoning, and hysteria**. With lower **toxin loads** and **peripheral** injuries local tetanus is seen. Spasm and rigidity are restricted to a limited area of the body. Mortality **is** greatly **reduced**.

An exception to this is cephalic tetanus when localized tetanus from a head wound affects the cranial **nerves; paralysis** rather than spasm predominates at presentation, but progression to generalized tetanus is common and mortality is high. Tetanus neon to rum causes more than 50% of deaths from tetanus worldwide but is very rare in developed countries (James and Manson, 1985). Neonates present within a week of birth with short history of failure to feed, vomiting, and convulsions. Seizures, meningitis, and sepsis are differential diagnoses (Penner *et al.*, 1986). Spasms are generalized and mortality is high. Poor umbilical hygiene is the cause of the disease but it is entirely preventable by maternal vaccination, even during pregnancy. Before the introduction of artificial ventilation, many patients **with severe** tetanus died from acute respiratory failure. With the

development of intensive care, it became apparent that severe tetanus was associated with marked autonomic instability. The sympathetic nervous system is most prominently affected. Clinically, increased sympathetic tone causes persistent tachycardia and hypertension (Gregorio's *et al.*, 1990).

Marked vasoconstriction and pyrexia are seen. Basal plasma catecholamine levels are raised. Autonomic storms occur with marked cardiovascular instability. Severe hypertension and tachycardia may alter **Nate** with profound hypotension, **bradycardia, or recurrent cardiac arrest**. These alterations are a **result** of, predominantly, rapid alterations in systemic vascular resistance rather than cardiac filling or performance. During these 'storms' plasma catecholamine levels are raised up to 10-fold, to similar levels to those seen in pheochromocytoma. Norepinephrine **is affected** more than epinephrine. Neuronal hyperactivity rather than adrenal medullary hyperactivity appears to predominate. In addition to the cardiovascular system, other autonomic effects include profuse salivation and increased bronchial secretions. Gastric stasis, ileus, diarrhoea, and high output renal failure may all be related to autonomic disturbance. The involvement of the sympathetic nervous system is established (Black *et al.*, 2010). The role of the parasympathetic system is less clear. Tetanus has been reported to induce **lesions** in the vagal nuclei, while locally applied toxin may lead to excessive vagal activity. Hypotension, bradycardia, and asystole may arise from increased vagal tone and activity.

Altered cardiovascular physiology

There have been relatively few studies of the effects of tetanus on the cardiovascular system. One problem is that the haemodynamic effects of both complications and treatment may mask the true effects of the disease itself. Udwardi studied 27 patients with Ablett grade III/IV disease who were stable and not on drugs likely to alter hemodynamics (Wadia, 1994). Nineteen had uncomplicated and eight complicated tetanus (with pneumonia, ARDS, sepsis). His extensive studies examined cardiovascular features of the disease: changes during poorly controlled spasms, **during** intense relaxation, during recovery, and the effect of sideloading in tetanus **compared with** the effect in healthy volunteers. He also **studied** patients during periods of considerable cardiovascular instability because of autonomic storms. Severe uncomplicated tetanus was marked by a hyperkinetic circulation. Tachycardia was universal with hypertension, raised stroke volume index, **and** raised cardiac index. Other findings were low **normal systemic** vascular resistance and normal left- and right-sided filling pressures. These

findings **were** similar to those of James and Manson (Wesley *et al.*, 1983). The hyperkinetic **state** was exaggerated **during** poor relaxation and increased spasm activity. The hemodynamic abnormalities became less marked during periods of full muscular relaxation but measurements only gradually returned to normal ranges during recovery from the disease (Wilkins *et al.*, 1988).

A fluid challenge of 2000 ml increased left heart filling pressures and cardiac index but these effects were very transient. During autonomic storms with marked cardiovascular instability, patients transitioned from a hyperstimulated state of hypertension (arterial pressure **up** to 220/120 mmHg) and tachycardia (heart rate 130±190 beats/min) to one of profound depression with hypotension (as low as 70/30 mmHg), bradycardia (50±90 beats/min) and a fall in CVP (reducing from 6 to 1 cm H₂O). Invasive monitoring showed these changes to be a result of a rapid, marked alteration in systemic **vascular** resistance index (SVRI), **falling from** 2300 to less than 1000 dynes/cm. There was little change in cardiac index or filling pressures (CDC, 2012). Patients with grade IV disease were less likely than those with less severe disease **to** raise cardiac index or **cardiac work** indices in response to fluid load or during alterations in vascular resistance seen during autonomic storms. One patient with severe sustained hypertension was found to have massively raised vascular resistance with SVRI greater than 4500 dynes/cm. In complicated tetanus, measurements varied widely with no consistent findings (Weiss *et al.*, 1983).

