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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 feat ures, and current management of tetanus.
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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 (Atkinason and wliam, 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 (Atkinason and wiliam, 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. (tkinason and wiliam, 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 (tkinason and wiliam, 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 harbour 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 clinicstaff, 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 i ntention 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 152 000 in Africa. The disease isuncommon in developed countries. In SouthAfrica 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 dramaticallyaccording to the facilities available. Trujillo and colleaguesreported a reduction in mortality from 44 to 15% after theintroduction of intensive care treatment. In developingcountries, without facilities for prolonged intensive care andventilatory support, deaths from severe tetanus exceed 50%with airway obstruction, respiratory failure, and renalfailure as prominent causes. A mortality of 10% has beensuggested as an acceptable goal in developed countries (Ahmadsyan and Salin, 1995). Modern intensive care should prevent death from acuterespiratory failure but as a result, in severe cases, autonomicdisturbance 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 respiratoryfailure.Important complications of ICU care includenosocomial infections, particularly ventilator-associated pneumonia, generalized sepsis, thromboembolism, and gastrointestinal haemorrhage. Mortality varies with patientage. In the USA, mortality in adults below 30 yr mayapproach zero, but in those over 60 yr is 52%. In Portugal, between 1986 and 1990 all age mortality varied between 32and 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 availablethis may be as low as 11% but other authors report rates close to 40%. Severe cases of tetanus generally require ICU admissionfor approximately 3±5 weeks. Recoverycan be expected to becomplete, with return to normal function. However, in one of the few follow up studies insurvivors 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 (Borgeat et al., 1994).

The light chainacts pre-synaptically to prevent neurotransmitter release from affected neurones. Released tetanospasmin sp reads to underlying tissue and binds to gangliosides GD1b a nd 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 intra-axonally and retro gradely to the cell body (Galazka and Gass, 1995). Transport occurs first in motor and later in sensory and autonomic nerves On ce in the cell body the toxin can diffuse out so affecting and entering nearby neurones. When spi nal inhibitory interneurones are affected symptoms occ ur. Further retrograde intraneural transport occurs with toxin spreading to the brain stem and midbrain. This passage includes retrograd transfer across synaptic clefts by a mechanism that is unclear.After internalization into i nhibitory neurones thedisulphide bonds linking the li ght 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 ne uro transmitter. The tetanospasmin light chain is a zinc metalloprotease, which cleaves synaptobrevin at a single point, there by preventing neurotransmitter release.The toxin has a predominant effect on inhibitory neurones, inhibiting release of glycine and gamma-aminobutyric acid (GABA) (Gyasi, 1993).

Interneurones inhibiting alpha motor neu rones are first affected and the motor neurones lose inhibitory control. Later (because of the longer path) prganglionic sympathetic neurones in the lateral horns and the parasympathetic centres 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, wh ich produces a ¯accid paralysis. However, in tetanus the disinhibitory effect on the motor neurone overwhelms any diminution of function at the neuromuscular junction.

Medullary and hypothalamic centres may also be affected. Tetanospasmin has a cortical convulsant effect in animal studies. Whether these mechanisms contribute to inter-mittent spasm and autonomic storms is unclear (Einterz 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 observedin cephalic teta nus and myopathies observed after recovery (Myers et al., 1982).

In other species, tetanus produces an illness characterized by placcid paralysis. Uncontrolled disinhibited efferent discharge from motor neurones in the cord and brainstem leads to intensemuscular rigidity and spasm, which may mimic convulsions. The reexinhibition of antagonist muscle groups is lost and agonist and antagonist muscles contract si multan eously (Mudges, 1985). Muscle spasms are intensely painful and ma y lead to fractures and tendon rupture. Muscles of the jaw, f ace, and head are often involved first because of their shorter axonalpathways. The trunk and limbs follow but peripheral muscles in the hands and feet are relatively spared. Disinhibited autonomic discharge leads to disturban ces in autonomic control,with sympathetic overactivity and excessive plasma catecholamine levels (Saissy et al., 1992).Neuronal binding of toxin is thought to be irre versible.Recovery requires the growth of newnerve terminalswhich explains the pro longed 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 maorales 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 (Udwadia,

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. Co ntamination of wounds with soil, manure, or rusty metal can lea d to tetanus. It can complicate burns, ulcers, gangrene, necr otic snake bites, middle ear infections, septic abortions, child-birth, intramuscular injections, and surgery. Injuries may be trivirutal and in up to 50% of cases the injury occur s indoors and /or is not considered serious enough to seek medical treatment (Abrutyn *et a l*., 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 dif®culty opening the mouth are often earl y symptoms. Masseter spasm causes trismus or`lockjaw'.

