8.6.23 Tetanus 1109

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programmes, in high-income coun- tries tetanus is rare but in countries with less developed vaccination schemes, tetanus continues to be a major problem. In 1988 the World Health Organization launched a major ini- tiative to eliminate neonatal tetanus, prompted by an estimated 800 000 neonatal deaths a year due to the disease. The initiative mainly employed a policy of maternal vaccination, thus maternal tetanus elimination was added to its aims in 1995 and a more inclu- sive vaccination strategy was employed. To date 37 out of 59 coun- tries targeted have achieved this goal. Aetiology, genetics, pathogenesis, and pathology Clostridium tetani is a Gram-positive spore-forming anaerobic ba- cillus able to infect and cause disease in both humans and animals. The bacterium is highly sensitive to oxygen but can survive in the environment as an extremely resistant metabolically inactive spore. Under suitable anaerobic conditions the spore germinates and the bacteria multiply, releasing a highly potent neurotoxin, tetanus toxin, which is responsible for the clinical features of tetanus. Aetiology Spores of C. tetani can be isolated from the environment throughout the world, particularly in soil, but are also found in human and animal faeces and even street dust. Germinant receptors on the spores recognize specific nutrients and mediate germination of the spores, an irreversible process that involves the loss of the peptido-glycan cortex and rehydration of the core with corresponding loss of resistant properties. An obligate anaerobe, C. tetani multiplies in low-oxygen tensions. During the exponential phase of vegetative growth tetanus toxin is released. Structurally similar to botulinum toxins, tetanus toxin is one of the most potent toxins known, with a median human lethal dose (LD 50) of only 2.5 ng/kg. Genetics and pathophysiology C. tetani was first sequenced in 2003 but few strains have been sequenced and, unlike C. botulinum, there appears to be much less genetic diversity. Tetanus toxin (also known as tetanospasmin or tet- anus neurotoxin) is a 150 kDa protein encoded on a plasmid. Non- pathogenic strains of C. tetani exist which do not produce tetanus toxin. Plasmid identification has been used clinically to support the diagnosis of tetanus following isolation of C. tetani. Amino acid sequences of this toxin appear highly-conserved in the five plas- mids sequenced to date. The toxin consists of a heavy and a light chain joined by a disulphide bond. The heavy chain mediates toxin entry into motor nerves, either locally or after circulation in the

 bloodstream. Its motor specificity is due to binding specific domains within the motor nerve membrane. The toxin is transported retro- gradely in the motor neurons to the central nervous system unlike the structurally similar botulinum toxins which remain in the per- iphery, hence the different clinical effects. The tetanus toxin enters the presynaptic neuron, and the light chain is translocated into the cytosol where it acts as a metalloprotease cleaving the SNARE pro- tein, vesicle associated monophosphate 2 (VAMP2), necessary for presynaptic vesicle docking and neurotransmitter release. This effect is limited to presynaptic inhibitory neurons, reducing central inhib- ition of motor neurons, and resulting in the increased muscle tone and spasms characteristic of tetanus. Epidemiology In countries with good immunization programmes and high levels of hygiene, tetanus has largely been eliminated, but in poorer regions tetanus remains a common cause of morbidity and mortality. The World Health Organization’s maternal and neonatal tetanus elim- ination initiative has made a significant impact on the number of cases of tetanus affecting women and newborn infants, but still an estimated 49 000 infants continue to die every year from the disease. The burden in older children and adults is unknown but is likely to be substantial as the major focus of preventative programmes has been immunizing pregnant women and infants, leaving other age- groups vulnerable to infection. Tetanus is caused by wound contamination with C. tetani. In neo- natal tetanus the entry site is usually the umbilical stump although traditional practices such as ear-piercing have also been

linked. In children and older infection often enters through very minor cuts and abrasions. However deeper wounds are often associated with worse prognosis. Global incidence of tetanus In 1988 an estimated annual total of 787 000 neonatal deaths due to tetanus prompted the World Health Assembly to call for the elimination of neonatal tetanus by 1995. Slow progress re- sulted in this goal being postponed several times. Nevertheless, remarkable progress has been made and 37 out of the 59 targeted countries have now reached this target: China eliminating the dis- ease in 2012 and India in June 2015 (see map, Fig. 8.6.23.1). The Fig. 8.6.23.1 MAP of maternal and neonatal tetanus (MNT) elimination. © World Health Organization 2017.

