Pneumococcal meningitis

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Abstract

Streptococcus pneumoniae is one of the most common causes of bacterial meningitis, with high mortality and morbidity rates. Although some of the signs and symptoms of meningitis may be absent, virtually all patients present with at least one of the classic triad symptoms of a fever, neck stiffness and altered mental status. It is imperative to start empiric antimicrobial treatment as soon as possible. Treatment is started with ceftriaxone, and needs to be switched to an appropriate alternative as soon as microbiological test results are available. Patients should be offered suitable analgesia and monitored for hydration and nutritional status. Appropriate follow-up care includes hearing tests, physiotherapy, occupational therapy, educational support, speech and language therapy, and referral to the mental health services, if necessary. The introduction of pneumococcal vaccination has reduced the incidence of invasive pneumococcal disease and resistant invasive pneumococcal disease. This article provides an overview of the causes, signs and symptoms, treatment, complications and prevention of bacterial, and specifically pneumococcal, meningitis.

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Introduction

Meningitis can be caused by a wide variety of infectious and non-infectious causes.[1] The estimated annual incidence of bacterial meningitis in the general South African population is 4 in 100 000. The incidence in children younger than one year of age is highest at 40 in 100 000, followed by an incidence of 7 in100 000 in children aged 1-4 years.[1] The majority of meningitis cases are caused by *Streptococcus pneumoniae* in African countries with high rates of human immunodeficiency virus (HIV) infection.[2] Pneumococcal meningitis was diagnosed in 34% of patients with invasive pneumococcal disease (IPD) in a study on children aged one year and younger, admitted to hospital for IPD second only to pneumonia, which occurred in 50% of this study population.[3] A report from the Netherlands on 696 cases of bacterial meningitis concluded that when compared to meningococcal meningitis, the mortality rate was significantly higher, and an unfavourable outcome was six times more common, with pneumococcal meningitis.[4]

Despite the availability of effective treatment, the case fatality rate for bacterial meningitis in adults in two large case series was approximately 25%. It should be noted that 21-28% of survivors present with transient or permanent neurological morbidity.[2]

Classification and aetiology

The meninges surround and protect the brain and spinal cord, and consist of three parts, i.e. the pia mater, arachnoid mater and dura mater.[5,6] Cerebrospinal fluid (CSF) between the arachnoid mater and pia mater (the subarachnoid space) and in the cerebral ventricles immerse the brain and cushion it against physical damage. Meningitis is inflammation of the arachnoid mater and the CSF. It is considered a medical emergency.[1]

Pathogenesis

S. pneumoniae is an encapsulated, Gram-positive, anaerobic diplococcal bacterium, with more than 90 known serotypes on its capsular surface.[7] The reservoir for *S. pneumoniae* in humans is the nasopharynx. Fifteen per cent of children are colonised by the time they are six months old, and 40% by 19 months of age.[7] Although most people are carriers of *S. pneumoniae,* only susceptible individuals develop noninvasive disease, i.e. sinusitis, otitis media or community-acquired pneumonia.[5,7]

Invasive disease occurs when *S. pneumoniae* enters the bloodstream, resulting in bacteraemia, leading to secondary

complications, such as arthritis, endocarditis and meningitis. After penetrating the meninges, bacterial replication within the subarachnoid space leads to an inflammatory response which further facilitates bacterial penetration.[7] Inflammation and swelling are followed by oedema, increased pressure and resultant ischaemia.[5,6] The mortality rate of untreated bacterial meningitis approaches 100%. Even with optimal treatment, there is a high failure rate and neurological sequelae, and especially with pneumococcal meningitis.[6]

Risk factors

Certain patients are at increased risk of developing invasive disease, including meningitis. These include certain underlying conditions, as well as the geographical location. Table I provides a summary of the risk factors for the development of invasive disease.

Table I: A summary of the risk factors for the acquisition of invasive pneumococcal disease in children and adults[2,6]

Children	Adults
• A CSF leak • A cochlear implant • Congenital or acquired asplenia • Splenic dysfunction • Sickle cell disease and other haemoglobinopathies • HIV infection • A low birthweight, applicable if younger than six months of age • Exposure to siblings and other children at day care* • Chronic heart disease • Chronic lung disease • Chronic renal failure and nephrotic syndrome • Immunosuppression due to immunosuppressive treatment or radiation, and conditions such as lymphomas or leukaemias, as well as solid organ transplantation • Congenital immunodeficiency	• A recent head trauma • Neurosurgery or medical devices, e.g. a CSF shunt • Surgical asplenia • Functional asplenia • HIV infection • Alcoholism • Injection drug use • Rhinorrhoea or otorrhoea • A recent infection, especially a respiratory or ear infection • Diabetes mellitus

CSF: cerebrospinal fluid, HIV: human immunodeficiency virus
*The risk in children aged 6-23 months increases for the first two months after starting day care, and decreases after six months