Spasm progressively extends to the facial muscles causin gthe typical facial expression, `risus sardonicus', and mu scles of swallowing causing dysphagia (Seo *et al.,* 2012) . Rigidity of theneck muscles leads to retraction of the head. Truncal rigiditymay lead to opisthotonus an d respiratorydifficulty withdecreased chest wall complian ce. In addition to increased muscle tone, there are episodicmuscular spa sms. These tonic contractions have a convul-sion like appear ance affecting agonist and antagonist muscle groups together. They may be spontaneous ortriggered by touch, visual, auditory, or emotional stimuli (Ugwa and Okolugbo, 2012).

Spasms may vary in severity and frequenc y but may bestrong enough to cause fractures and tendon a vulsions.

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 who lebody (James, 1998). The differential diagnosis include 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 lim ited area of the body. Mortality is greatly reduced.

Anexception to this is cephalic tetanus when lo calized tetanus from a head wound affects the cranial nerves; par alysis rather than spasm predominates at presentation, but progression to generalized tetanus is common and mortali tyis high. Tetanus neona torum 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 ash ort history of failure to feed, vomiting, and `convulsion s'.Seizures, meningitis, and sepsis are differential diagn oses (Penner *et al*., 1986). Spasms are generalizedand mortality is high.Poor umbilical hygiene is the cause of the disease but it isenti rely preventable by maternal vaccination, even duringpr egnancy. Before the intro duction of artificial ventilation, manypatients with severe tetanus died from acute respiratoryfailure. With the development of intensive care it becameapparent that se vere tetanus was associated with markedautonomic insta bility. The sympathetic nervous systemis most prominentl y affected. Clinically, increased sympathetic tone causes persistent tachycardia and hypertensiong (Gregorakos *et al*., 1990) .

Marked vasoconstriction and pyrexia are seen. Basal plasmacatecholamine levels are raised.`Autono mic storms'occur with marked cardiovascular in stability. Severe hyper-tension and tachycardia may alter nate with profound hypotension, bradycardia, or recurrent cardiac arrest. These alterations are a result of, predominantly, r apid alterations in systemic vascular resistance rather than cardiac filling or performance. During these `storms'pl asma catecholamine levels are raised up to 10-fold, to similar levels to those seen in phaeochromocytoma. Norepinephrine is affected more than epinephrine. Neuronal hyperactivity rather thanadrenal medullaryhyperactivity appears to predominate.

In addition to the cardiovascular system, other autonomicef fects include profuse salivation and increased bronchial secretions. Gastric stasis, ileus, diarrhoea, and high outp utrenal failure may all be related to autonomic disturbanc e.The involvement of the sympathetic nervous system i sestablished (Black *et al*., 2010). The role of the parasympathetic system is lessclear. Tetan us has been reported to induce lesions in thevagal nu clei, while locally applied toxin may lead toexcess ive vagal activity. Hypotension, bradycardia, andasyst ole may arise from increased vagal tone and activ-ity.

Altered cardiovascular physiology

There have been relatively few studies of th e effects oftetanus on the cardiovascular system. One pr oblem is thatthe haemodynamic effects of both com plications andtreatment may mask the true effects of th e disease itself.Udwadiastudied 27 patients with Abl ett gradeIII/IVdisease who were stable and not on dru gs likely toalter haemodynamics (Udwadia, 1994). Nineteen had uncomplicated and eightcomplicated tetanus (with pneumonia, ARDS, sepsis). Hisextensive studies examined cardiovascular features of thedisease: changes during poorly controlled spasms, during intense relaxation, during recovery, and the effect of uidloadi ng in tetanus compared with the effect in healthy volunteers. He also studied patients during periods ofconsiderable cardiovascular instabilit y because of autonomic storms.Severe uncomplicated teta nus was marked by a hyperkinetic circulation. Tachyca rdiawas universal with hypertension, raisedstroke volu me index, and raised cardiacindex. Other findings were low normal systemic vascularresistance and nor mal 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 duringp oor relaxation and increased spasm activity. The haemodyn amic abnormalities became less marked during periods of full muscular relaxation but measurements only graduallyreturned to normal ranges during recovery from th e disease (Wilkins *et al*., 1988).