8.6.23 Tetanus 1111 proportion of global neonatal deaths due to tetanus has fallen from 14% in 1993 to 1.79% in 2008. Three main strategies have been employed to attain these results: immunization, improved sur- veillance, and improved birth hygiene. Although most effort has focused on increasing immunization coverage, improved birth hy- giene has also an important effect, and indeed much of the success of China's elimination campaign has been attributed to achieving a vast increase in numbers of women delivering in healthcare facil- ities. It should however be noted that, as elimination is defined as less than one case per 1000 live births in every district of a country, it is still possible for neonatal cases to be seen after 'elimination' has occurred. The true worldwide incidence of tetanus occurring in age- groups beyond the neonatal period is unknown as most countries do not collect accurate data. However, the current focus on infant immunization schedules means that although infants and children are often protected against tetanus, lack of subsequent booster dosing means significant numbers of older children and adults are unprotected. In some countries males may receive booster doses with military service, but generally men are more vulnerable as they are not covered by maternal and neonatal tetanus elimin- ation schemes. Outbreaks of tetanus after natural disasters such as the Haiti earthquake in 2010 and Tsunami of 2005 have been reported. In such situations contamination of wounds in unvac- cinated individuals is compounded by poor access to healthcare in disaster areas. Risk groups in high-income countries In developed countries tetanus is rare but has not and can never be eradicated. Elderly people born before routine national immuniza- tion are particularly vulnerable. People who inject drugs are also a high-risk group due to the increased chance of sustaining a contam- inated wound. In addition to poor hygiene, mixing or cutting drugs may increase the chance of an anaerobic focus of infection. Heroin may be cut with quinine, which is acidic and leads to local tissue necrosis and has been reported to be associated with particularly severe cases of tetanus. Clinical features Skeletal muscle spasm is the characteristic feature of tetanus, par- ticularly the facial muscles (causing 'lockjaw' and 'risus sardonicus', Fig. 8.6.23.2) and extensor spinae (opisthotonus, Fig. 8.6.23.3). Severe spasms can impede respiration which, if not controlled, is usually the primary cause of death in tetanus. Dysfunction of the autonomic nervous system also occurs and is clinically apparent as fluctuating blood pressure and variable heart rate. Presentation Symptoms of tetanus evolve gradually over a period of days and weeks or, in very severe cases, hours. The time course of tetanus is divided into specific periods. The incubation period is the period from inoculation to the first symptom (therefore may be un- known if no entry site is found) and is usually around 7–14 days (slightly shorter in neonates and inoculation is assumed to occur at birth, thus is equal to age at first symptom). The period of onset is the period from the first symptom to the first spasm and is usu- ally 2–5 days. Both these periods can be shorter in severe disease which tends to progress more rapidly. The initial symptoms on admission by 2422 patients (excluding neonates) admitted to the Hospital for Tropical Diseases Ho Chi Minh City are shown in Table 8.6.23.1. As tetanus develops muscle tone gradually increases until spasms

occur. In the face trismus (‘lockjaw’) is common and the characteristic risus sardonicus is seen due to spasm of facial muscles. Involvement of the erector spinae group of muscles re- sults in opisthotonus. Sometimes tetanus is confined to a local Fig. 8.6.23.2 Risus sardonicus. Courtesy of the late Professor Sornchai Looareesuwan. Fig. 8.6.23.3 Opisthotonus. Copyright D. A. Warrell.

