Acute Bacterial Meningitis: A rational approach to management

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Abstract

Bacterial meningitis is one of a select group of febrile illnesses that may rapidly progress unless suspected early by the family practitioner. Unless appropriate therapy is initiated without delay, the outcome is often fatal. This article provides the family practitioner with an overview of current best practice when treating bacterial meningitis. Emphasis is placed on a high index of suspicion, particularly in certain patient groups like children where unusual atypical presentations are common. Empirical treatment options by age group for immediate therapy is discussed and the useful array of diagnostic modalities available is catalogued. The issue of chemoprophylaxis for close contacts of meningococcal disease patients and the importance of immediate notification are succinctly discussed. On a prevention note, the appropriateness of providing vaccination to travellers is considered.

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Introduction

Acute bacterial meningitis was first recognized as a fatal disease in 1805 and despite the availability of potent antibiotics, morbidity and mortality from the disease remain very high. [1,2] The incidence of bacterial meningitis is approximately 5 cases per 100 000 population.[3] Poor outcomes remain common and, a recent report on bacterial meningitis in infants found that sixty-one percent who survived developed disabilities and neurological deficits,[4] while a review of 493 episodes of bacterial meningitis in adults documented an overall case fatality rate of twenty-five percent. [5] This article provides an update on an approach to the diagnosis, investigations, empirical therapy, and preventive measures in bacterial meningitis.

Discussion

Diagnosing bacterial meningitis

The organisms, which most frequently cause acute bacterial meningitis, vary according to the age of the patient. In the neonatal period and in infants up to 3 months of age, *Escherichia coli, Listeria monocytogenes* and Group B streptococcus are the most common pathogens. In infants and young children from 3 months to 6 years of age, *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis* are the most important pathogens. In adults, *Streptococcus pneumoniae* and

Neisseria meningitidis predominate and in the elderly, *Streptococcus pneumoniae* and *enteric Gram-negative bacilli* are the most common pathogens (Table I). In HIV infected patients, *Streptococcus pneumoniae* is the most important bacterial cause of meningitis. Community–acquired *Gram negative bacillary meningitis* occurs with increasing frequency in patients suffering from diabetes, malnutrition, chronic illnesses and alcoholism.[3]

In most patients, the clinical presentation of meningitis is a combination of systemic symptoms including a short-lived prodromal respiratory illness or sore throat, followed by fever, malaise, vomiting, and features of central nervous system involvement i.e. headache, photophobia, neck stiffness and alteration(s) of consciousness. The disturbance in consciousness progresses through irritability, seizures, confusion, drowsiness, stupor, and coma. Dehydration and vascular collapse may lead to shock (Waterhouse-Friderichsen syndrome), especially in meningococcocal septicemia. Since, acute bacterial meningitis especially that due to *Neisseria meningitidis* can be lethal in hours, accurate diagnosis and treatment are urgent. Hence, any unexplained fever in infants accompanied by irritability, poor feeding, vomiting, lethargy, and seizures should alert the family practitioner to the possibility of acute bacterial meningitis. Meningitis in young people may present as a manic illness, psychosis or be confused with drug abuse. A careful examination for abrupt neck flexion in the supine position resulting in involuntary flexion of the hip **(Brudzinski's sign)**, and / or attempts to extend the knee from the flexed-thigh position being met with strong passive resistance **(Kernig's sign)** are strongly suggestive of meningitis. In the elderly, the presentation may be atypical with absence of fever or stiff neck, but the presence of mental confusion should draw attention to the possibility of bacterial meningitis. A list of the differential diagnoses of acute bacterial meningitis is presented in Table II.

Table I: Most likely organisms in acute bacterial meningitis according to patient age.