The hyperkinetic circulation is largely because of increased basal sympathetic activity and muscle activity, with a lesser effect from raised core temperature. The low-normal SVRI is because of extensive vasoconstriction in metabolically active muscles. As **oxygen** extraction ratio does not alter in tetanus, the increased demand must be delivered by increased blood flow (Southon and Blaise, 1986). Poor spasm **control** exaggerates these effects. Fluid loading **causes** only transient rise in filling pressures, cardiac index, and LVSWI. Because the circulation is widely vasodilated and hence is a high capacitance system in comparison to normal controls. In uncomplicated tetanus, the cardiovascular system, therefore, mimics that of the normal patient undergoing intense exercise (Monticello and Shiloh, 1995). Grade **IV patients** appear less able to increase cardiac performance and, therefore, are more susceptible to profound hypotension and shock during acute vasodilatory storms. The mechanism is unclear but may relate to sudden withdrawal of catecholamine stimulation or a direct action of **tetanus toxin** on the **myocardium**. Altered myocardial function may be because of persistently raised catecholamine levels but abnormal function may occur even in the

absence of sepsis or high catecholamine levels (Wright *et al.*, 1989).

Altered respiratory physiology

Muscular rigidity and spasms of the chest wall, diaphragm, and abdomen lead to a restrictive defect. Pharyngeal and laryngeal spasms predict respiratory failure or life-threatening airway obstruction. Poor cough from rigidity, spasms, and sedation leads to atelectasis and the risk of pneumonia is high (Ablet, 1967). The inability to swallow copious saliva, profuse bronchial secretions, pharyngeal spasms, raised intra-abdominal pressure, and gastric stasis all increase the risk of aspiration, **which** is common. Ventilation/perfusion mismatching is also common (Bucanan *et al.*, 1979). Consequently, **hypoxia** is a **main** form finding in moderate or severe tetanus even when the chest **is** radiologically clear. Breathing **air**, oxygen tensions of between 5.3±6.7 kPa are common. In artificially ventilated patients, increased A-gradients persist. Oxygen delivery and **utilization** may be compromised even without super-added lung pathology. Acute respiratory distress syndrome may occur as a specific complication of tetanus. Minute ventilation may be altered by a variety of causes. Hyperventilation **may** occur because of fear, autonomic disturbance, or alteration in brainstem function. Hypocarbia (PCO₂ 4.0±4.6 kPa) is usual in mild to moderate disease (Curter *et al.*, 1973). Hyperventilation storms may lead to severe hypocarbia (PCO₂ <3.3 kPa). In severe disease, hypoveilation from prolonged spasms and apnoea occurs. Sedation, exhaustion and altered brainstem function may also lead to respiratory **failure**. Respiratory **drive** may be deficient leading to recurrent life-threatening apnoeic periods (UNICEF, 2010).

Altered renal physiology

In mild tetanus, renal function is preserved. In severe disease reduced glomerular filtration rate and impaired renal tubular function are frequent. Contributory causes of renal failure include dehydration, sepsis, rhabdomyolysis, and alterations in renal blood flow secondary to catecholamine surge. Renal failure may be oliguric or polyuric. Clinically important renal impairment is associated with autonomic instability and histology is normal or shows acute tubular necrosis (Kanarek *et al.*, 1973). Management Treatment strategies involve three management principles: organisms present in the body should be destroyed to prevent further toxin release; toxin present in the body, outside the CNS should be neutralized; and the effects of toxin already in the CNS should be minimized. Neutralization of unbound toxin Human tetanus immune globulin 3±6000 units is given (Pearce, 1996). Removal of the source of infection Where present, obvious wounds

should be surgically debrided. Penicillin has been widely **used** for **many** years but is a GABA antagonist and associated with convulsions. Metronidazole is probably the antibiotic of choice. It is safe **and comparative** studies with penicillin suggest at least as good results. Erythromycin, tetracycline, chloramphenicol, and clindamycin are all accepted as alternatives.