section 8 Infectious diseases 1112 group of muscles producing only local muscle spasm. If this occurs in the head, it is termed ‘cephalic tetanus’ (Fig. 8.6.23.4). Unlike local tetanus elsewhere, this form is potentially dan- gerous if laryngeal muscle spasms cause airway obstruction leading to asphyxiation. This occurs commonly in generalized tetanus and is a life-threatening emergency. Respiratory tract secretions are increased in tetanus due, perhaps, to a combin- ation of autonomic nervous system stimulation and pharyngeal and laryngeal muscle spasms that prevent swallowing. Spasm and hypertonus of the respiratory muscles is a serious occurrence that, without artificial respiratory support, is a common cause of death in tetanus. Neonatal tetanus has a similar clinical picture (Fig. 8.6.23.5), with infants usually presenting with difficulty feeding followed by frank spasms. The World Health Organization (WHO) case- definition of neonatal tetanus is ‘an illness occurring in a child who has the normal ability to suck and cry in the first two days of life but who loses this ability between days 3 and 28 of life and becomes rigid and has spasms’. Natural history In centres with facilities to control muscle spasm and provide mechanical ventilation, autonomic system effects are responsible for a second group of major complications. The syndrome of auto- nomic instability usually takes the form of labile hypertension and tachycardia associated with increased circulating catecholamines. However, it may manifest as more sustained hypertension and tachycardia or, less commonly but more seriously, with periods of hypotension and bradyarrythmias. It is associated with acute renal failure and acute respiratory distress syndrome (ARDS). More recently, facilities for ventilation and improved neonatal critical care monitoring has meant that autonomic nervous system dysfunction has also been described in neonates. Although there are fewer published descriptions, it is likely this follows a similar course to that in adults. Patients with severe tetanus typically re- quire long periods (several weeks) of mechanical ventilation and long periods in hospital. As a consequence, secondary hospital- acquired infection is common, further impacting on morbidity and mortality. A variety of scores have been used to describe clinical severity and prognosis in tetanus. The Ablett score is the most commonly used severity score and is shown in Table 8.6.23.2. Scores used by Philips and Patel have been used to predict severity, but the more Table 8.6.23.1 Features on admission at hospital for tropical diseases Symptom Percentage of admissions Trismus 98 Dysphagia 83 Back pain 94 Muscle stiffness 95 Muscle spasms 46 Difficulty breathing 7 Fever 8 Fig. 8.6.23.4 Cephalic tetanus. Courtesy of Dr Pedro Pardal, Belém, Brazil. (a) (b) Fig. 8.6.23.5 Neonatal tetanus. Copyright D. A. Warrell.

8.6.23 Tetanus 1113 recent Tetanus Severity Score showed superior predictive value in Vietnamese patients. These scores are all simple to use and are cal- culated from baseline data and features of the history. In neonatal tetanus, birth weight and age at presentation are the most important predictors of outcome. Diagnosis Tetanus is a clinical diagnosis. The presence of generalized muscle rigidity and trismus are characteristic of tetanus. In neonatal tet- anus the ability to suck and cry before the onset of symptoms is an important feature differentiating it from other conditions affecting feeding. In most cases C. tetani is not isolated from wounds and its cul- ture is not required for diagnosis. In vaccinated individuals, the per- sistent presence of toxigenic C. tetani has been described without associated clinical disease. Nevertheless, in unvaccinated