Signs and symptoms

The signs and symptoms of pneumococcal meningitis are similar to those of other types of bacterial meningitis.[6] Most patients present with fever, and the signs and symptoms of meningeal inflammation, including headaches, neck stiffness and altered mental status.[1] Although one or more of these findings may be absent, virtually all patients present with at least one of the classic triad symptoms, i.e. a fever, neck stiffness and altered mental status.[8] Although most adults have a high fever, a small percentage present with hypothermia, but almost none of the patients with bacterial meningitis have a normal temperature.[9] Patients with pneumococcal meninigitis are more likely to present with the classic triad, whereas patients with meningococcal meningitis often present with a rash. The elderly present with lethargy and an altered level of consciousness, but without fever. Other manifestations in adults include photophobia, vomiting, seizures, cranial nerve palsies, papilloedema, arthritis and the late presentation of hearing loss.[1,5,9]

Clinical presentation in children is age related. Symptoms in children include respiratory distress, jaundice, anorexia, vomiting, diarrhoea, restlessness, irritability, back pain and/or a bulging fontanelle.[2] The symptoms of meningeal inflammation in children are often preceded by those of an upper respiratory tract infection.[2] Children with pneumococcal meningitis are more likely to present in a semi-comatose or comatose state, and to have focal neurological findings, e.g. cranial nerve palsy, than children with meningitis due to other bacterial infections.[6]

Treatment

The basic principles of treatment

It is imperative that antimicrobial treatment is started as soon as possible; if possible within three hours of admission. Primary healthcare treatment guidelines in South Africa recommend initial emipiric treatment with intramuscular ceftriaxone, i.e. 80 mg/kg for children and 2 g for adults, before referral to a hospital.[10]

The only way to identify the causative organism is by performing laboratory tests. Preferably, testing should be carried out before antimicrobial treatment is started to ensure accurate results. Whenever possible, blood samples, and if it is safe, CSF samples via lumbar puncture, should be obtained, to identify the causative organism. Empiric treatment should be started directly after the lumbar puncture, while waiting for the results. Patients with focal neurological signs, new seizures, papilloedema or an altered level of consciousness should first undergo neuroimaging to determine whether or not it is safe to perform a lumbar puncture. Blood samples should be obtained before neuroimaging in these cases. Empiric treatment should start immediately after the blood samples have been obtained to avoid delaying treatment.[6,7] Patients with meningitis should be treated with an intravenous antimicrobial agent because of the general limitation of antimicrobial penetration into the central nervous system.[8] The penetration of antimicrobial agents into the CSF is enhanced in the presence of meningeal inflammation. As the inflammation subsides, the penetration decreases. Therefore, it is important to continue with the maximal parenteral dose to maintain adequate CSF concentration.[4]

Since humoral immunity is impaired within the CSF, it is important to choose an antimicrobial agent with a bactericidal effect to obtain optimal microbiological cure.

Poor clinical responses have been observed in patients treated with bacteriostatic therapy.[4]

Antimicrobial treatment

Treatment for bacterial meningitis of unknown aetiology should be started with intravenous ceftriaxone[1] or cefotaxime.[11] Ceftriaxone should not be administered to patients who are also receiving concomitant intravenous calcium-containing fluids. Cefotaxime is the preferred antimicrobial agent in these patients, and is also the preferred treatment in patients younger than three months of age.[1] Treatment should be reassessed when the microbiological results become available, or if there is no response to treatment within 72-96 hours of treatment.[11] If the organism is known to be *S. pneumoniae* and sensitive to penicillin, patients should be treated with intravenous benzylpenicillin for 10 days.[11] The duration of treatment is a guide only, and should be based on the individual clinical course and response to treatment.[1]

Patients who are allergic to penicillin should be treated with chloramphenicol if the tests indicate sensitivity.[11] Patients with an anaphylactic allergy to cephalosporins can be treated with vancomycin and ciprofloxacin, or moxifloxacin. Chloramphenicol or meropenem can also be used as alternatives. However, meropenem should be used only if absolutely necessary.[1]

Chemoprophylaxis is not necessary for the contacts of patients with pneumococcal meningitis.[6]

Drug-resistant Streptococcus pneumoniae

All strains of *S. pneumoniae* were uniformly sensitive to penicillin until outbreaks of antibiotic-resistant strains occurred in South Africa in the late 1970s. Since then, widespread resistance has developed to several classes of antibiotics, including the macrolides and lincosamides, tetracyclines, fluoroquinolones and glycopeptides.[12]

Risk factors for the development of drug-resistant *S. pneumoniae* include the following:[7,12]

- Antimicrobial use within the previous 90 days
- Extremes of age
- Underlying immunosuppressive condition, i.e. HIV infection, splenectomy, haematological malignancy, a transplant or chemotherapy within the previous four weeks and autoimmune disease
- Institutionalisation
- Nosocomial and nursing home acquisition of infection
- Clonal dissemination in a crowded environment
- Epidemiological and geographical association
- Community or household exposure.

