Meningococcal disease

BACKGROUND Despite significant advances in the prevention and management of *Neisseria meningitidis* infection, invasive meningococcal disease continues to occur with significant morbidity and mortality.
OBJECTIVE This article aims to provide an overview of the aetiology, pathogenesis, transmission, epidemiology, clinical presentation, diagnosis, treatment and prevention of meningococcal disease.
DISCUSSION *Neisseria meningitidis* is now the commonest cause of meningitis and is a significant cause of septicaemia, particularly in children and young adults. The initial diagnosis may be difficult but early recognition and treatment is essential. Transmission occurs during close contact and prophylaxis is important to prevent invasive disease in contacts. The conjugate meningococcal C vaccine has recently been funded for all children aged 1-19 years in Australia.

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Few bacterial infections attract as much public attention, or indeed elicit as much fear and anxiety among the general public and health care workers, as invasive meningococcal disease. Despite advances in prevention and treatment, the rate of infection with *Neisseria meningitidis* is increasing in parts of Australia and leads to significant morbidity and mortality. The recent introduction of conjugate vaccines for serogroup C may lead to a significant reduction in disease burden in coming years.

Microbiology

Neisseria meningitidis is a Gram negative diplococcus (*Figure 1*). It has a complex cell envelope which contains outer membrane proteins of various function that allow subtyping of the organism into different strains which is useful for epidemiological purposes. In addition, lipopolysaccharide attached to the outer membrane is a potent endotoxin which is released in large quantities into the circulation during meningococcal sepsis. Lipopolysaccharide is the major cause of endothelial cell damage which leads to the characteristic petechial rash and the systemic inflammatory response syndrome of fulminant meningococcaemia. Pathogenic strains produce a polysaccharide capsule that helps the organism evade the host's phagocytic cells. The complete genetic sequences of serogroup A and B meningococci have now been determined[1,2] which has demonstrated the organisms ability to recombine its genetic sequences and to scavenge genetic material from the environment. This leads to the remarkable ability of the meningococcus to modify its capsular and surface proteins and to evade our immune system.

Transmission and carriage

Bacteria are shed in secretions and large respiratory droplets (greater than 5 μm in size) that only travel 0.5–1.0 metres. The bacteria survive for only short periods outside the body. Transmission in the community usually occurs from an asymptomatic host. Transmission from person-to-person occurs during coughing, sneezing, kissing, sharing food or utensils and other close contact. Carriage rates vary depending on the population studied. Rates as high as 60–80% have been observed in military recruits living in closed environments. Rates in adolescents are 15–25% but in the general community are usually less than 5%.[3] Carriage can either be intermittent or more chronic but the median duration is approximately nine months.[4] Following exposure, the majority of people develop asymptomatic colonisation. A few may experience localised infection such as sinusitis and a very small number will develop invasive infection. Invasive meningococcal disease usually occurs within 2–10 days of

Table 1. Risk factors for invasive meningococcal disease

Bacterial factors
Polysaccharide capsule
Antigenic variability
IgA protease
Transferrin binding proteins
Host factors
Lack of specific antibody
Age (<4 years, 15–25 years)
Crowding
Recent respiratory infection
Cigarette smoking (active and passive)
Immune deficiencies
Asplenia

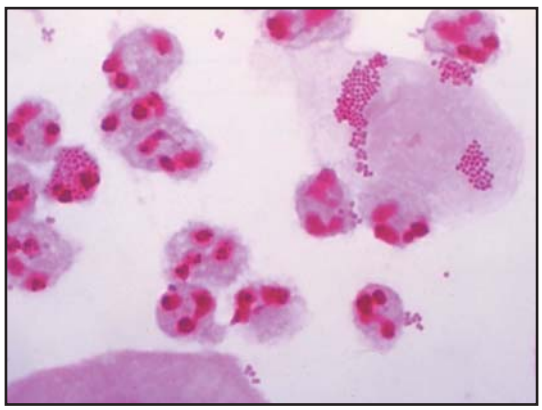

Figure 1. Gram stain of *Neisseria meningitidis* in petechial exudate

exposure to a new strain of the organism. Why certain individuals develop invasive infection depends on the delicate balance between bacteria and host (*Table 1*).[5]

