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Clostridium tetani as a pathogenic organism

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Abstract

Clostridium tetani, the etiologic agent of tetanus, produces a toxin that causes spastic paralysis in humans and other vertebrates. *Clostridium tetani* releases two toxins tetanolysin and tetanospasmin at the wound site. The tetanolysin is a hemolysin, which is not known to contribute toward tetanus symptoms; however the tatanospasmin affects the central nervous. The autonomic nervous system is also affected by the tetanus toxin, causing cardiac arrhythmias, severe sweating, and labile blood pressure. This is extremely difficult to manage and is a common cause of sudden death. As a consequence catecholamine levels are high and this may contribute to the high incidence of acute renal dysfunction seen in severe tetanus. *Clostridium tetani* is mostly acquiring resistance to antibiotics because of its lower outer membrane permeability. Treatment of *Clostridium tetani* causing infections or disease becomes a challenge for biological world. This bacterium shows resistance against many antibiotics due to mutations in their genes and due to some modifying enzymes. Treatment goals include interrupting the production of toxin, neutralizating the unbound toxin, controlling muscle spasms, managing dysautonomia and appropriate supportive management. Specific therapy includes intramuscular administration of tetanus immunoglobulin to neutralize circulating toxin before it binds to neuronal cell membranes. The disease can be prevented by immunization with tetanal toxoid and appropriate wound care.

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Introduction

Clostridium tetani is Gram-positive, rod shaped, motile, anaerobic, pathogenic organism (Hajra *et al*., 2015). The size of *Clostridium tetani* is 4.0 µm in length and 0.4µm in width while in some literature the size of *Clostridium tetani* is 2.5 µm in length (Hajra *et al*., 2015).The *Clostridium tetani*found in single and in pair form. It is spores forming bacteria of the genus Clostridium (Kenneth,2004). *Clostridium tetani* spores resemble tennis rackets or drumsticks and the spores are extremely hard (Hajra *et al*., 2015). Due to this property the heat and most antiseptics could not disturb its chemical structure of the organism's (Farrar *et al*., 2000).

Clostridium tetani habitat

Clostridium tetani is a cosmopolitan found almost everywhere but its natural habitat is soil, dust, and intestinal tracts of various animals. The bacteria remain inactive for a long time unless they enter in a suitable place (Hajra *et al*., 2015).

Pathogenesis of Clostridium tetani

Under anaerobic conditions the tetanus bacillus secretes two toxins: tetanospasmin and tetanolysin (Pinder, 1997). Tetanolysin is capable of locally damaging tissue while (Pinder, 1997) tetanospasmin leads to the clinical syndrome of tetanus. This toxin may constitute more than 5% of the weight of the organism (Mellanby, 1968). It is a two-chain polypeptide of 150 000 Da which is initially inactive (Wright and Lalloo, 1989). 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 (Wright and Lalloo, 1989). The carboxyl terminus of the heavy chain binds to neural membrane and the amino terminus facilitates cell entry (Wright and Lalloo, 1989). The light chain acts pre-synaptically to prevent neurotransmitter release from affected neurones (Erdmann *et al*., 1975). Released tetanospasmin spreads to underlying tissue and binds to gangliosides GD1b and GT1b on the membranes of local nerve terminals (Erdmann *et al*., 1975). If toxin load is high, some may enter the bloodstream from where it diffuses to bind to nerve terminals throughout the body. The toxin is then internalized and transported intra-axonally and retrogradely (Erdmann *et al*., 1975) to the cell body (Kerr, 1979). Transport occurs first in motor (Bevan and Wendon, 1984), and later in sensory and autonomic nerves (Wellhoner, 1979). Once in the cell body the toxin can diffuse out so affecting and entering nearby neurones. When spinal inhibitory interneurones are affected symptoms occur (Bleck, 1987). Further retrograde intraneural transport occurs with toxin spreading to the brainstem and midbrain. This passage includes retrograde transfer across synaptic clefts by a mechanism that is unclear (Bleck, 1987). Only little is known about protein secretory systems in Clostridia. Until now, it has not been understood how the tetanus toxin, which lacks a typical N-terminal signal peptide, is exported. Because protein secretion is an important part in establishing a pathogenic phenotype, it is worth having a closer look at secretory systems and secreted proteins of *C. tetani* (Mukherjee *et al*., 2002).