Control of rigidity and spasms

Avoidance of unnecessary stimulation is mandatory, but the mainstay of treatment is sedation with a benzodiazepine. Benzodiazepines augment GABA agonism, by inhibiting an endogenous inhibitor at the GABA_A receptor. Diazepam may be given by various routes, is cheap and widely used, but long-acting metabolites (oxazepam and desmethyldiazepam) may lead to cumulation and prolonged coma. Doses as high as 100 mg/h have been reported. Midazolam has been used **with** less **apparent** cumulation (Farrar *et al.*, 2000). Additional sedation may be provided by anticonvulsants, particularly phenobarbitone (which further enhances GABAergic activity) and phenothiazines, usually chlorpromazine. Propofol has been **used** for sedation **with** rapid **recovery** on stopping the infusion. When sedation alone is inadequate, neuromuscular blocking agents and intermittent positive pressure ventilation may be required for a prolonged period. Traditionally, the long-acting agent alcuronium has **been** used. However, alcuronium **inhibits** catecholamine re-uptake and could worsen autonomic instability in severe cases (Wells and Wikin, 1996).

There have been isolated reports of worsening hypertension and tachycardia associated with its use. But Dancereported no difference in complications in those treated with pancuronium compared with other neuromuscular blocking drugs. Vecuronium is free from cardiovascular side effects and histamine release but is relatively short acting. The use of an atracurium infusion in tetanus for 71 days has been reported. In this patient, with normal renal and hepatic function, there was no cumulation of laudanosine, the epileptogenic metabolite of atracurium. Long acting agents are preferable as they lend themselves to administration by intermittent bolus rather than requiring infusion (Keltie *et al.*, 1967). Prolonged use of amino steroid neuromuscular blocking agents (vecuronium, alcuronium, rocuronium, and pancuronium), particularly by infusion, has been associated with critical illness neuropathy and myopathy, but **this has** not been reported in tetanus. Of the newer agents, pipercuronium and rocuronium are long acting 'clean' agents but are expensive (Uganda, 2011). Individual drugs have not been compared in randomized trials. The use of dantrolene to control refractory spasms has been

reported in one case. Neuromuscular blocking drugs were unnecessary. After its administration, paroxysmal spasms stopped and the patient's condition improved. Sedation with propofol has allowed control of spasms and rigidity without the use of neuromuscular blocking drugs. Examination of the EMG and neuromuscular function during propofol boluses showed an 80% reduction **in** EMG activity without alteration of function at the neuromuscular junction. However, drug levels were closer to anaesthetic than sedative concentrations and mechanical ventilation would be required. Intrathecal baclofen (a GABA_B agonist) has been reported in several small series with varying success (Peat *et al.*, 1988).

Treatment

Mild tetanus

Mild cases of tetanus can be treated with: tetanus immunoglobulin (TIG) also called tetanus antibodies or tetanus antitoxin (Howard *et al.*, 1995). It can be given as intravenous therapy or by intramuscular injection. metronidazole IV for 10 days diazepam oral or IV.

Severe tetanus

Severe cases will require admission to intensive care. In addition to the measures listed above for mild tetanus (Black *et al.*, 2010) Human tetanus immunoglobulin injected intrathecally (increases clinical improvement from 4% to 35%) Tracheotomy and mechanical ventilation for 3 to 4 weeks. Tracheotomy is recommended for securing the airway because the presence of an endotracheal tube is a stimulus for spasm. Magnesium, as an intravenous (IV) infusion, to prevent muscle spasm. Diazepam as a continuous IV infusion. The autonomic effects of tetanus can be difficult to manage (alternating hyper- and hypotension hyperpyrexia/hypothermia) and may require IV labetalol, magnesium, clonidine, or nifedipine. Drugs such as diazepam or other muscle relaxants (Peduto *et al.*, 1983), can be given to control the muscle spasms. In extreme cases it may be necessary to paralyze the patient with curare-like drugs and use a mechanical ventilator. In order to survive a tetanus infection, the maintenance of an airway and proper nutrition are required. An intake of 3,500 to 4,000 calories and at least 150 g of protein per day is often given in liquid form through a tube directly into the stomach (percutaneous endoscopic gastrostomy), or through a drip into a vein (parenteral nutrition). This high-caloric diet maintenance is required because of the increased metabolic strain brought on by the increased muscle activity. Full recovery takes 4 to 6 weeks because the body must regenerate destroyed nerve axon terminals (King and Cave, 1991).