Transmission occurs during prolonged close contact and the risk of invasive disease following household exposure is between 200 and 1000 times the rate in the general population.[6] Secondary attack rates are estimated to be 0.25% in adults, 10% in children less than one year of age, and between 2–5% in military recruits. Twenty percent of secondary cases are due to co-primary infections rather than transmission from the index case. Children in day care centres are also at increased risk. In one study, during a community epidemic in Belgium, the rate of meningococcal infection in children under two years of age was 76 times that of children in the community, and in children aged 2–5 years it was 23 times the rate in the general population.[7]

Transmission from patients to health care workers is often feared and there are anecdotal reports of this occurring. Once antibiotic therapy is commenced, the numbers of bacteria in the nasopharynx fall. Therefore, transmission to health care workers occurs during close contact early in the illness and is particularly associated with procedures such as mouth-to-mouth resuscitation, endotracheal intubation and suctioning. For these

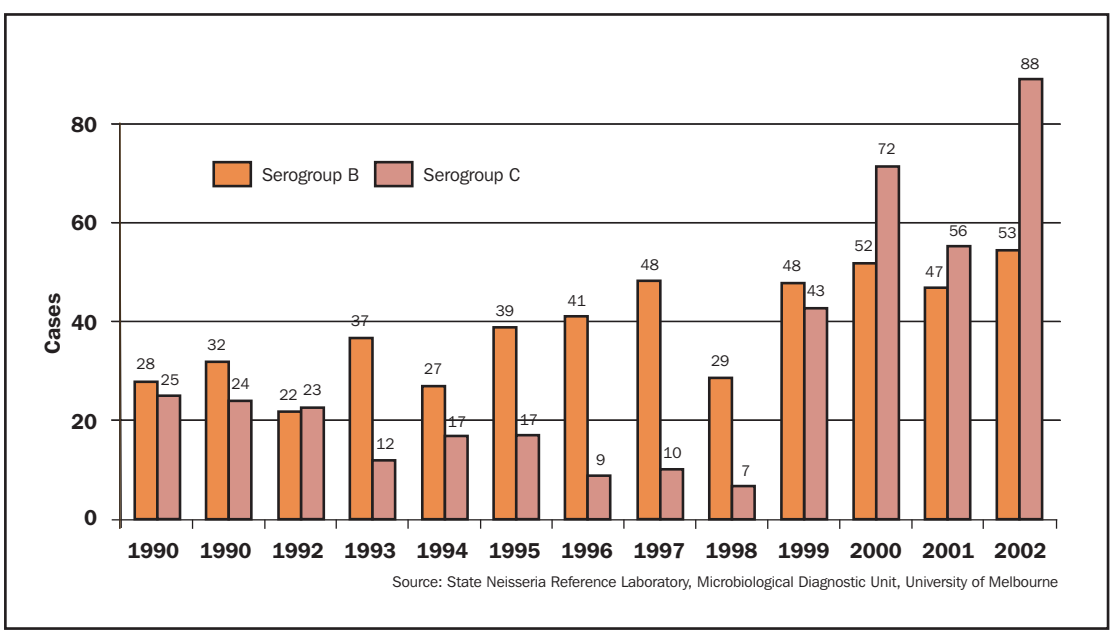

Figure 2. Serogroup B and C meningococcal infection in Victoria, 1990–2002

Table 2. Clinical signs of meningitis

Neonates
Nonspecific
Bulging fontanelle
Irritability
Vomiting
Fever
Seizures
Toddlers
Fever
Vomiting
Irritability
Seizures
Children (>18 months)
Fever
Vomiting
Neck stiffness
Confusion
Kernig's sign

reasons, patients with invasive meningococcal disease should be placed in a single room or in shared rooms with at least one metre between beds. Staff should wear masks for the first 24 hours, particularly for respiratory procedures. Over a 15 year period (1982 to 1996) in England and Wales, the attack rate among health care workers was 0.8/100 000. This rate was higher than in the age matched general population with a relative risk of 25 (95% confidence interval 5–76). All of the infected health care workers had more than 30 minutes of face-to-face contact in the first 24 hours of the patient's admission.[8] The relative risk in bacteriology staff is even higher. From 1985 to 1999 in England and Wales, the relative risk was estimated to be 184 (95% CI: 60–431). All cases were related to inappropriate handling of cultures of meningococci or laboratory accidents.[9] A similar retrospective review from the United States during a five year period from 1996 to 2000 demonstrated a relative risk of 65.[10] These data support the current NHMRC recommendation of vaccinating laboratory workers who frequently handle meningococcal cultures. Other clinical staff are not at such increased risk to warrant routine vaccination. Chemoprophylaxis following significant exposure is the preferred method of protection from colonisation and invasive infection.