popula- tions, culture of C. tetani from a wound is supportive of a diagnosis of tetanus. More recently polymerase chain reaction (PCR) has been used to detect toxin from cultures of C. tetani, confirming that the isolated bacteria is of a pathogenic species. Although tetanus has occasionally been reported in the presence of ‘protective’ levels of antibody, serum concentrations of antibody greater than 0.1 IU/ml measured by enzyme-linked immuno- sorbent assay (ELISA) are usually taken to exclude a diagnosis of tetanus. Differential diagnosis The differential diagnosis includes local causes of trismus and pharyngeal muscular spasms such as oropharyngeal infections, tumours, or temporomandibular joint pathology. Headaches and nuchal rigidity occur in meningitis, but this occurs without generalized muscle tone abnormality and conscious level may be reduced. Rabies, like tetanus, may result from an infected animal bite, but its incubation period is usually much longer. Hydrophobic spasms can resemble tetanic spasms, particularly in the case of cephalic tetanus. Strychnine is a competitive antagonist of the inhibitory neuro- transmitter glycine that causes hyperreflexia and severe muscle spasms leading to convulsions. It may be very hard to distinguish this from tetanus, but the diagnosis may be suspected by a history of ingestion and confirmed by toxicological tests of urine, serum, or gastric contents. Dystonic reactions to antidopaminergic drugs may cause muscle tone abnormality but may also be associated with ab- normal eye or tongue movements which do not occur in tetanus. Anticholinergics and withdrawal of the precipitating drug can eliminate these. In children and neonates, hypoglycaemia, hypocalcaemia, and meningoencephalis can present with some of the features of tet- anus, however a more careful history and clinical examination should differentiate these. Treatment The three principals of management are removal of toxin, spasm control, and control of autonomic disturbance. Wounds should be cleaned adequately and, if necessary surgi- cally debrided. Antibiotics are given to prevent any further bac- terial multiplication—either penicillin or metronidazole. In a series of 45 clinical isolates of toxin producing C. tetani, all were sensi- tive to penicillin and metronidazole. An open, nonrandomized controlled trial of 173 patients by Ahmadsyah showed reduced mortality in those treated with metronidazole compared to peni- cillin, however a subsequent randomized controlled trial testing two penicillin preparations against metronidazole in 161 patients showed no difference. Penicillin is a noncompetitive inhibitor of GABA-A receptors and in large doses is known to cause seizures and thus could potentiate the effects of tetanus toxin. In view of this and trial evidence, metronidazole is usually the recommended antibiotic. Antitoxin should be given to neutralize any unbound tetanus toxin and, if given early enough, may limit the severity of tetanus. Recent debate has continued about appropriate dose and route of antitoxin. Currently doses of 3000–6000 IU of human tetanus immunoglobulin (HIG) intramuscularly are recommended, or 500–1000 IU/kg equine antitoxin. However, these doses were based on observational studies from the 1960s and some recent recommendations suggest lower doses are safe. The use of equine antitoxin is associated with the risk of anaphylactic reactions or serum sickness, although with modern preparations these are less common. Data from some randomized controlled trials and case series suggest that intrathecal administration of antitoxin may confer further benefit; however, many of these trials are open to bias and the results of two meta-analyses give conflicting results. As tetanus tends to occur in the world’s poorest regions, there is usually a limited range of treatment options. Chlorpromazine, Table 8.6.23.2 Ablett score for tetanus Grade Clinical features I • Mild to moderate trismus (little or no dysphagia) • General spasticity • No respiratory embarrassment • No spasms II • Moderate trismus • Well-marked rigidity • Mild to moderate but short spasms • Moderate respiratory embarrassment with an increased respiratory rate greater than 30 breaths/min • Mild dysphagia III • Severe trismus • Generalized spasticity • Reflex prolonged spasms • Increased respiratory rate

greater than 40 breaths/min • Apnoeic spells • Severe dysphagia • Tachycardia greater than 120 beats/min IV • Grade III and violent autonomic disturbances involving the cardiovascular system • Severe hypertension and tachycardia alternating with relative hypotension and bradycardia, either of which may be persistent