Supportive intensive care treatment

Weight loss is universal in tetanus (Kerr, 1981). Contributory factors include inability to swallow, autonomic induced alterations in gastrointestinal

function, increased metabolic rate from pyrexia and muscular activity and prolonged critical illness. Nutrition should, therefore, be **established** as early as possible. Enteral nutrition is **associated with** a lower incidence of complications and is cheaper than parenteral nutrition. Percutaneous gastrostomy may avoid the complications associated with nasogastric tube feeding (Philbin et al., 1981), **and** is easily performed on the intensive care unit under sedation. Infective complications of prolonged critical illness including ventilator-associated pneumonia are common in tetanus (Powles and Gantal, 1985).

Prevention

Unlike many infectious diseases, recovery from naturally acquired tetanus does not usually result in immunity to tetanus. This is due to the extreme potency of the tetanospasmin toxin. Tetanospasmin will likely be lethal before it will provoke an immune response. Tetanus can be prevented by vaccination with tetanus toxoid (Law et al., 1997). The CDC recommends that adults receive a booster vaccine every ten years, (Schiavo et al., 1992), and standard care practice in many places is to give the booster to any patient with a puncture wound who is uncertain of when he or she was last vaccinated, or if he or she has had fewer than three lifetime doses of the vaccine. The booster may not prevent a potentially fatal case of tetanus from the current wound, however, as it can take up to two weeks for tetanus antibodies to form (Seedat et al., 1980).

In children under the age of seven, the tetanus vaccine is often administered as a combined vaccine, DPT/DTaP vaccine, which also includes vaccines against diphtheria and pertussis. For adults and children over seven, the Td vaccine (tetanus and diphtheria) or Tdap (tetanus, diphtheria, and acellular pertussis) is commonly used (WHO, 2013). The World Health Organization certifies countries as having eliminated maternal or neonatal tetanus. Certification requires at least two years of rates of less than 1 case per 1000 live births. In 1998 in Uganda, 3,433 tetanus cases were recorded in newborn babies; of these, 2,403 died. After a major public health effort, Uganda in 2011 was certified as having eliminated tetanus (Shibuya et al., 1981).

Vaccination

Byron Plant explains: "Vaccination is the more commonly used term, which actually consists of a 'safe' injection of sample taken from a cow suffering from cowpox... Inoculation, a practice probably as old as the disease itself, is the injection of the variola virus taken from a pustule or scab of a smallpox sufferer into the superficial layers of the

skin, commonly on the upper arm of the subject. Often inoculation was done 'arm to arm' or less effectively 'scab to arm'..." Inoculation oftentimes caused the patient to become infected with smallpox, and in some cases the infection turned into a severe case (Hariharan et al., 1984). Vaccinations began in the 18th century with the work of Edward Jenner and the smallpox vaccine (Dodshi et al., 2014)

As the organism is ubiquitous and infection does not confer immunity, prevention is through vaccination. Tetanus vaccine has been available since 1923. Routine vaccination began **in** the UK in 1961. Vaccination is started at 2 months of age with three **injections** performed at monthly intervals. The second **injection** confers immunity with the third **prolonging** its duration. A booster is given before the age of 5 yr. Similar **responses** occur in older children and adults' Neonatal **immunity** is provided by maternal vaccination **and transplacental** transfer of immune- no globulin (Adelve et al., 2012). This may be impaired in the presence of maternal HIV infection. Immunity is not lifelong. Revaccination at 10-yr intervals **is** recommended **in** the USA. In the UK, **two boosters spaced 10 yr** apart are recommended in adulthood, so the recommendations do not extend to vaccination beyond the third decade. In the USA, more than 70% of cases **and** 80% of deaths occur in those over 50 yr. Similar proportions are reported in Europe. In the UK and USA, serological surveys have demonstrated an increasing proportion of patients with **inadequate** immunity as age increases: 49±66% of patients **over 60 yr had antibody levels** below the protective **level** Some have never been vaccinated, while others have Pearce, 1996).