Epidemiology

Meningococcal infections have been notifiable in Australia since 1949 and the establishment of a laboratory based surveillance system known as the National Neisseria Network in 1994 has allowed the standardised typing of strains causing disease across Australia.[11] Peaks of meningococcal disease activity occur in winter and spring. Periodic epidemics occur when new strains emerge. There is a bimodal age distribution with the peak incidence in the six month to four year, and the 15–25 year age groups. The overall rate in Australia is 3.1 cases per 100 000 population, but the rate in indigenous people is nearly six times higher.

On a global level, the greatest burden of meningococcal disease occurs in the so-called meningitis belt which stretches across sub-Saharan Africa. Every few years an epidemic of meningococcal serogroup A disease leads to rates of infection as high as 500–800 cases per 100 000. In Australia, serogroup B causes the majority of infections and serogroup C about one-third of cases. However, in Victoria and to a lesser degree in New South Wales, serogroup C has come to predominate in the past four years, particularly in the adolescent age group (*Figure 2*). New Zealand has experienced an outbreak of serogroup B disease that has continued since 1991 with rates of disease 10 times that experienced in Australia.[12]

Clinical presentation

Clinical presentation ranges from localised infection such as conjunctivitis to invasive infection such as meningitis and septicaemia. With the success of the *Haemophilus influenzae* type b vaccine, the meningococcus has become the leading cause of bacterial meningitis. Meningitis presents with headache and fever and may progress to confusion and seizures with signs of meningeal irritation such as neck rigidity and photophobia (*Table 2*). It may or may not be associated with meningococcaemia. Meningococcaemia carries the highest mortality of the invasive meningococcal infections. The feared progression to septic shock with disseminated intravascular coagulation can occur within hours. Signs and symptoms, particularly early in the disease, may be mild. Fever and vomiting may be the only complaints in children. The petechial rash (*Figure 3a, b*) that is the well known harbinger of infection may be subtle or be hidden under clothes, therefore, a complete physical examination is essential. The petechiae do not blanch with pressure and as the disease progresses may coalesce into larger ecchymoses. A maculopapular or urticarial rash has also been described which may mimic other viral exanthema.

Meningococcal pneumonia[13] is more common in

the elderly and presents with cough, fever and respiratory distress. Associated septicaemia is rare. Patients pose a significant risk to others as large numbers of bacteria are expelled during coughing. Meningococci are a rare cause of pharyngitis and sinusitis. Meningococci, like gonococci, can cause urethritis or they may colonise the genital tract asymptomatically. Oro-genital sexual contact may predispose to transmission. Meningococcal infection during the first six months of life is rare because of the presence of passively acquired maternal antibody. Neonatal infection can, however, occur when the mother has meningococcaemia around the time of delivery or when the baby is colonised while passing through the mother's genital tract. This can present as conjunctivitis or the infant may develop early or late onset sepsis.

The case fatality rate for invasive meningococcal disease in Australia is between 5–10%. The fatality rate for meningococcaemia is higher than with meningitis. Prompt antibiotic and supportive therapy can improve the prognosis. Permanent neurological sequelae are less common than with other forms of bacterial meningitis. Up to 4% of survivors can have significant scarring or loss of extremities from severe ischaemic damage.

