Introduction

Vaccination is widely considered to be one of the greatest medical achievements of modern civilisation. Yet, despite this life-saving innovation, ancient diseases such as tetanus, diphtheria and pertussis still exist in the 21st century. In this article, we review the historical facts, microbiology, pathogenesis, diagnosis, treatment and prevention of tetanus, diphtheria and pertussis in South Africa.

Tetanus

Synonyms for tetanus are lockjaw, klem-in-die-kaak (Afrikaans) and umhlathingqi (Zulu). Tetanus is a potentially fatal disease caused by an exotoxin produced by Clostridium tetani. The disease is characterised by an acute onset of hypertonia, painful muscular contractions and generalised muscle spasms. The muscle stiffness usually involves the neck and jaw, and then becomes generalised.1,2

History

Records dating as far back as the fifth century BC have been found to contain descriptions of tetanus. The tetanus bacterium was discovered in 1884, and later isolated by Japanese bacteriologist, Shibasaburo Kitasato, in 1889. Kitasato isolated the bacteria from an infected person, showed that they caused disease when injected into animals, and reported that the toxin could be neutralised by specific antibodies. The protective effect of passively transferred antitoxin was demonstrated in 1897, and passive immunisation was later used in humans for treatment and prophylaxis during World War I. Tetanus toxoid (TT) was developed in 1924.2

Pathophysiology

Most cases of tetanus result from lacerations, or small puncture wounds, which become contaminated with C. tetani spores that germinate and produce toxin.1 The incubation period from the time of injury to the onset of symptoms may vary from a few days to weeks, depending on the site of injury and the infectious dose. Peripheral wounds generally have a longer incubation period.1

The spores germinate under anaerobic conditions, and release a neurotoxin called tetanospasmin. Tetanospasmin is distributed via the lymphatic and vascular circulations to the end-plates of all nerves, where it then enters the nervous system peripherally at the myoneural junction, and is then transported into neurons of the central nervous system.2

Once the toxin becomes fixed to neurons, it can't be neutralised by antitoxin, and the neurons become incapable of neurotransmitter release, leading to the characteristic symptoms of tetanus. Recovery of nerve function from tetanus toxins requires development of new nerve terminals and formation of new synapses.2

Four types of tetanus have been described:

- Generalised tetanus is the most common form, and often presents with a descending pattern. Toxin passes into the blood and lymph, followed by absorption by motor nerves. Characteristic lockjaw and facial spasms are followed by generalised painful spasms, which may be associated with fever and other systemic symptoms. During spasms, the airway may become obstructed, resulting in respiratory failure. Spasms are often initiated by external stimuli which may be as insignificant as the sound of footsteps or a flash of light.1,5
- In localised tetanus, toxins travel along peripheral nerves, causing disease confined to the extremities. Localised tetanus usually resolves spontaneously, but may last for months.1
- Cephalic tetanus is a rare form of tetanus, which results...
from head wounds or otitis media. Patients present with facial nerve palsies. The infection may be localised, or may become generalised.3-6
- Neonatal tetanus (NNT) is a major cause of infant mortality in developing countries. Infection results from contamination of the umbilical cord during unsanitary delivery conditions, as well as a lack of maternal vaccination.4 A review of all hospital admissions in the Mpumalanga province between 1996-2000, on the case definition for NNT, found that most cases occurred as a result of the cultural practice of applying cow dung or rat faeces to the umbilical stump in the neonatal period.7 This form of tetanus has a poor prognosis.6

In 1989, the World Health Assembly called for global NNT elimination. Elimination is defined as less than one case of NNT per 1 000 live births in every district of every country.3 South Africa has achieved and maintained this goal since 2002.8 (The number of cases of NNT has dropped from 177 cases in 1988, to a range of six to ten cases between 1998-2006).9

Diagnosis

Diagnosis is clinical, and does not rely on bacteriological confirmation.1

Treatment

All wounds should be cleaned, and foreign or necrotic tissue removed. Supportive therapy may include ventilatory support and drugs that treat rigidity, reflex muscle spasms and tetanic seizures.1-6 Tetanus immune globulin (TIG) is recommended for persons with tetanus. It can only help remove unbound tetanus toxin, possibly shortening the course of disease and reducing its severity.1,6 Theoretically, antibiotics such as metronidazole and penicillin G may prevent multiplication of C. tetani, halting the production of toxin. However, efficacy is questionable.2 Tetanus disease does not confer immunity. Persons recovering from tetanus should complete or commence active immunisation against tetanus.1

Prevention

TT is available as a single-antigen preparation (‘Tetavax®’), combined with diphtheria toxoid as adult tetanus-diphtheria (Td), e.g. Diftavax®, and with diphtheria toxoid, acellular pertussis and inactivated polio, as Tdap-IPV (Adacel® Quadrac). TT is also available as combined DTaP-HepB-IPV/Hib (Infanrix® Hexa), DTaP-IPV/Hib (Pentaxim®), DTaP (Infanrix®) and DTwP-HepB (Tritanrix®), for paediatric use (refer to Table I).