Conclusions

Tetanus is fortunately a common disease in the Ethiopia and isentirely preventable by vaccination . It remains **major** health problems of the worldwide. In developed countries, several cases present every **year in the elderly** and unimmunized population. Mortality in these cases remains high. Prolonged intensive care support may be necessary but most treatment is based on limited evidence. Major therapeutic challenges lie in the control of muscular rigid ityand spasms, the treatment of autonomic disturbance and the prevention of complications associated with prolongedcritical illness. Return to normal function can be expected in those who survive.

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References

- [1]. Ablett, J. J. L. (1967): Analysis and main experiences in 82 patients treated in the Leeds Tetanus Unit. In: Ellis M, ed. Symposium on Tetanus in Great Britain. Boston Spa, UK: National Lending Library.
- [2]. Abrutyn E. Tetanus. In: Isselbacher K. J, Wilson J, **Fauci A, et al., eds. (1995):** Harrison's Principles of Internal Medicine 13th end. New York:McGraw-Hill Inc.
- [3]. Adeleye, A. O.; and Azeez, A. L. (2012): "Fatal tetanus complicating an untreated mild open head injury: a case-illustrated review of cephalic tetanus". *Surg Infect (Larchmt)*. 13 (5): 317–20. doi:10.1089/sur.2011.023. PMID 23039234.
- [4]. Ahmadsyah, I. And Salim, A. (1985): Treatment of tetanus: an open study to compare the efficacy of procaine penicillin and metronidazole. *BMJ*.
- [5]. Ajayi, E.; Obimakinde, O. (2011). "Cephalic tetanus following tooth extraction in a Nigerian woman". *J Neurosci Rural Pract*. 2 (2): 201–2. doi:10.4103/0976-3147.83597. PMC 3159367. PMID 21897694.
- [6]. Ambache, N., and Lippold, O.C.J. (2000): Bradycardia of central origin produced by injections of tetanus toxin into the vagus nerve. *J Physiol*.
- [7]. Apte NM, Karnad DR (October 1995). "Short Report: The Spatula Test: A Simple Bedside Test to Diagnose Tetanus". *American Journal of Tropical Medicine and Hygiene*. 53 (4): 386–7. PMID 7485691.
- [8]. Atkinson, and William (2012): Tetanus Epidemiology and Prevention of Vaccine-Preventable Diseases (12 ed.). Public Health Foundation. pp. 291–300. ISBN 9780983263135. Retrieved 12 February 2015.
- [9]. Attygalle, D., and Rodrigo, N. (1997): Magnesium sulphate for control of spasms in severe tetanus. Can we avoid sedation and artificial ventilation? *Anaesthesia*.
- [10]. Black, R.E.; Cousens, S.; Johnson, H.L.; Lawn, J.E.; Rudan, I.; Bassani, D.G; Jha, P; Campbell, H.; Walker, C.F.; Cibulskis, R; Eisele, T; Liu, L; Mathers, C; Child Health Epidemiology Reference Group of WHO and UNICEF (Jun 5, 2010). "Global, regional, and national causes of child mortality in 2008: a systematic analysis.". *Lancet*. 375 (9730): 1969–87. doi:10.1016/S0140-6736(10)60549-1. PMID 20466419.
- [11]. Borgeat A., Popovic V., and Schwander D. (1994): Efficacy of a continuous infusion of propofol in a patient with tetanus. *Crit Care Med*.
- [12]. Borgeat, A., Dessibourg C., Rochani M., and Suter P. M. (1991): Sedation by propofol in tetanus is it a muscular relaxant? *Intensive Care Med*.
- [13]. Brauner, J. S.; Vieira, S. R.; and Black, T. P. (2002): "Changes in severe accidental tetanus mortality in the ICU during two decades in Brazil". *Intensive Care Medicine*. 28 (7): 930–5. doi:10.1007/s00134-002-1332-4. PMID 12122532.
- [14]. Brooks V.B, and Asanuma H. (1994): Pharmacological studies of recurrent cortical inhibition and facilitation. *Am J Physiol*
- [15]. Brown J.L., Sinding H., Mathias C.J. (1994): Autonomic disturbance in severe tetanus: failure of parenteral clonidine to control blood pressure. *J Infect*.
- [16]. Buccafusco J.J., Lapp C.A., Westbrook K.L., Emsberger P. (1995): Role of medullary III midazolone and alpha 2-adrenergic receptors in healthy naive responses evoked by central administration of clonidine analogs in conscious spontaneously hypertensive rats' *Pharmacol Exp Ther*
- [17]. Buchanan N., Smit L., Cane R. D, De Andrade M. (1979): Sympathetic overactivity in tetanus: fatality associated with propranolol.
- [18]. Curtis DR, Felix D, Game CJA, McCulloch RM. (1973): Tetanus toxin and the synaptic release of GABA. *Brain Res*.
- [19]. "CDC Features - Tetanus: Make Sure You and Your Child Are Fully Immunized". Retrieved 2010-08-30.
- [20]. de Moraes-Pinto MI, Almeida ACM, **Kenj G, et al.** (1996): Placental transfer and maternal acquired neonatal IgG immunity in human immunodeficiency virus infection. *J Inf Dis*
- [21]. Del Pilar Morales, E.; Bertrán Pasarell, J.; Cardona Rodriguez, Z.; Almodovar Mercado, J. C.; and Figueroa Navarro, A. (2014): "Cephalic tetanus following penetrating eye trauma: a case report". *Bol Asoc Med P R*. 106 (2): 25–9. PMID 25065047.
- [22]. Dob DP, McLure H.A., Soni N. (1998): Failed intubation and emergency percutaneous tracheostomy. *Anaesthesia*.
- [23]. Doshi, A.; Warrell, C.; Dahdaleh, D.; Kullmann, D. (2014): "Just a graze? Cephalic tetanus presenting as a stroke mimic". *Pract Neurol*. 14 (1): 39–41.