section 8 Infectious diseases 1114 phenobarbitone, or diazepam are the most commonly available drugs. Many areas lack facilities for mechanical ventilation so muscle-relaxant effects must be titrated against respiratory suppres- sion. In most countries benzodiazepines are the first line agents. Diazepam is often the most common choice due to its widespread availability and low cost, but other preparations such as midazolam are more suited to long-term administration. High dose regimens may be required with doses up to 100 mg/hr diazepam reported. In 1966 Hendrickse reported one of the few randomized trials com- paring diazepam, chlorpromazine and phenobarbitone with chlor- promazine and phenobarbitone alone in 104 neonates and 45 older children. Mortality in the neonates was identical but in the older children the death rate was almost halved in those treated with diazepam, although numbers were too small to reach statistical significance. The use of many other muscle relaxants in tetanus has been de- scribed in case reports. Intrathecal baclofen has been the subject of over 30 case reports. As a GABA-B agonist it has been reported to control spasms in tetanus. However, it requires intrathecal adminis- tration (usually via continuous infusion) and is also associated with respiratory depression, therefore it cannot be advised in settings without mechanical ventilation. In a series of 22 patients treated in Portugal, intrathecal baclofen was successful in controlling spasms in all but one patient. However, 19 patients required mechanical ventilation and one patient suffered meningitis due to infection of the spinal catheter. Magnesium sulphate has been used to treat both spasms and autonomic dysfunction in tetanus. It is a calcium antagonist causing presynaptic neuromuscular blockade as well as vasodila- tation and reduced catecholamine release. In a case series of 40 patients in Sri Lanka, early use of magnesium sulphate was asso- ciated with the successful avoidance of mechanical ventilation in 57% of patients. Three randomized controlled trials of magnesium sulphate in tetanus have been performed subsequently. In two trials, comparing magnesium with diazepam in a total of 78 pa- tients with moderate and severe tetanus, improved spasm control was found in magnesium-treated patients. In one of these trials, magnesium sulphate was associated with less respiratory depres- sion than diazepam, but mechanical ventilation was still required in 4/18 patients and mortality rates were high (9/18 in magne- sium vs. 10/18 with diazepam). One large double-blind random- ized controlled trial compared adjunctive magnesium sulphate in 197 patients with severe tetanus and found that although magne- sium did not reduce the requirement for mechanical ventilation, requirement for other muscle relaxants was reduced. This trial also looked at the effects of magnesium on autonomic dysfunction and found improved cardiovascular stability with reduced levels of circulating catecholamines. In this trial blinding procedures meant that doses could not be titrated against clinical effect and it is possible that lower concentrations may have been achieved. In contrast, trials with less blinding may have achieved higher serum concentrations of magnesium. Control of autonomic dysfunction in tetanus is notoriously dif- ficult due to often rapid fluctuations in blood pressure. For this reason, short-acting calcium antagonists and β-blockers are pre- ferred but often episodes of hypotension occur. Careful fluid man- agement is necessary to optimize intravascular volume and cardiac output in this situation. Vasopressor and inotrope infusions may also be required. As tetanus does not confer natural immunity it is necessary to fully vaccinate patients with a primary course of tetanus toxoid to confer protection in future. Prevention Tetanus is prevented by immunization and good hygiene. As tetanus is a noncommunicable disease, there is no herd immunity effect and unvaccinated

individuals are equally vulnerable irrespective of the community around them. Tetanus vaccines are made from tetanus toxoid adsorbed onto aluminium to increase immunogen- icity. They are available as single dose tetanus toxoid or combined with diphtheria toxoid, either high dose diphtheria toxoid (DT) for use in children under 7 years, or low dose diphtheria toxoid (dT) for use in older people. Combinations of DT or dT are available with whole cell or acellular pertussis and Haemophilus influenza B, hepatitis B, and polio. Tetanus toxoid alone or in combination is safe and effective with infrequent and mild adverse effects. It can be used in pregnancy and immunodeficiency; however, in these cases immune responses may be diminished. Current WHO recommendations are for six-dose schedules: a pri- mary course of three doses in infancy followed by boosters between 4 and 7 years and 12 and 15 years and in adult life (e.g. first preg- nancy). Some 86% of the world's children now receive a three-dose primary course of diptheria, tetanus toxoid, and pertussis (DTP3). However, it is likely that the primary vaccination series produces protective antibody for 6–10 years, but without boosting, individ- uals are vulnerable to tetanus. In the United Kingdom a total of five doses is recommended, unless others are deemed necessary after sustaining tetanus-prone wounds. In nonimmunized adolescents and adults or those with un- known/incomplete vaccination history, a three-dose primary course is recommended. The first two doses should be given at least four weeks apart and the third at least 6 months after the second. In these people a total of five doses is expected to confer lifelong protection. This schedule is also recommended for pregnant women with the first two doses given in pregnancy (usually dT). The time course of antibody response to vaccination means that in unimmunized individuals a single tetanus dose will not protect against tetanus in those sustaining tetanus-prone wounds and additional protection is given by giving antitoxin (see Table 8.6.23.3). People already vaccinated may have a more rapid antibody response. In one study booster doses in previ- ously vaccinated people, protective levels were achieved within 2 days. However, in high-risk injuries, antitoxin is still re- commended. As tetanus vaccine is an inactivated vaccine, the coadministration of vaccine and immunoglobulin is theoretic- ally possible. In vivo studies are limited to previously vaccinated populations and while there may be some short-term attenuation of immune response, it appears that long-term immunity in al- ready immune individuals is not affected. Rapid diagnostic tests are now available for the detection protective levels of antibodies and have been found useful to identify people requiring tetanus boosters in emergency departments.

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