In South Africa, primary vaccination against tetanus is administered at six, ten and fourteen weeks of age, and again at 18 months, according to the Expanded Programme on Immunisation (EPI) Schedule. A preschool booster is administered at the age of six years, followed by a recently introduced 12-year booster. It is hoped that if this schedule is maintained, it will not be necessary to vaccinate pregnant women (in order to prevent neonatal tetanus) in the future.10

Post-exposure prophylaxis

All wounds should be thoroughly cleaned and debrided. Some injuries are considered to be tetanus prone, and tetanus immunisation should be administered as per Table III.
Tetanus, diphtheria and pertussis: ancient diseases in modern times

Burns or wounds that require surgery, that is delayed for more than six hours.

Burns or wounds that show a significant degree of devitalised tissue.

A puncture-type injury, particularly where there has been contact with soil or manure, and wounds containing foreign bodies.

Compound fractures.

Wounds or burns in patients who have systemic sepsis.

Diphtheria

Synonyms for diphtheria are witseerkeel (Afrikaans) and isifo esivimbanisa umphimbo (Zulu).

History

Diphtheria, meaning “leather hide” in Greek, was first described by Hippocrates in the fifth century BC. However, the earliest references to the disease date back to ancient Egypt and Syria. In the 17th century, the disease swept through Europe and Spain, where it became known as el garatillo (the strangler), as well as to Italy and Sicily, where it was called “the gullet disease”. In the 18th century, the disease reached the American colonies and often killed whole families in a few weeks. Here it was referred to as the “strangling angel of children”. The name refers to the wing-shaped, white membrane that formed on children’s tonsils in the early stages of the disease, and to the way in which it obstructed their breathing.

Over the last 50 years, the incidence of diphtheria has declined significantly in the developed world, but still remains endemic in the developing world. In South Africa, the number of cases has declined sharply since the 1980s. In the 1990s, 29 cases were reported, followed by four cases between 2000-2005. All documented cases in 2008, 2009 and 2010 had fatal outcomes.

Corynebacterium diphtheriae

Corynebacterium diphtheriae was first described by Klebs in 1883. In 1890, Emil von Behring, together with his university friend, Erich Wernicke, developed the first effective therapeutic serum against diphtheria. In 1901, Von Behring went on to win the first Nobel Prize in physiology/medicine.

C. diphtheriae is an aerobic, noncapsulated, nonmotile, gram-positive bacillus. Toxin production can only occur when the bacilli themselves are infected by a bacteriophage (virus) carrying the genetic information for the toxin.

Table II: Vaccination schedule for the prevention of maternal and neonatal tetanus

<table>
<thead>
<tr>
<th>First pregnancy</th>
<th>Second pregnancy</th>
<th>Third pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT1 at first antenatal visit</td>
<td>TT4 single dose</td>
<td>TT5 (tetanus immunisation complete)</td>
</tr>
<tr>
<td>TT2 four weeks later</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT3 six months later</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a = Tetanus toxoid (TT)

Table III: Tetanus immunisation following injuries. Adapted from the UK Health Protection Agency (HPA) Immunoglobulin Handbook.

<table>
<thead>
<tr>
<th>Immunisation status</th>
<th>Clean wound</th>
<th>Tetanus-prone wound</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>Vaccine</td>
</tr>
<tr>
<td>Fully immunised</td>
<td>Not required.</td>
<td>Not required.</td>
</tr>
<tr>
<td>Primary immunisation complete; boosters incomplete, but up to date</td>
<td>Not required (unless booster is due imminently).</td>
<td>Not required (unless booster is due imminently).</td>
</tr>
<tr>
<td>Primary immunisation incomplete; or boosters not up to date</td>
<td>Arrange additional doses at appropriate intervals to complete immunisation schedule.</td>
<td>Arrange additional doses at appropriate intervals to complete immunisation schedule.</td>
</tr>
<tr>
<td>Not immunised; or unknown immunisation status</td>
<td>Arrange additional doses at appropriate intervals to complete immunisation schedule.</td>
<td>Arrange additional doses at appropriate intervals to complete immunisation schedule.</td>
</tr>
</tbody>
</table>

a = A tetanus prone injury is considered to be high risk if there is heavy contamination with substances likely to contain tetanus spores, and/or extensive devitalised tissue.
Pathophysiology