A uid challenge of 2000 ml increased left heart fillingpressures and cardiac index but these effect s were verytransient. During autonomic storms with mar ked cardiovascular instability, patients uctuated from a hy per stimulated state of hypertension (arterial pressure up to 220/120 mmHg) and tachycardia (heart rate 130±190 beats min) to oneof profounddepression with hypotension (as lo w as 70/30mm Hg), bradycardia (50±90 beats min) and a f all in CVP(reducing from 6 to 1 cm H2O). Invasive mon itoring showedthese changes to be a result of a rapid, mark ed alteration insystemic vascular resistance index (SVRI), fallingfrom2300 to less tha n 1000 dynes s cm. There was littlechange in cardiac i ndex or filling pressures (CDC, 2012). Patients withgrade IV disease were less likely tha n those with less severe disease to raise cardiac index or cardiacwork indices inresponse to ¯uid load or during alterations in va scularresistance seen during autonomic storms. One patien t withsevere sustained hypertension was found to have ma ssivelyraised vascular resistance with SVRI greater t han 4500dynes s. In complicated tetanus, measurements varied widely with no consistent findings (Wejss *et al*., 1983).

The hyperkinetic circulation is largely b ecause of increased basal sympathetic activity and muscle activity, with a lesser effect from raised core temperature. The low-normal SVRI is because of extensive vasod ilation in meta bolically active muscles. As oxygen extraction ratiodoes not alter in tetanus, the increased demand must bedelivered by increased blood flow (South orn and Blaise, 1986). Poor spasm control exaggerates these effects. Fluid loading causes only atransie nt rise in filling pressures, cardiac index, and LVSWI, beca use the circulation is widely vasodilated and hence is ahigh capacitance system in comparison to normal control s.In uncomplicated tetanus, the cardiovascular system, ther efore, mimics that of the normalpatient undergoing intense exercise (Monteculco and Shiqllo, 1995). Grade IV patients appear less able to increa secardiac performance and, therefore, are more susceptible to pro found hypot en sion and shock during acute vasodilatory storms. The me chanism is unclear but may relate to sudden withdrawal of catecholamine stimulation or a direct a ction of tetanus toxin on the myocardium. Altered m yo cardialfunction may be because of persistently raised ca techola- 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. Pha ryngeal and laryngeal spasms predict respiratory failure or life- threat ening airway obstruction. Poor cough from rigidity, spasms, and sedation leads to atelectasis and the risk of pneumonia ishigh (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/perf usionmismatching is also common (Bucanan *et al*., 1979). Consequently, hypoxia is auni form finding in moderate or severe tetanus even when thech est is radiologically clear. Breathing air, oxygen tensions of between 5.3±6.7 kPa are common. In artificial lyventilated patients, increased A-agradients persist. Oxygen delivery and utilization may be compromisedeven without super-

added lung patho logy. Acute respiratorydistress syndrome may occur as a specific complication oftetanus. Minute ventilation may b e altered by a variety ofcauses. Hyperventilation may occur because of fear,autonomic disturbance, or alteration in brainstem function.Hypocarbia (PCO_2 4.0±4. 6 kPa) is usual in mild to moderatedisease (Curtir *et al*., 1973). Hyperventilation `storms' may lead to sever e hypocarbia (PCO_2 <3.3 kPa). In severe disease, hypov e ntilation from prolonged spasms and apnoea occurs. Sedation,exhaustion and altered brainstem function may al so lead torespiratory failure. Respiratory drive may be defciientleading to recurrent life-threatening apnoeic periods (UNICEF, 2010).

Altered renal physiology

In mild tetanus, renal function is preserve d. In severedisease reduced glomerular ®ltration rate and i mpaired renaltubularfunction are frequent. Contributory causes of renal failure include dehydration, sepsis, rhabdo myo losis, and alterations in renal blood flow secondary to catecholamine surgeRen al failure may be oliguric or polyuric.Clinically im portant renal impairment is associated withautonomic i nstability and histology is normal or showsacute tubula r necrosis (Kanarek *et al*., 1973). ManagementTreatment strategiesinvolve three managemen t principles:

organisms present in the body should be destroye d toprevent further toxin release; toxin present in the body, outside the CNS should be neutralized; andthe effects oftoxin already in the CNS should be minimized.Neutral ization of unbound toxinHuman tetanus immune globulin 3±6000 units is giveni.m (Pearce, 1996).Removal of the source of infectionWhere present, obvious wounds should be surgicallydebrided. Penicillin has been widely used for many years but is a GABA antagonist and associated with conv lsions. Metronidazole is probably the antibiotic of choice.