Clostridium tetaniaffect in humans

Tetanus disease is one of the most dramatic and globally prevalent diseases of humans and has been reported for over 24 centuries. The manifestation of the disease, spastic paralysis, is caused by the second most poisonous substance known, the tetanus toxin, with a human lethal dose of approx 1 ng /kg (Bruggemann *et al*., 2003). However the hundreds of thousand incidences of *Clostridium tetani*-mediated infection are still being reported in some developing countries of Africa and Asia including Pakistan (Nazar and Hajra, 2015). A World Health Organization (WHO) survey has shown that tetanus in developing countries caused about 200,000 deaths per year (Nazar and Hajra, 2015).In the USA, mortality in adults below 30 years may approach zero, but in those over 60 years is 52% (Cook *et al*., 2001).

Neonatal tetanus

Neonatal tetanus in particular has been chosen as the focus of a global prevention project (Lam *et al*., 2014).

At the end of the 1980s, high rates of disease, with correspondingly high mortality, were seen as unacceptable given the availability of a cheap and effective prevention method maternal vaccination(Lam *et al.*, 2014). The World Health Organization and its partners the United Nations Children's Fund and United Nations Population Fund launched a programme aiming to 'eliminate' neonatal tetanus from 57 (later expanded to 59) countries (Lam *et al.*, 2014). Neonatal tetanus elimination is defined as less than one case per 1000 live births in every district in a country, thus achieving elimination does not mean complete eradication and countries achieving elimination may still report cases (Lam *et al.*, 2014). The elimination of maternal tetanus, defined as tetanus occurring during pregnancy or within 6 weeks of any form of termination, was added to the target in 2000 (Fauveau *et al.*, 1993). Elimination is assumed to occur alongside neonatal tetanus elimination (Fauveau *et al.*, 1993). There are few data regarding maternal tetanus specifically but a study in 1993 estimated an annual incidence of 15 000– 30 000 cases (Fauveau *et al.*, 1993).In Africa, mortality from neonatal tetanus without artificial ventilation was reported as 82% in 1960 (Sykes, 1960). Severe cases of tetanus generally require ICU admission for approximately 3±5 weeks (Udawadia, 1994).

Clostridium tetaniaffect in animals

Tetanus disease is one of the most dramatic and globally prevalent diseases of vertebrate animals, and has been reported for over 24 centuries. The manifestation of the disease, spastic paralysis, is caused by the second most poisonous substance known, the tetanus toxin (Bruggemann *et al.*, 2003).

Treatment & control of Clostridium tetani

Mortality from tetanus varies between approximately 10 and 80% (Thwaites *et al.*, 2015).But the disease is completely preventable by vaccination and post-exposure prophylaxis (Thwaites *et al.*, 2015). Tetanus toxoid vaccination became available in the UK in the 1950s and routine vaccination began in 1961(Thwaites *et al.*, 2015). A combined 'DTP' diphtheria-tetanus-pertussis vaccine is used in children and a combined tetanus-diptheria 'Td' vaccine containing a smaller amount of diphtheria toxoid is recommended for adults instead of tetanus toxoid alone as it will increase population immunity to diphtheria. In the UK primary immunization courses use a combined DTaP/IPV/Hib (diphtheria, tetanus, pertussis, polio, haemophilus influenzae B) vaccine whereas a Td/IPV (tetanus diphtheria polio) vaccine is used in adults (Departments of Health Immunisation against infectious disease, 2105). Neonates are protected from tetanus by passive transfer of maternal antibody across the placenta (Thwaites *et al.*, 2015). Pregnant mothers who have not received full immunization require two dose of tetanus toxoid spaced at least one month apart to generate sufficient antibody for this purpose. A third dose is recommended after delivery to promote long-term immunity (Borrow *et al.*, 2006). Approximately 80% of maternal antibodies are still present in infants one month after delivery thus protection is maintained until a primary vaccination course is given and is maximal at the most vulnerable period when umbilical infection may occur (Borrow *et al.*, 2006).