- doi:10.1136/practneurol-2013-000541. PMID 24052566.
- [24]. Dutta TK, Padmanabhan S, Hamide A, Ramesh J. (1994): Localised tetanus mimicking incomplete **transverse myelitis**. *Lancet*.
- [25]. Edmonds, Molly. "Causes of Tetanus". HowStuffWorks. Retrieved 9 November 2015.
- [26]. Enters E. M, Bates M.E. (1991): Caring for neonatal tetanus patients in rural primary care setting in Nigeria: a review of 237 cases.
- [27]. Elimination of Maternal and Neonatal Tetanus". UNICEF. Retrieved 17 February 2014.
- [28]. Farrar, J. J.; Yen, L. M.; Cook, T.; Fairweather, N.; Binh, N.; Parry, J.; and Parry, C. M. (2000): "Tetanus". *Journal of Neurology, Neurosurgery, and Psychiatry*. 69 (3): 292–301. doi:10.1136/jnnp.69.3.292. PMC 1737078. PMID 10945801.
- [29]. Fischer J. R, Baer R. K. (1996): Acute myopathy associated with combined use of corticosteroids and neuromuscular blocking agents.
- [30]. Galazka A, Gasse F. (1995): The present state of tetanus and tetanus vaccination. *Curr Topics Microbiol Immunol*
- [31]. Gregorakos L, Kerezoudi E, Dimopoulos G, Thomaidis T. (1990): Management of blood pressure instability in severe tetanus: the use of clonidine. *Intensive Care Med*.
- [32]. Gyasi HK, Fahr J, Kurian E, Mathew M. (1993): Midazolam for prolonged intravenous sedation **in patients with tetanus**. *Mid E J Anesth*
- [33]. Handel J, McCallum D. (1995): A different form **of** nutrition delivery. *Hosp Update*
- [34]. Hariharan D, Pather M, Rocke D.A, Wesley AG. (1984): Renal functioning tetanus. *Intensive Care Med*
- [35]. Howard A.B, Alexander RW, Taylor WR. (1995): Effects of magnesium on nitric oxide synthase activity in endothelial cells. *Am J Physiol* 1995; 269: C612±8
- [36]. James MFM, Manson EDM. (1985): The **use of magnesium sulphate** infusions in the management **of** very severe tetanus. *Intensive Care Med*
- [37]. James MFM. (1998): Magnesium sulphate **for** the **control** of spasms in severe tetanus. *Anaesthesia*
- [38]. Kanarek DJ, Kaufman B, Zwi S. (1973): Severe sympathetic hyperactivity associated with tetanus. *Arch Int Med*
- [39]. Kelly SR, Gray RC, Dundee JW, McCulloch H. (1968): Catecholamine levels in severe tetanus. *Lancet*;
- [40]. Kerr J.H. (1981): Insensible **fluid** losses in severe tetanus. *Intensive Care Med* King WW, **Cave DR**. (1991): Use of esmolol to control autonomic instability of tetanus. *Am J Med*
- [41]. Kwon, J. C.; Park, Y.; Han, Z. A.; Song, J. E.; Park, H. S. (2013): "Trismus in cephalic tetanus from a foot injury". *Korean J Intern Med*. 28 (1): 121. doi:10.3904/kjim.2013.28.1.121. PMC 3543954. PMID 23346010.
- [42]. Law RC, Carney AS, Manara AR. (1997): Long-term outcome after percutaneous dilational **tracheostomy**. *Anaesth hesia*
- [43]. Maternal and Neonatal Tetanus Elimination by 2005" (PDF). UNICEF. November 2000. Retrieved 2007-01-26.
- [44]. "Maternal and Neonatal Tetanus Elimination Initiative" (PDF). Pampers UNICEF 2010 campaign: 2.
- [45]. Mayo Clinic Staff. "Tetanus". The Mayo Clinic. Retrieved 12 June 2013.
- [46]. Montecucco C, Schiavo G. (1995): Structure and function of tetanus and botulinum toxin. *Q Rev Biophys*.
- [47]. Mudge GH. (1985): Agents affecting **volume and composition** of body fluids. In: Goodman LS, Gilman A (eds). *The Pharmacological Basis of Therapeutics*, 6th edn. New York: Macmillan
- [48]. Myers MG, Beckman CW, Vording RA, Hankins WA. (1982): Primary immunisation with tetanus and diphtheria toxoids: reaction rates and immunogenicity in older children and adults. *JAMA* ;
- [49]. Pearce JM (1996): "Notes on tetanus (lockjaw)". *Journal of Neurology, Neurosurgery, and Psychiatry*. 60 (3): 332. doi:10.1136/jnnp.60.3.332. PMC 1073859. PMID 8609513.
- [50]. Peat SJ, Potter DR, Hunter JM. (1988): The prolonged use of atracurium in a patient with tetanus. *Anaesthesia*
- [51]. Peduto VA, Pisanu GM, Piga M. (1993): Midazolam, propofol, and clonidine for sedation and **control** of autonomic dysfunction **in** severe generalized tetanus. *Minerv Anesth*
- [52]. Penner R, Neher E, Dreyer F. (1986): Intracellularly injected tetanotoxin inhibits **exocytosis in** bovine **adrenal chromaffin** cells. *Nature*.