Age	Bacteria
Birth to 3 months	*Escheria. coli, Listeria monocytogenes,* Group B streptococcus, *Klebsiella pneumoniae*
3 months - 6 years	*Hemophilus influenzae type b, Neisseria meningitidis, Streptococcus pneumoniae*
6 - 60 years	*Neisseria meningitidis, Streptococcus pneumoniae*
Above 60 years	*Streptococcus pneumoniae, Gram-negative bacilli, Neisseria meningitidis*

Table II: Differential diagnoses of acute bacterial meningitis

- Malaria
- Typhoid
- Tick bite fever
- Viral enecphalitis
- Viral meningoenencephalitis
- Drug overdose / intoxication
- Pneumonia
- Septicaemia
- Urinary tract infections

Investigations

In meningitis, the cornerstone of laboratory diagnosis is examination of the cerebrospinal fluid (CSF) after lumbar puncture. The classic findings are an elevated opening pressure, increase in white blood cells with a predominance of polymorphonuclear leucocytes, low glucose and elevated protein concentrations. Gram staining of the CSF coupled with culture is necessary to identify the causative organism(s), as a microscopically normal CSF does not exclude meningitis particularly in early meningococcal disease and in immunocompromised patients. A culture and antibiotic susceptibility test is mandatory and will be available in 24-48 hours after incubation. Lumbar puncture has been associated with occasional deaths due to brainstem herniation. Furthermore, there are a few additional tests available for identifying the pathogens that cause meningitis. These include:

Latex agglutination test: This is a rapid test for the detection of bacterial antigen. The test is most sensitive for *Hemophilus influenzae* b (81 – 100%), followed by *Streptococcus pneumoniae* (50 – 69%) and *Neisseria meningitidis* (30 – 70%) with a specificity of 96 – 100% for all three bacterial antigens. This test is reliable in confirming the presence of meningitis in a patient however; a negative Latex agglutination test does not exclude meningitis. The test is most useful in patients with partially treated meningitis where the Gram stain and culture are both negative.

Polymerase chain reaction (PCR): Previous antibiotic treatment reduces

the chance of obtaining a positive Gram stain or culture of the CSF by about half. Polymerase chain reaction amplification of bacterial DNA to detect meningococci in cerebrospinal fluid or blood is now used widely in England and Wales. When performed on peripheral blood, it is much more sensitive than blood culture, but specificity is yet to be evaluated in large, clinically relevant populations.[6] This test is particularly useful in the 50% of untreated patients in whom blood cultures produce negative results and in patients who receive parenteral antibiotics before samples are taken.

Skin scrapings (in meningococcal disease): Since 1917, physicians have been taking skin biopsies as an adjunct to standard diagnostic tests to diagnose meningitis. Gram staining of skin scrapings of rashes seen in meningococcal meningitis is a reliable test, as the cutaneous lesions are manifestations of dissemination mediated by blood circulation. In a study on the reliability of the test, it was found that it gave a positive result in 80% of meningococcal rashes, which is a higher success rate than that reported for aspiration or biopsy of lesions.[7] This procedure is simple and highly rewarding in rashes when meningococcal infection is suspected. It is important to note that a negative result does not exclude meningococcal meningitis.

Empirical therapy in bacterial meningitis

The three major factors affecting the bactericidal activity of an antibiotic in CSF are its relative degree of penetration into the CSF, concentration, and intrinsic activity in infected CSF. The concentration of antibiotic in cerebrospinal fluid needed for maximal bactericidal activity is not known but in experimental meningitis, maximal bactericidal activity occurs when the concentration of an antibiotic is 10-30 times the minimal bactericidal concentration against the organism *in vivo*.[8,9] One explanation for this difference is that infected CSF decreases the activity of the antibiotic and, the increased concentration of protein reduces the concentration of active free drug of highly protein-bound beta-lactams such as cephalosporins.[8] Since the activity of beta-lactam e.g. penicillin G on bacterial cell-wall synthesis depends on bacterial cell division, fever may impair its bactericidal effect *in vivo*.[10]

There are a number of issues in the empirical treatment of meningitis that need to be understood. The following questions are the most often asked:

- When should the initial dose of antibiotic be given in bacterial meningitis?
- What empirical antibiotic should be prescribed in bacterial meningitis?
- Are "steroids" necessary in the management of bacterial meningitis?