Overcrowding, substandard living conditions, poor health, immunocompromised states, or incomplete immunisation facilitate susceptibility to diphtheria, and are risk factors associated with transmission of the disease.\(^2\) Human carriers (usually asymptomatic) are the main reservoir of infection.\(^1,3\) Susceptible persons acquire toxigenic diphtheria bacteria in the nasopharynx via respiratory droplets, nasopharyngeal secretions, and, rarely, via fomites. In cutaneous disease, contact with exudates may result in disease transmission.\(^1\) \(C. \) diphtheriae\(\) adheres to mucosal epithelial cells and causes a localised inflammatory reaction, following which exotoxin is produced, which inhibits cellular protein synthesis and causes necrosis and membrane formation. The toxin produced at the site of the membrane is absorbed into the bloodstream and distributed to other body tissues.\(^1,3,21\)

The incubation period is two to five days, with a range of one to 10 days.\(^3\) Diphtheria can involve almost any mucous membrane.

The disease is classified based on the site of infection:\(^1\)
- Anterior nasal diphtheria;
- Pharyngeal and tonsillar diphtheria;
- Laryngeal diphtheria;
- Cutaneous diphtheria;
- Ocular diphtheria.

Other sites of infection have included the external ear and genital mucosa.\(^1,3,15\) Septicaemia caused by \(C. \) diphtheriae\(\) is rare, but fatal.\(^3\)

The pharynx and tonsils are the most common sites of diphtheria infection. Early symptoms are usually non-specific, resembling a typical viral upper respiratory tract infection.\(^1,12\)

Within two to three days, a bluish-white membrane forms and extends, covering as little as a patch on the tonsils, or as much as most of the soft palate. Extensive membrane formation may result in respiratory obstruction. Forcible attempts to remove the membrane cause bleeding, as it is adherent to the tissue.\(^3\)

If left untreated, diphtheria can lead to breathing problems, myocarditis, or nerve damage. Nerve damage may cause muscle weakness in the arms, legs and throat, or even paralysis of the muscles that control breathing.\(^2\)

Diagnosis

The diagnosis can be confirmed by a throat swab culture and demonstration of toxin by Elek culture plate, or polymerase chain reaction (PCR) detection, where available. In South Africa, the Elek test is performed at the Green Point National Health Laboratory Service in the Western Cape.\(^1,19\)

Treatment

Persons with suspected diphtheria, as well as all close contacts, should be treated with erythromycin or penicillin. Treatment should be initiated as soon as possible, as it is most effective in the early stages of disease, improves the course of diphtheria, and decreases transmissibility.\(^1,3,21\)

The disease is generally not contagious 48 hours after antibiotics are initiated.\(^1\) Diphtheria antitoxin treatment is only effective if given very early in the course of illness, and is not available in SA.\(^1\) Contacts should be monitored for symptoms for at least seven days after last exposure, and booster immunisation should be provided to those who have not received a booster in the previous 12 months.\(^18\)

Prevention

A single-antigen diphtheria toxoid is not available. Diphtheria toxoid is available, combined with TT as adult tetanus-diphtheria (Td), e.g. Diftavax\(\). Diphtheria toxoid is also available as combined Tdap-IPV (Adacel “Quadra”), DTaP (Infanrix\(\)), DTaP-HepB-IPV/Hib (Infanrix\(\) Hexa), TDaP-IPV/Hib (Pentaxim\(\)) and DTwP-HepB (Tritanrix\(\)). See Table I.

Paediatric formulations contain three to four times more diphtheria toxoid than adult formulations. It is advised that children younger than seven years of age receive paediatric diphtheria, and that persons over the age of seven years receive the adult diphtheria formulations.\(^3\)

A series of three correctly spaced diphtheria toxoid doses in adults, or four correctly spaced doses in infants, should provide a protective level of antitoxin in more than 95% of individuals. Antitoxin titres do wane with time, and boosters are recommended 10 years after the last dose.\(^1\)

Pertussis

Synonyms for pertussis are whooping cough, kinkhoes (Afrikaans) and ugonqogonqo (Zulu).

