Treatment of acute bacterial meningitis

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Ever since the early days when causative antimicrobial treatment of bacterial meningitis was introduced, it has been a constant race between changes in the incidence of the different causative organisms and their sensitivity to the antimicrobial drugs available and introduction of new antimicrobials; a competition which seems unavoidable but which has given very limited therapeutic or prophylactic gains.

The overall mortality of bacterial meningitis is still 7-14 per cent if caused by *N. meningitidis*, 3-10 per cent of *H. influenza*, 30-60 per cent for *S. pneumoniae* and more than 20 per cent for *Listeria monocytogenes*\(^1\), despite intensive care and modern antibiotics.

Acute bacterial meningitis is therefore still a great medical challenge, also when it comes to choosing the best antimicrobial treatment.

Incidence of acute bacterial meningitis

In the United States the incidence of bacterial meningitis ranges between 5.4 and 7.3 per 100,000\(^2\), an incidence which has been increasing within the last 20 years. The increase is not explained by changes in age distribution of the population, as the age specific incidence rate has increased more than 10-fold for Gram negative meningitis and sepsis caused by *H.influenzae* and *N. meningitidis*\(^3\)\(^,\)\(^4\)\(^,\)\(^5\). The same overall increase is seen in Europe, although there are considerable geographical differences in the distribution of individual bacterial species. In addition to more permanent geographical differences, *N. meningitidis* epidemics may change the incidence pattern dramatically.

According to the statistical information from the health information section, Ministry of health, (kindly prepared by Dr. A. Lambourne) approximately 440-490 cases of acute meningitis are being reported yearly for the last 5 years. If the Omani population is 2 million the incidence of meningitis (bacterial as well as aseptic) is 2.4:10,000. Estimating that 50% are aseptic, this brings the incidence of acute bacterial meningitis to 1.2:10,000.

Geographical differences in the incidence of different bacterial species

In Europe and sub-Saharan Africa, *N. meningitidis* is the commonest cause of bacterial meningitis in older children and adults. *H. influenzae* is the commonest in the United States and in Australia and *S.pneumoniae* in some African states\(^1\)\(^,\)\(^2\). How Oman fits into this is so far unknown as there are no publications or information available on the causes of bacterial meningitis at present.

Age related differences in the incidence of the different bacterial species

Neonatal meningitis is predominantly caused by...
group B streptococci. Eschericia coli K1 and Listeria monocytogenes, all acquired from the mother or from nursing staff. H. influenzae is the commonest cause in children aged up to 6 years, followed by N. meningitidis and S. pneumoniae. Later in life, N. meningitidis and S. pneumoniae prevails and in the elderly L. monocytogenes becomes of significance again.

The changes with age may reflect the loss of maternal antibodies together with a relative immunodeficiency early and late in life giving room for more opportunistic pathogens.

With a high percentage of the population in Oman being below the age of 10, one would expect a particularly high incidence of H. influenzae meningitis.

Changes in incidence of bacterial pathogens causing meningitis due to selection

The excessive use of sulphonamides in the past caused a selection of the sulphonamide resistant N. meningitidis type B on behalf of the previous type A. More recently S. pneumoniae and N. meningitidis have been found resistant to not only sulphonamides but also penicillin in same areas. The N. meningitidis type C changed to type Y in areas where type C vaccine was used extensively.

The increase in H. influenzae meningitis in the United States is believed to be caused by a reduction in the natural immunity developing in young adults due to the lesser exposure to benign H. influenzae infections, all treated very early with antibiotics.

The use of antibiotics is rising in Oman and so changes in the prevalence of aetologies are likely to be happening at the moment, which together with changes in antibiotic sensitivity will need close observation.

Immunosuppressive treatment is becoming increasingly frequent in Oman in the management of malignant haematological and autoimmune diseases and in relation to organ transplantations.

Bacterial meningitis in the immunosuppressed is often caused by otherwise rare opportunistic pathogens of which Listeria monocytogenes is the most frequent. Patients infected with the Human Immunodeficiency Virus are similarly susceptible to less virulent pathogens.

Changes in host susceptibility to bacterial meningitis

Ethnic differences in the susceptibility to bacterial meningitis has been described, not only based on congenital deficiencies in complement or immunoglobulin production. It is difficult to decide whether such "idiopathic" ethnic differences are caused mostly by different socioeconomic condition or whether some unknown inherited factors exist. Of known predisposing factors are conditions which are very frequent in Oman like pregnancy, diabetes mellitus and most significant of all, homozygous sickle cell disease. The preoccupation of the reticuloendothelial cells in sickle cell disease increases the risks of particularly pneumococcal meningitis by 36 times. With the high prevalence of sickle cell disease and diabetes in Oman it is likely that the overall incidence of meningitis would be higher than what has been found in Europe or U.S.A. and also include a larger percentage caused by encapsulated bacteria like S. pneumoniae and H. influenzae which again would give a less favourable prognosis.