- [53]. Philbin DM, Moss J, Atkins CW, *et al.* (1981): The use of H1 and H2histamine antagonists with morphine anaesthesia: a double blindstudy. *Anesthesiology*.
- [54]. Pinder M. (1997): **Controversies in the management of severe tetanus.** *Intensive Care Med.*
- [55]. Porter, J. D., Perkin, M. A., Corbel, M. J., Farrington, C. P., Watkins, J. T., and Begg, N. T. (1992): "Lack of early antitoxin response to tetanus booster". *Vaccine*. 10 (5): 334–6. doi:10.1016/0264-410X (92)90373-R. PMID 1574917.
- [56]. Powles AB, Ganta R. (1985): Use of vecuronium in the management of tetanus. *Anaesthesia*
- [57]. Reid PM, Brown D, Coni N, Sama A, Waters M. (1996): Tetanusimmunisation in the elderly **population.** *JAcc Emerg Med.*
- [58]. Reis E, Freire E, Alexandrino S. (1994): Tetanus in an ICU in Portugal.Epidemiology, incubation and complications. *Int J Intensive Care;*
- [59]. Roche DA, Wesley AG, Pather M, Calver A D, Hariharan D. (1986): Morphine in tetanus ± the management of sympathetic nervous system overactivity. *S Afr Med J*
- [60]. Saissy JM, Demaziere J, Vitris M, *et al.* (1992): Treatment of severetetanus by intrathecal injections of baclofen without arti@cialventilation. *Intensive Care Med*
- [61]. Schiavo G, Benfenati F, Poulain B, *et al.* (1992): Tetanus and botulinum-B neurotoxins **block neurotransmitter release** by proteolytic cleavage of synaptobrevin. *Nature*
- [62]. Seedat YK, Omar MAK, Seedat MA, Wesley A, Pather M. (1981): Renal failure in tetanus. *BMJ*.
- [63]. Sea, D. H.; Cho, D. K.; Kwon, H. C.; Kim, T. U. (2012): "A case of cephalic tetanus with unilateral ptosis and facial palsy". *Ann Rehabil Med.* 36 (1): 167–70. doi:10.5535/arm.2012.36.1.167. PMC 3309317. PMID 22506253.
- [64]. Shibuya M, Sugimoto H, Sugimoto T, Shimazu T, Uenishi M, Yoshioka T. (1989): The use of continuous spinal anesthesia in severe tetanus with autonomic disturbance. *J Trauma*
- [65]. Simonsen O. (1989): Vaccination against tetanus and diphtheria: evaluations of immunity in the Danish population, guidelinesfor vaccination and methods for control of vaccination programmers. *Dan Med J*
- [66]. Southern PA, Blaise GA. (1986): Treatment of tetanus-induced autonomic nervous **system dysfunction** with **continuous epidural blockade.** *Crit Care Med*
- [67]. Sutton DN, Tremlett MR, Woodcock T E, and Nielsen MS. (1990): Management of autonomic **dysfunction** in **severe** tetanus: the use of magnesium sulphate and clonidine. *Intensive Care Med*