History

The earliest known description of pertussis infections was given by Guillaume De Baillou, who described an epidemic that occurred in France in 1578. “Kinkehost” is mentioned in Vita Godrici, from around 1190. It has also been suggested that the description of the “perinthus” cough by Hippocrates (around 400 BC) might possibly be whooping cough, perhaps combined with other diseases such as viral respiratory infections.\(^2\)
**Bordetella pertussis**

*Bordetella pertussis* is an aerobic, non-motile, Gram-negative coccobacillus. Humans are the only reservoirs, and infection is spread via aerosolised droplets from coughing by infected individuals. The disease is highly contagious, and it is estimated that approximately 80-90% of susceptible individuals who are exposed will develop the disease.

**Pathophysiology**

*B. pertussis* bacteria attach to the ciliated respiratory epithelium, where they produce toxins that paralyse the cilia and cause inflammation of the respiratory tract, which interferes with the clearing of pulmonary secretions.

The incubation period of pertussis is usually seven to ten days, with a range of four to 21 days. The course of the disease is divided into three stages:

- The catarrhal phase lasts one to two weeks, and is characterised by low-grade fever, rhinorrhoea and progressive cough.
- The paroxysmal phase lasts several weeks, and is characterised by episodes of severe and spasmodic coughing with a distinctive whoop, often with cyanosis and vomiting. Paroxysmal attacks occur more frequently at night, with an average of 15 attacks per 24-hour period. Persons do not appear to be ill between attacks. Young infants may not have the strength to whoop, but do have paroxysms of coughing. However, the cough may be absent, and the infant may present with spells of apnoea and cyanosis.
- The convalescent phase lasts one to three weeks, and is characterised by a gradual, but continuous decline of cough, as the patient returns to normal. Patients who develop subsequent respiratory infections months after the onset of pertussis may experience paroxysms.

Compared with older children and adults, infants younger than six months with pertussis are more likely to have severe disease, to develop complications, and to require hospitalisation. In addition, pertussis is one of the causes of sudden infant death syndrome.

Secondary bacterial pneumonia is the most common complication, and the cause of most pertussis-related deaths. Complications among adolescents and adults include syncope, sleep disturbance, incontinence and rib fractures. Less common central nervous system (CNS) complications, such as seizures and encephalopathy, are thought to result from severe paroxysm-induced cerebral hypoxia and apnoea, metabolic disturbances, and small intracranial haemorrhages.

**Diagnosis**

Diagnosis is essentially clinical. Although some tertiary institutions have the means to do so, laboratory confirmation is not conducted routinely in South Africa. Furthermore, bacteriological confirmation of suspected pertussis is often missed, as *B. pertussis* requires special growth factors to grow on artificial media, and does not seem to persist far beyond the catarrhal stage. PCR testing is more sensitive than culture, and is the preferred diagnostic method where available.

**Treatment**

The macrolide antibiotics, erythromycin, clarithromycin and azithromycin, are preferred for the treatment of pertussis in patients older than one month. Azithromycin is preferred in the treatment of infants less than one month of age. The South African Standard Treatment Guidelines and Essential Drug List recommends the use of oral erythromycin 10-15 mg/kg/dose, six hourly for 14 days in the treatment of pertussis. Infected persons should be excluded from work, school or daycare for five days following commencement of antibiotics.

**Prevention**

A single antigen pertussis vaccine is not available. See Table I for available preparations. Vaccination is an essential preventative strategy against pertussis. Unless specifically contraindicated, all children should receive pertussis vaccines at six, ten and fourteen weeks of age, followed by additional doses at 18 months, and again at six years of age. Unfortunately, neither vaccination, nor natural disease, confer lifelong protective immunity against pertussis. Immunity wanes after five to ten years from the last pertussis vaccine dose, causing older children and adults to be susceptible to infection again. It is therefore assumed that infection frequency is likely to be highest in adolescents and adults, who as a result, are the main source of infection in infants.

**Post-exposure prophylaxis**

Symptomatic infection of household contacts can be prevented if administration of post-exposure prophylaxis is initiated within 21 days of the onset of the cough in the index patient. The same antimicrobial agents and dosing regimens used in the treatment of pertussis are recommended for post-exposure prophylaxis of pertussis.

**Conclusion**

Tetanus, diphtheria and pertussis are serious, potentially life-threatening, but vaccine-preventable diseases. The
nursing practitioner may have a pivotal role in preventing unnecessary illness or deaths by educating and counselling patients and families to create an awareness of these illnesses, and to emphasise the importance of vaccination.

References