Changes in sensitivity to antimicrobials

A number of changes in the past has already been mentioned. Of greatest concern at the moment are the following facts: The first report on ampicillin resistant H. influenzae came in 1974 and only 15 years later, 30% of all isolates in Spain and Belgium were found to be resistant. The ampicillin resistance varies greatly from country to country, related to the use of antibiotics. Multiresistant strains of H. influenzae were first reported from Thailand in 1980, 3 years later 18 percent of all H. influenzae in Barcelona were resistant to ampicillin and chloramphenicol together with a large number of other antibiotics, except for β-lactamase resistant cephalosporins. This resistance is caused by a plasmid mediated enzymatic inactivation and can as such spread to microorganism which has not been exposed to the antibiotics in question.

A recent survey in Oman has shown that 33 percent of H. influenzae isolates were resistant to ampicillin and 5.68 per cent were resistant to chloramphenicol. The true chloramphenicol resistance might be even higher as the number of isolates tested were small. The percentage of
resistant *H. influenzae* is most likely going to increase dramatically within the next few years, as it has happened in most other countries. For the last 10-20 years, reduced sensitivity to penicillin among *S. pneumoniae* isolates has been reported from an increasing number of countries (6). Highly resistant strains are still confined to fewer countries. The latter being often resistant to both penicillin and chloramphenicol, while being sufficiently sensitive, although reduced, to third generation cephalosporins to allow cure. Multiple gene mutations are involved in this resistance altering the penicillin binding proteins, and the progression of resistance may thus be slower than what is the case for *H. influenzae*. No resistance has been reported in Oman yet but it would be advisable to continue in-vitro penicillin sensitivity testing.

β-lactamase producing *N. meningitidis* has very recently been identified as a problem in a number of western countries. Again, the alarming thing is the rapidly increasing incidence (from 1 : 3264 to 9 : 168 in a few years in Barcelona) (5).

These resistant organisms were sensitive to third generation cephalosporins. Sensitivity testing of positive cerebrospinal fluid (CSF) cultures of any kind done at the Royal hospital in 1991 (total of 1668) showed that the overall resistance to ampicillin was 2.5%; chloramphenicol 1.1% and to cefotaxime 0.5%. Only 13 strains of *H. influenza* were cultured, all sensitive to ampicillin and 19 strains of *S. pneumonia*, of which 1 was resistant to chloramphenicol.

The figures are extremely small and therefore inconclusive, but at least show the need for a continuous surveillance of bacterial sensitivity in order to be ahead of the occurrence of primary treatment failure due to resistance. (The data were kindly provided by Dr. H.M.A. Hussain, specialist, dept. of microbiology, Royal hospital).

**Initial empiric antibiotic treatment of acute bacterial meningitis**

The prognosis with respect to survival as well as sequelae is mostly dependant upon early start of sufficient antibiotic treatment. Treatment should not await the results of CSF investigations and should cover as many pathogens as possible, at least the four major pathogens: *N. meningitidis, H. influenzae, S. pneumoniae* and *L. monocytogenes*. The treatment should be standardised as far as possible and be the same for paediatric as well as adult patients if possible in order to reduce any possible confusion and delay.

Chloramphenicol with or without ampicillin is the most widely used empiric treatment in Oman, as it was in the past in most other places in the world. Despite the well known risks of fatal pancytopenia (6) and its relative contraindication in neonates due to "grey baby" syndrome, and the fact that chloramphenicol is only bacteriostatic, the treatment was in the past found reliable in most cases.

As the incidence of multiresistant *H. influenzae* increased, the use of chloramphenicol ceased and β-lactamase resistant cephalosporins became widely accepted as the initial treatment of meningitis or sepsis (10,15).

Carefully controlled studies have demonstrated that the treatment of acute bacterial meningitis with third generation cephalosporins (like cefotaxime or ceftriaxone) are as effective as ampicillin and chloramphenicol if not better (15). Ceftriaxone, which is the only second generation cephalosporin penetrating the blood-brain barrier sufficiently to be used in the treatment of meningitis, has shown in recent studies to give a delayed sterilisation of the cerebrospinal fluid and possibly a higher incidence of hearing impairment, compared to those receiving ceftriaxone.