Laboratory diagnosis

The laboratory diagnosis of meningococcal disease has evolved over the past 15 years with the development of nucleic acid amplification techniques. A quarter of all diagnoses are now made using nucleic acid amplification methods.[14] The meningococcus is a fastidious organism that requires ideal conditions in which to grow. With the early administration of antibiotics, often before the collection of specimens for culture, the rate of positive cultures is decreased. The sensitivity of culture from CSF is 90%, and from blood cultures, 50%. This is reduced to 50% and 10% respectively if antibiotics have been administered before collection.[15] Gram negative diplococci may be seen in Gram stains performed on exudate expressed from a petechial lesion (*Figure 1*) or in the buffy coat in 10–20% of patients. Nucleic acid amplification has a sensitivity and specificity of greater than 90% and is less affected by the prior administration of antibiotics. Current methods allow strain typing for epidemiological purposes. The detection of IgM antibodies can be performed in the convalescent period and may be useful if other tests fail to confirm the diagnosis.

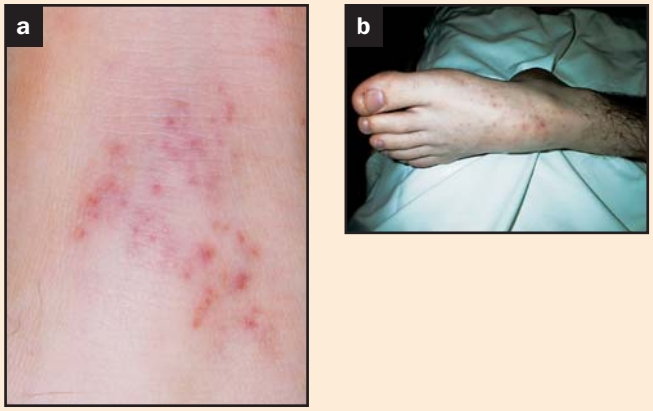

Figure 3a, b. Petechial rash on dorsum of foot

Treatment

Penicillin G remains the drug of choice for the treatment of invasive meningococcal disease. However, penicillin resistant strains are now emerging in parts of the world and treatment failure has been described with meningitis.[16] Resistance is due to altered penicillin binding proteins 2 or 3. In Australia, benzylpenicillin remains the recommended first line treatment but third generation cephalosporins may be used in patients with hypersensitivity to beta-lactam antibiotics.[17] Antibiotics should be commenced as soon as the diagnosis is suspected (*Table 3*). If possible, blood cultures should be collected before administration of antibiotics and sent with the patient to hospital. Treatment regimens have become shorter; 7–14 days used to be recommended for meningitis, but 5–7 days is now considered sufficient. Other supportive management for the critically ill patient includes measures to preserve tissue perfusion and recombinant activated protein C that inhibits the

Table 3. Initial antibiotic treatment when meningococcal disease is suspected

Benzylpenicillin intravenously or intramuscularly		
Age	<1 year	300 mg
	1–9 years	600 mg
	>9 years and adults	1200 mg

If penicillin allergic, use ceftriaxone 50 mg/kg (up to 2 g) IV or IM

inflammatory and procoagulant pathways stimulated by bacterial lipopolysaccharide.[18]

Disease prevention

Chemoprophylaxis

Chemoprophylaxis and immunisation are the two primary approaches to prevention of invasive meningococcal disease. Chemoprophylaxis is offered to close contacts of an index case. These include members living in the same household, childcare centre contacts in the previous seven days, and those who have performed mouth-to-mouth resuscitation. All contacts should be treated concurrently so that organisms are not reintroduced. Prophylaxis should be offered within 24 hours of the index case falling ill. The index case should receive antibiotics (such as a third generation cephalosporin) which will eradicate nasopharyngeal carriage to prevent transmission after hospital discharge.

Several regimens have been used (*Table 4*) for chemoprophylaxis. Rifampicin is approximately 85% effective. No liquid preparation is available. The majority of people will experience an orange discolouration of urine and other secretions. Rifampicin should not be used in pregnancy as it is teratogenic in animals. Rifampicin induces the hepatic cytochrome P-450 enzyme system and therefore affects the metabolism of many drugs including warfarin, antiepileptics and oral contraceptive agents. Alternative barrier contraception is recommended for one menstrual cycle following the use of rifampicin. More recently, both ceftriaxone and ciprofloxacin have been used. Both are more than 95% efficacious in eradicating carriage. Ceftriaxone is safe in pregnancy and requires only a single intramuscular dose. Ciprofloxacin should be avoided during pregnancy and breastfeeding.