When should the initial dose of antibiotics be given in bacterial meningitis? Given the knowledge that acute bacterial meningitis especially that due to the meningococcus can be lethal in hours, immediate initiation of antibiotic therapy is advocated on suspicion of disease. Although it is always preferable to first take a CSF sample so that definitive diagnosis is possible, an accusation of failure to treat promptly is a common reason for malpractice litigation.[11] The argument arises from fear that a delay in therapy of a few hours may adversely affect the prognosis and outcome of the disease, but clinical data are inconclusive on this matter. Once established on empirical therapy, subsequent treatment has to be guided by the patient's clinical response and by the culture and sensitivity results of the CSF. Obviously if the patient improves clinically, then empirical therapy is continued. In over 20 published studies comparing morbidity and mortality in patients with bacterial meningitis according to the duration of symptoms before presentation at the hospital, about half did not show any correlation between the duration of symptoms and the clinical outcome.[12] Also, the clinical outcome of bacterial meningitis is affected by many variables including age, coexisting illness, virulence of the organism, and severity of the illness. Until there is sufficient data contrary to immediate empirical therapy, it is safer to institute prompt antibiotic treatment.

What empirical antibiotic should be prescribed in bacterial meningitis? The choice of antibiotic will depend on the most likely pathogens based on the patient's age and underlying health status.[13] In infants, ampicillin combined with an aminoglycoside is still the initial treatment of choice.[14] In children, empirical therapy of bacterial meningitis should include coverage of *Hemophilus influenzae, Streptococcus pneumoniae* and *Neisseria meningitidis*.[15] In adults, empirical treatment should cover for Streptococcus pneumoniae and *Neisseria meningitidis*.[16] *Streptococcus pneumoniae* resistant to penicillin has emerged as a major problem in certain parts of South Africa and most demonstrate intermediate resistance to penicillin, accounting for about 50% of isolates in young children.[17] Unlike pneumonia caused by these strains where high doses of penicillin can still lead to a good response, it is not adequate in bacterial meningitis. A third generation cephalosporin, notably ceftriaxone, is the therapy of choice, particularly with the increase in HIV-related disease. In the elderly, the same antibiotics used in the adult patient will suffice. Ceftriaxone is also appropriate for *Haemophilus influenzae* and *Neisseria meningitidis* infections but treatment with ampicillin is necessary for the rare cases of *Listeria meningitis* (Table III). Therapy should be modified when the results of CSF culture and antibiotic sensitivity become available.

Are "steroids" necessary in the management of bacterial meningitis? Over the last few years, several trials have indicated that when steroids are given early in the treatment of bacterial meningitis, they dampen the inflammatory response and reduce the incidence of deafness and other neurological complications associated with the disease in children. This is evident in randomised

controlled trials done in children with meningitis due to *Haemophilus influenzae*, but is appreciable also for other common forms.[16,17] Unfortunately, the benefits in adults are far less clear where infection is with *Streptococcus pneumoniae* or *Neisseria meningitidis*. Steroids e.g. dexamethasone potentially reduce brain oedema and consequently lower intracranial pressure, as well as leakage of serum proteins into the CSF. Also, the concentration of arachidonic acid metabolites and production of cytokines are reduced. When steroids are administered in children with bacterial meningitis, it is important that the diagnosis is clear as conditions like brain abscess or tuberculous meningitis may be masked, misdiagnosed and worsened by steroids. When steroids are given, high doses should be administered i.e. intravenous dexamethasone 0.15mg/kg six hourly for the first four days.[16]

Preventive measures in meningitis In recent years, outbreaks of meningococcal meningitis have been reported in many African countries within the "Sahel meningitis belt" and it is important that South Africans travelling into this area are aware of this risk. *Neisseria meningitidis* serogroup A is by far the most common organism in epidemics of cerebrospinal meningitis in Africa and factors that affect its spread include overcrowding, acute respiratory tract infections, prolonged drought and decreasing antibody levels in the population. For the family practitioner, it is imperative to be sure, of the advice given to travelling patients, communities, family members, or health staff who become exposed to patients suspected of meningococcal meningitis. A good knowledge of the vaccine requirements for travellers into the African "meningitis belt" and Moslem pilgrims to Saudi Arabia is essential.