When it comes to selecting the most suitable third generation cephalosporins there are various considerations.

Ceftriaxone has the advantage of having a serum half-life of approximately 8 hours, making once daily administration sufficient compared to a half-life of 1 hour for cefotaxime.

Ceftriaxone was found to sterilise the cerebrospinal fluid more rapidly with fewer fatal cases in one study compared to cefotaxime while another study failed to confirm the difference (15).

Ceftriaxone competes with bilirubin for albumin binding sites, which could be a disadvantage in the treatment of neonates. The use of ceftriaxone in neonates is therefore usually discouraged even though a dose reduction might be sufficient. Diarrhoea is a reversible side effect of most
SINGLE AND COMBINED VACCINES

Brucellosis Cholera Diphtheria Hepatitis B
Influenza Measles Meningitis Mumps
Pertussis Pneumococccia Poliomyelitis Rabies
Rubella Tetanus Tuberculosis Typhoid
Yellow Fever

PASTEUR MÉRIEUX
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58, av. Leclerc 69007 Lyon - France
ampicillin and sensitivity) Continued antibiotic treatment (after Q 6 hourly patients ceftriaxone has to be reduced to Ceftriaxone therefore of particular importance to start a allergy, cephalosporins extent the possibility of a reduced sensitivity of to third generation resistant ampicillin for the coverage of N. meningitidis, they are present (33%) and will most likely spread very rapidly in the future. It is therefore of particular importance to start a continuous surveillance of the causative pathogens and their sensitivity in bacterial meningitis in Oman, the result of which should be published at regular intervals.

**Recommendations**

Ceftriaxone 100mg/kg IV Q 24 hourly plus ampicillin 35mg/kg IV Q 4 hourly. (Dose of ceftriaxone has to be reduced to 50mg / kg in patients < 1 month or > 75 years old).

In case of penicillin / cephalosporin allergy:

Chloramphenicol 25 mg / kg, maximum of 1.0g IV Q 6 hourly (dose has to be reduced in neonates of less than 1 month old).

Continued antibiotic treatment (after identification and sensitivity)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Treatment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. influenzae</td>
<td>Ceftriaxone 100mg / kg IV Q 4 hourly for 10 days.</td>
</tr>
<tr>
<td>L. monocytogenes</td>
<td>Ampicillin 35mg / kg IV Q 4 hourly for 14 days.</td>
</tr>
<tr>
<td>E. coli</td>
<td>Ceftriaxone 100mg/kg IV Q 24 hourly for 10 days.</td>
</tr>
<tr>
<td>Staph. aureus</td>
<td>Methicillin / cloxacillin 35 mg / kg IV Q 4 hourly + fucidine 500mg IV Q 8 hourly for 14 days.</td>
</tr>
<tr>
<td>Others</td>
<td>According to sensitivity.</td>
</tr>
</tbody>
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Dose and length of treatment may have to be increased in case of primary focal infections, otitis, osteomyelitis, sinusitis and brain abscess.

**Steroids in meningitis**

Despite timely and appropriate antimicrobial therapy of bacterial meningitis, neurological sequelae still occurs despite the bactericidal effect of the third generation cephalosporins. In children severe hearing loss occurs in 15-17 per cent of the cases. The mechanism of damage with the liberation of a whole range of cytokines including tumour necrosis factor, initiated by the release of endotoxin from the Gram negative bacteria, is now well known. There is a clear evidence that dexamethasone reduces the liberation of such cytokines but the clinical benefits of dexamethasone are less certain. The conclusion at present seems to be that there is a reduction in hearing loss from H.influenzae meningitis in children by administration of dexamethasone (0.6mg/kg/day in four divided doses for 4 days, the first dose given as early as possible).

But dexamethasone cannot at present be recommended as routine adjunctive treatment in all bacterial meningitis before further evidence has been gained.

The use of anti-endotoxine and anti-serum against specific cytokines is still only at experimental level but gives hopes for further reduction in mortality and sequelae in the future.

**References**

1. McGee ZA, Bangner JR. Acute meningitis. In Mandell GL, Douglas RC, Bennett JE (Eds.) Principles and practice of
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Readers are advised to refer, in conjunction with this article, to pages 27 to 29 of Medical Newsletter, Vol. VIII. No. 2, November 1991 issue, as well as pages 43 to 46 of this issue, dealing with the antibiotic resistance pattern of common organisms in the Royal hospital.

Editor