- [68]. Tetanus, Collins Dictionary. com. Collins English Dictionary - Complete & Unabridged 11th Edition. Retrieved October 01, 2012
- [69]. Todar, Kenneth. "Tetanus". *Lectures in Microbiology.* University of Wisconsin, Madison - Dept. of Bacteriology.
- [70]. Trujillo MH, Castillo A, Espana J, Manzo A, and Zerpa R. (1987): Impact of intensive care management on the prognosis of tetanus. Analysis of 641 cases. *Chest*.
- [71]. Udwardia FE. (1994): Haemodynamics in severe **in** tetanus. In: UdwardiaFE, ed., *Tetanus.* New York: Oxford University Press,
- [72]. Udwardia, F.E. (1994): Pulmonary function in tetanus. In: Udwardia FE, ed., *Tetanus.* New York: Oxford University Press,
- [73]. Uganda announces elimination of Maternal and Neonatal Tetanus". Retrieved 2011-07-14.
- [74]. Ugwa, G. I.; Okolugbo, N. E. (2012): "Orogenic tetanus: case series". *West Afr J Med.* 31 (4): 277–9. PMID 23468033.
- [75]. Vandeleur, J.; Birmingham, M.; Gasse, F.; Kurian, M.; Shaw, C.; and Garnier, S. (2003): "Tetanus in developing countries: an update on the Maternal and Neonatal Tetanus Elimination Initiative". *Vaccine.* 21 (24): 3442–5. doi:10.1016/S0264-410X (03)00347-5. PMID 12850356.
- [76]. Weiss BP, Strassburg MA, and Feeley JC. (1983): Tetanus and diphtheriaimmunity in an **elderly population** in Los Angeles County. *Am Pub Health*
- [77]. Wells, C. L., and Wilkins, T. D. (1996): "Clostridia: Spore forming Anaerobic Bacilli". In Baron, S.; et al. *Baron's Medical Microbiology.* Univ of Texas Medical Branch. ISBN 0-9631172-1-1.
- [78]. Wesley AG, Hariharan D, Pather M, Roche DA. (1983): Labetalol in tetanus. The treatment of sympathetic nervous system overactivity. *Anaesthesia*
- [79]. Wilkins CA, Richter MB, Hobbs WB, Whitcomb M, Bergh N, and Carstens J. (1988): Occurrence of *Clostridium tetani* in soil and horses' *Afr Med J*

- [80]. Witlin AG, and Saibai BM. (1998): Magnesium sulfate therapy in preeclampsia and eclampsia. *Obs Gyn*
- [81]. World Health Organization (2013) "Current recommendations for treatment of tetanus during humanitarian emergencies". *Disease Control in Humanitarian Emergencies* (English). WHO? Retrieved 12 June 2013.
- [82]. Wright DK, Lalloo UG, Nayaiger S, Govender P. (1989): Autonomic nervous system dysfunction in severe tetanus: current perspectives. *Crit Care Med*.

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