Table 4. Antimicrobial chemoprophylaxis

Rifampicin	Infants <1 month 5 mg/kg/dose orally twice per day for two days
	Children/adults 10 mg/kg/dose (up to 600 mg) orally twice per day for two days
Ceftriaxone	Children <12 years 125 mg intramuscularly single dose
	Children >11 years/adults 250 mg intramuscularly single dose
Ciprofloxacin	Children >11 years/adults 500 mg orally single dose

Immunisation

In Australia two types of meningococcal vaccine are available.

Table 5. Summary of eligibility for the National Meningococcal C Vaccination Program

Stage	Target group	Significant dates	Setting
Early 2003	Infants at 12 months as part of routine schedule vaccinations	Children born on or after 1/1/02	GP or other immunisation provider
	Pre-school children turning 1–5 years in 2003	Children born from 1/1/98 to 31/12/01 are elegible in 2003	GP or other immunisation provider
2003	Senior secondary school students	Turning 15–19 years in 2003	School based immunisation program
2004-2005	Primary and secondary school students	Turning 6–14 years in 2003	School based immunisation program

Commencing in late 2005, the free meningococcal C vaccine will be available through GPs for all remaining eligible children and adolescents (turning 6–19 years of age in 2003) who were not vaccinated through school based programs. There will be minor differences in the way the program is rolled out in states and territories. Further information is available from state or territory health departments or from: www.immunise.health.gov.au.
Source: Program delivery, eligibility and information guidelines for Meningococcal C Conjugate Vaccine Immunisation Program. Commonwealth Department of Health and Ageing. (Updated March 2003).
http://www.immunise.health.gov.au/meningo_gp_fact.pdf

Quadrivalent meningococcal polysaccharide vaccines

These contain antigens from serogroups A, C, Y and W135. They provide short lived protection for 2–3 years and are ineffective in children aged less than two years. Repeated vaccination can lead to immune tolerance with hypo-responsiveness so their main use is in travellers to high risk areas, during localised outbreaks with a serogroup that is represented in the vaccine, and in patients with underlying conditions that increase their risk of invasive meningococcal disease. Adverse events such as injection site reactions and fever are usually mild.

Monovalent serogroup C conjugate vaccines

These have recently been licensed in Australia. The serogroup C polysaccharide is linked to a carrier protein such as tetanus or diphtheria toxoid to transform it into a T-cell dependent antigen. This enhances the immune response, particularly in children less than two years of age, and leads to the induction of memory T-cells, providing long lived immunity. The conjugate vaccines can be given to all age groups including infants from six weeks of age. Only a single dose is required for adults and children over one year of age. The vaccines may be administered simultaneously with other vaccines included in the standard schedule. These vaccines are well tolerated with 10% of vaccinees experiencing minor local reactions and less commonly more generalised symptoms of fever, irritability, headache, vomiting or diarrhoea.

In the United Kingdom, where vaccination of children has been performed since November 1999, there has been a 91–95% reduction in serogroup C disease.[19] In Australia, a vaccination program for all children under 20 years of age will be rolled out over the next two years (*Table 5*).

Conclusion

The advances in our understanding of meningococcal disease and its management and prevention have been dramatic. The determination of the genetic sequence of the organism has identified many surface proteins that may be potential future vaccine candidates. These may allow us to develop a vaccine against serogroup B which has not been possible to date because of the similarity of the serogroup B antigen with structures on the surface of many human cells.[20] Multivalent conjugate vaccines are currently in development and will be essential to reduce the burden of disease in Africa and other countries with endemic disease.

SUMMARY OF IMPORTANT POINTS

- The meningococcus can alter its surface structures to evade the immune system.
- Carriage rates are generally 5–30%, but can be higher during epidemics.
- Health care workers are at slightly increased risk of infection.
- Smoking can increase the risk of infection four-fold.
- Nucleic acid amplification (eg. PCR) improves detection if antibiotics have been administered.
- Benzyl penicillin remains the drug of choice in Australia.
- Early antibiotic administration improves outcome.
- Conjugate serogroup C vaccines are effective in infancy and provide long term protection.

Conflict of interest: none declared.

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