What should be done for contacts of patients with meningococcal meningitis? Close contact with the nasopharyngeal secretions of a patient with meningococcal disease is necessary for transmission. The risk is thus significantly higher for family members or other very close contacts.[20] It is therefore essential to offer rifampicin, ciprofloxacin or ceftriaxone prophylaxis to members of the same household, nursery school class, "kissing" contacts or those that shared eating utensils in the days prior to onset of clinical disease. The standard approach for adults remains rifampicin 600mg twice a day for two days. An alternative is to use a single dose of ciprofloxacin 500mg and, this has proved effective for prophylaxis with the added advantage of improved compliance. It must be emphasized that chemoprophylaxis is not 100% effective, so close contacts should be advised of the symptoms of disease and immediate presentation on the onset of symptoms. Doctors, nurses and associated health workers who are directly exposed to nasopharyngeal secretions or pulmonary oedema from such patients, largely through resuscitation, intubation or airways toilet, may therefore be at increased risk of disease and should be offered antibiotic prophylaxis.[21] Effective community response to outbreaks will only be assured if every case of proven meningococcal disease is immediately reported to local or provincial health authorities, as required by law.

Protecting travellers against meningitis It is important that the pre-travel consultations be used to check the routine immunisation status of travellers. When considering bacterial meningitis, this is of particular importance for infants (BCG and *Haemophilus influenza* type b) and in the elderly (pneumococcal vaccine). Meningococcal meningitis outbreaks occur in regular cycles in the "Sahel

Table III: Treatment of acute bacterial meingitis according to patient age.

Age	Treatment
Birth to 3 months	**Ampicillin** IV 200mg/kg/24 hours (6 hourly) for 14 days plus **Gentamicin** IV 2,5mg/kg 8 hourly for 10-14 days (give 12 hourly in neonates <7 days of age)
3 months - 6 years	**Ceftriaxone** IV 80mg/kg/24 hours as a single dose for 10-14 days -or- **Cefotaxime** IV 200mg/kg/24 hours (8 hourly) for 10-14 days
6 - 60 years	**Ceftriaxone** IV 4gm/day divided in 12 hourly doses for at least 10-14 days (first choice due to penicillin-resistant pneumococci) -or- **Benzylpenicillin** IV 20-24 MU/day in 4-6 divided doses for 7 days
Above 60 years	**Ceftriaxone** IV 4gm/day divided in 12 hourly doses for at least 10-14 days (first choice due to penicillin-resistant pneumococci) -or- **Benzylpenicillin** IV 20-24 MU/day in 4-6 divided doses for 7 days

meningitis belt" which stretches from Senegal to Ethiopia and, *Neisseria meningitidis* serogroup A is by far the most common causal organism. [22] In recent years there have been outbreaks in Mozambique and Nepal. The most profound outbreaks to have affected travellers have however occurred amongst pilgrims to Mecca, Saudi Arabia. One study calculated that the incidence rate per month of stay of menigococcal meningitis in international travellers to any destination was 0.4 per million travellers, compared to 2000 per million for pilgrims to Mecca.[23] Thus compulsory immunisation demanded by the Saudi Arabian government appears well grounded. Travellers to hyper-endemic areas who may have close contact with the local population should be advised to consider vaccination. Currently available vaccines offer protection against serogroup A and C meningococci which are the main agents of epidemics. It is thus essential that family practitioners and travel clinics that advise travellers ensure that they remain updated on the global occurrence of meningococcal disease outbreaks. The conjugated HiB (*Haemophilus influenzae B*) conjugate vaccine is an additional vaccine that has provided remarkable public health progress. Its addition in the Expanded Program on Immunisation in many countries in recent years has seen a marked decrease in the occurrence of serious infections due to *Haemophilus influenzae B* meningitis in early childhood.

Conclusion

In summary, acute bacterial meningitis especially that due to *Neisseria meningitidis*, can be lethal in hours. It is mandatory to make an accurate diagnosis and institute empirical treatment immediately. Hence, any unexplained fever in infants accompanied by irritability, poor feeding, vomiting, lethargy, and seizures should alert the family practitioner to the possibility of acute bacterial meningitis. Also, meningitis in young people may present as a manic illness, psychosis or be confused with drug abuse. A good knowledge of the CSF findings, investigations, and treatment protocols according to the age groups is essential. It is hoped that the family practitioner will adopt our rational approach to managing patients with acute bacterial meningitis, their contacts and give relevant advice to travellers as the latter visit countries within Africa's "meningitis belt" and Saudi Arabia.

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