It is safe and comparative studies with penicillin suggest at least as good results. Erythromycin, tetracyc line, chloramphenicol, and clindamycin are all acceptedas alternatives.

Control of rigidity and spasms

Avoidance of unnecessary stimulation is mandat ory, but themainstay of treatment is sedation with a ben zodiazepine.Benzodiazepines augment GABA agonism, b y inhibiting an endogenous inhibitor at the GABAA receptor. Diaze pammay be given by various routes, is cheap and widely used,but long acting metabolites (oxazepam and desmet hyldiazepam) may lead to cumulation and prolonged coma. Dosesas high as 100 mg h have been reported. Midazolam has been used with less apparent cumulation (Farrar *et al*.,2000). Additionalsedation may be provided by antico nvulsants, particularly pheno barbitone (which further enhances GABAergic activity) and phenothiazines,usually chlorpromazine. Propofol has been used for sedation with rapid reco very on stopping the infusion. When sedation alone is inadequate, neuromuscula r blocking agents and intermittent positive pressure venti - lation may be required for a prolonged period. Traditionall y, the long acting agent pancuronium has been use d. However, pancuronium inhibits catechol amine re-uptakeand could worsenautonomic instability in severe cases (Wells and Wikin, 1996).

There have been isolated reports of worsening hy pertensionand tachycardia associated with its use. But Dancereported no difference in complications in those trea ted withpancuronium compared with other neuromuscular blockingdrugs. Vecuroniumis free from cardiovascula r sideeffects and histamine release but is relative ly shortacting. The use of an atracurium infusion in tetanusfor 71 days has been reported. In this patient, with n ormalrenal andhepatic function, there was no cumulati on oflaudanosine, the epileptogenic metabolite of atrac urium.Longeracting agentsare preferableas they lend thems elvesto administration by intermittent bolus rather than req uiringinfusion (Kelty et al., 1967). Prolonged use of aminosteroid neuro muscular blocking agents(vecuronium, pancuronium, rocuronium, and pancuronium), particularlyby infusion, has bee nassociated with critical illness neuropathy and myopathy, but thishas not been reported in tetanus. Of the newe ragents,pipecuronium and rocuronium are long acting `clean' agents but are expensive(Uganda,2011). Individual dr ugs havenot been compared in randomized trials.

The use of dantrolene to controlrefractory spasms hasbe en reported in one case. Neuromuscular blocking drugs were unnecessary After its administration, paroxysmalspasms stopped and the patient's condition i mproved.Sedation with propofol has allowed control of sp asms andrigidity without the use of neuromuscular blocki ng drugs. Examination of the EMG and neuromuscular function during propofol boluses. showed an 80% reduction in EMG activity without alteration of function at theneur o muscular junction. However, drug levels were close rto anaesthetic than sedativeconcentrations and mechanical ventilation would be required.Intrathecalbaclofen

(a GABAB agonist) has beenreported in several s mall 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 factorsinclude inability to swallow, autono mic induced alterationsin gastrointestinal function, increased metabolic rate from pyrexia and muscular activity and prolonged critical illne ss.

Nutrition should, therefore,be established as early aspossible. Enteral nutrition is associatedwith a l owerincidence of complications and is cheaper than par enteralnutrition. Percutaneous gastrostomy may avoid the c omplications associated with nasogastric tube feeding (Prilbin et al., 1981), and iseasily performed on the intensivecare unit under sedation.Infective complications of prolonged critical illnessincluding ventilator-associated pneumonia are common intetanus (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, (Schiovo *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 Organisation 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 (Shyaibuya *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 (Hariparsad *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.Tetanusvaccine has been avail able since 1923. Routine vaccination began in the UK in 1961. Vaccina tion is started at 2 months of age with three injections performed at mont hly 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 immu- noglobulin (Adelve *et al*., 2012). This may be impaired in the presence of maternal HIV infection. Immunity is not life long. 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 recommen dations 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. Simil ar 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 comman disease in the Ethiopia and isentirely preventable by vaccin ation. Itremains 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 necess ary but
most treatment is based on limited evidence. Major
therapeutic challenges lie in the control of muscular rigi d
ityand spasms, the treatment of autonomic disturbance and t heprevention of complications associated with prolo ngedcritical illness. Return to normal function can be e xpected in those who survive.

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