Adults with penicillin-resistant strains should be treated with ceftriaxone. Despite the reported high prevalence of ceftriaxone resistance, the majority of resistant isolates still respond to high-dose ceftriaxone or cefotaxime.[1] Vancomycin should only be added when the minimum inhibitory concentration for ceftriaxone is confirmed to be 1 µg/ml or higher, or if there is a poor response after 48 hours of high-dose treatment with ceftriaxone.[1] Penicillin-allergic patients treated with chloramphenicol should be treated with intravenous vancomycin and oral rifampicin when the strains are resistant to chloramphenicol.[11]

Supportive treatment

Over- and under-hydration are associated with an adverse outcome. Therefore, it is important to monitor the fluid and electrolyte balance in patients with meningitis. Increased intracranial pressure can lead to patients becoming comatose. Elevation of the head of the bed to a 30° angle and hyperventilation are used to maintain the intracranial pressure at an optimal level.[4] Patients should be nursed in quiet, semi-dark surroundings, and attention given to nutritional status.[13] Adequate analgesia must be ensured with paracetamol, ibuprofen or morphine, or an effective combination of all three.[11]

Cortisone therapy (dexamethasone) prior to or with the first dose of antibiotic therapy is recommended by some specialists in developed countries to limit neurological sequelae in patients with pneumococcal meningitis.[7] It was shown in a meta-analysis of two large, well-designed studies in Thailand and Malawi that the administration of dexamethasone did not significantly reduce death or neurological disability in patients with meningitis.[1] Since the majority of participants in the study in Malawi were HIV-positive, the results of this study are particularly relevant to South Africa. Thus, treatment guidelines in South Africa do not recommend the use of adjunctive corticosteroids in patients with pneumococcal meningitis.[1]

Complications

Increased intracranial pressure due to inflammation and swelling leads to oedema and ischaemia in the brain.[5,6] Other acute complications include cerebral infarction, seizures, shock and inappropriate antidiuretic hormone secretion. Infection also spreads and causes arthritis, pneumonia and pericarditits. Disseminated intravascular thrombosis occurs.[6,13] Approximately half of all patients develop complications which improve with time. However, permanent moderate or severe disability persists in 22% of patients.[5] Some effects only present months or even years after the patient has recovered from pneumococcal disease.[5] Long-term neurological sequelae include deafness, blindness, motor paralysis and mental retardation.[13] Behavioural and emotional changes, such as temper tantrums and being clingy in children, as well as irritability and despondency in adults, are quite common, and such patients require referral to the mental health services. Damage to the brain and central nervous system also results in learning difficulties, speech and language problems, and

problems with coordination and movement, cerebral palsy and paralysis.[5]

Doctors should monitor and recommend appropriate follow-up care for patients who recover from pneumococcal disease. This includes physiotherapy, occupational therapy, speech and language therapy, educational support and hearing tests.[5]

Prevention

The risk of pneumococcal infection can be reduced through vaccination. In South Africa, the pneumococcal conjugate vaccine (PCV) was introduced as routine vaccination of children in 2009.[14] The PCV-7 vaccine protected against seven of the *S. pneumoniae* strains. The PCV-10 and PCV-13 vaccines are currently available in South Africa, and protect against 10 and 13 strains, respectively.[15,16]

By 2012, the PCV-7 vaccine had reduced the incidence of invasive pneumococcal disease by 49%. The benefits were not only achieved from direct effects in patients who had been vaccinated, but were also obtained by indirect protection where exposure to infection was reduced in patients who had not been vaccinated, termed the "herd effect".[14] The higher the proportion of vaccinated persons, the lower the likelihood of an unprotected person coming into contact with an infected person.[7] In 2003, twice as many cases of IPD were prevented through the indirect effects of pneumococcal transmission than through its direct effect of protecting vaccinated children.[12] In addition to "herd" immunity, the introduction of PCV-7 also decreased the incidence of drug-resistant IPD[12] by more than 50% in South Africa.[14]

Conclusion

Pneumococcal meningitis is a medical emergency. Antimicrobial treatment should be started as soon as possible to reduce the risk of complications and neurological sequelae. Empiric treatment with ceftriaxone is recommended as soon as possible in South Africa, and should be adjusted as soon as the laboratory results are available. Treatment should continue for at least 10 days, but must be based on the clinical course and response to treatment. The use of supplementary cortisone to reduce neurological complications with pneumococcal meningitis is not recommended in South Africa. Routine vaccination against *S. pneumoniae* was included in the childhood vaccination schedule for South Africa in 2009, and protects via direct and indirect mechanisms. Vaccination is also recommended in other patients, based on individual risk factors.

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