Management of Clostridium tetani

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 (Cook *et al.*, 2001).Where present, obvious wounds should be surgically debrided (Edmondson and Flowers, 1979). Penicillin has been widely used for many years but is a GABA(gamma-amino butyric acid) antagonist and associated with convulsions (Johnson and Walker, 1945). Metronidazole is probably the antibiotic of choice. It is safe and comparative studies with penicillin suggest at least as good results (Ahmadsyah and Salim, 1985). Erythromycin, Tetracycline, Chloramphenicol, and Clindamycin are all accepted as alternatives (Alfery and Rauscher, 1979). 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 GABAA (gamma-amino butyric acid A) receptor (Lipman *et al.*, 1987). 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±1 have been reported (Lipman *et al.*, 1987). Midazolam has been used with less apparent cumulation (Gyasi *et al.*, 1993). Additional sedation may be provided by anticonvulsants, particularly phenobarbitone (which further enhances GABAergic activity) (Jenkins and Luhn, 1962) and phenothiazines, usually Chlorpromazine (Dance and Lipman, 1994).

Many different approaches to the treatment of autonomic dysfunction have been reported. Most are presented as case reports or small series. There is a lack of comparative or controlled studies. In general, outcome measures have been limited to haemodynamic data rather than survival or morbidity. Non-pharmacological methods of preventing autonomic instability rely on fluid loading of up to 8 litres day±1 (Wright *et al.*, 1989). Sedation is often the first treatment. Benzodiazepines, Anticonvulsants, and particularly Morphine are frequently used. Morphine is particularly beneficial as cardiovascular stability may occur without cardiac compromise (Rie and Wilson, 1978). Dosages vary between 20 and 180 mg day±1. Proposed mechanisms of action include replacement of endogenous opioids Bleck(1987). Reduction in reflex sympathetic activity and release of histamine (Philbin *et al.*, 1981). Phenothiazines, particularly chlorpromazine are also useful sedatives; anticholinergic and aadrenergic antagonism may contribute to cardiovasular stability (Prys-Roberts *et al.*, 1969). Initially b-adrenergic blocking agents, such as Propranolol, were used to control episodes of hypertension and tachycardia(Prys-Roberts *et al.*, 1969). But profound hypotension, severe pulmonary oedema and sudden death were all found to occur (James and Manson, 1985). Labetolol, which has combined a- and badrenergic blocking effects has been used, but no advantage over propranolol was demonstrated possibly because its a activity is much less than its b activity (Dundee and Morrow, 1979) and mortality remained high (Wesley *et al.*, 1983). In recent years, the short-acting agent, esmolol, has been used successfully (King and Cave, 1991). Although good cardiovascular stability was achieved, arterial catecholamine concentrations remained elevated. Sudden cardiac death is a feature of severe tetanus. The cause remains unclear but plausible explanations include sudden loss of sympathetic drive, catecholamine-induced cardiac damage and increased parasympathetic tone or `storms'. Persisting beta block could exacerbate these causes because of negative inotropism or unopposed vasoconstrictor activity, leading to acute cardiac failure, particularly as sympathetic crises are associated with high systemic vascular resistance and normal or low cardiac output. Isolated use of b-adrenergic block with long acting agents, therefore, cannot be recommended. Postganglionic and a-adrenergic blocking agents such as bethanidine, guanethidine, and phentolamine have been successfully used with propranolol (Prys-Roberts *et al.*, 1969). Along with other similar agents such as trimetaphan, phenoxybenzamine, and reserpine (Pinder, 1997). A disadvantage of this group of drugs is that induced hypotension may be difficult to reverse, tachyphylaxis occurs and withdrawal can lead to rebound hypertension(Pinder, 1997).

Weight loss is universal in tetanus (Edmondson and Flowers, 1979). 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 (Handel and McCallum, 1995) 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 (Gregorakos *et al.*, 1997). Securing the airway early in the disease and preventing aspiration and sepsis are logical steps in minimizing this risk. As artificial ventilation is often necessary for several weeks.Tracheostomy is usually performed after intubation (Edmondson and Flowers, 1979).

Conclusion

The *Clostridium tetani* is a causative agent of tetanus, spastic paralysis, a vaccine preventable disease, caused by the second most poisonous substance known, the tetanus toxin (tetX).Tetanus is most remarkable and globally prevalent disease of humans and vertebrate animals. The estimated worldwide deaths from tetanus were 213,000 in 2002 including 198,000 in children under 5 years of age including neonatal tetanus. This study aimed for isolation of causative agent of tetanus. *Clostridium tetani* its animal and biochemical testing along with the antimicrobial susceptibility.

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