

Meningitis

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Introduction

Acute meningitis is a serious disease with high rates of mortality and long-term morbidity. Early treatment of bacterial meningitis improves outcomes and it is therefore important to treat suspect cases presumptively prior to hospitalisation. This applies in any setting, but is even more important in remote locations where admission to hospital might be delayed.

Meningitis may follow an acute or chronic course and the causes of these respective forms of the disease differ. However, the indolent nature of the chronic form means that pre-hospital diagnosis and treatment is often not possible. Thus it makes sense to target empirical treatment towards the known causes of the acute meningitis and to match this with the local epidemiology of the infection.

Epidemiology of meningitis in the NT

The authors are not aware of any studies done (after searching PubMed, NT CDC Bulletins and inquiring through colleagues) examining the overall relative frequency of the causative agents of meningitis in the NT. However, a study of the causative agent of 69 cases of childhood bacterial meningitis (excluding the neonatal period) in the NT between 1985–89 revealed that 58% were caused by Hib, 22% by pneumococcus and 16% were culture negative.¹ Only two cases were caused by meningococcus (with another two cases which were probable). This study also revealed that the incidence rate of meningitis in Aboriginal children less than five years of age was 337/100 000 per year, or 5.69 times that of non-Aboriginal children.¹

Looking at the rest of Australia, a study looking at the causes of paediatric bacterial meningitis in South Australia between 1979–89 found that, out of 80 episodes, 60 (75%) were caused by Hib, 10 (12.5%) by pneumococcus, 4 (5%) by meningococcus, 3 (3.7%) by Group B strep and one each by E. Coli, Moraxella and an enterococcus.² Similar findings were reported over a similar time in Western Australia.³

The three most common causes of meningitis are notifiable to the Centre for Disease Control. The numbers of cases in the NT over the 12 years to 2001 of Hib and meningococcal disease is depicted in the following figures.⁴

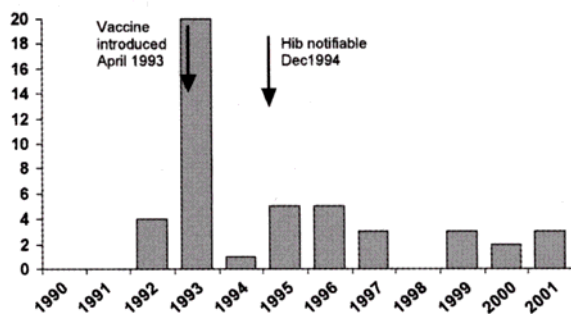


Figure 1: Notified cases of invasive *Haemophilus influenzae* type b disease in the NT 1990–2001. (Source: NT Notifiable diseases database)

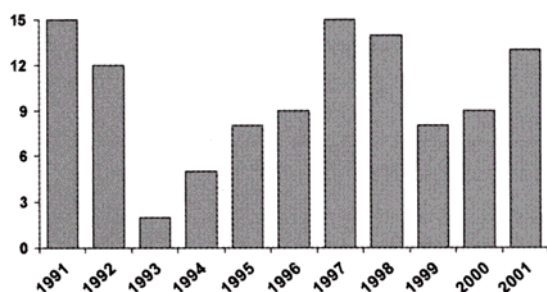


Figure 2: Notified cases of meningococcal disease NT 1990–2001. (Source: NT Notifiable diseases database)

It should be noted that these graphs include all cases of meningococcal and Hib disease and not just those of meningitis.

The following graph summarises recent data on pneumococcal meningitis for which there is an enhanced dataset in the NT.

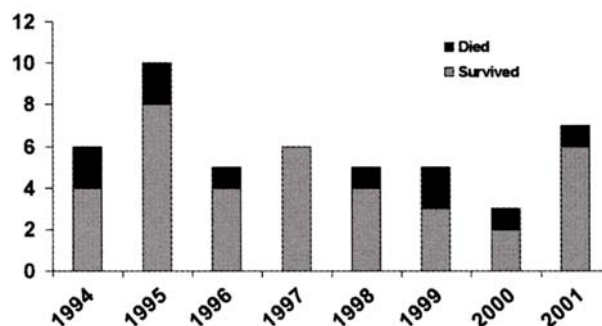


Figure 3: Number of notified case of pneumococcal meningitis including outcome, NT 1994–2001. (Source: NT Notifiable Diseases database)

In the 10 years to 2001 there were only four cases of Listeriosis, one case in 1994 and three in 2000.⁴

Aetiology and treatment

Most commonly acute meningitis is caused by viruses or bacteria. Other infectious agents such as rickettsiae, yeasts, spirochetes, protozoa and helminths have also been recognised as causes. There are also non-infectious causes such as tumours, drugs and connective tissue disease (SLE).⁵

The infectious causes* of meningitis which might be relevant in the NT are listed in table 1 below.⁵

Table 1: Potential infectious causes of acute meningitis in Northern and Central Australia

Viruses

- Enteroviruses (Cocksackie and Echo viruses)
- Mumps virus
- Herpe sviruses
- HIV
- Adeno viruses
- Parainfluenza viruses types 2 and 3
- Influenza virus
- Measles virus

Rickettsia

Scrub typhus (*Orientia tsutsugamushi*)

Bacteria

Haemophilus influenzae
Neisseria meningitidis
Streptococcus pneumoniae
Listeria monocytogenes
Streptococcus agalactiae (Group B strep)
Propionibacterium acnes
Staphylococcus epidermidis
Enterococcus faecalis
Escherichia coli
Klebsiella pneumoniae
Pseudomonas aeruginosa
Salmonella spp.
Nocardia spp.
Mycobacterium tuberculosis
Burkholderia pseudomallei

Spirochetes

Treponema pallidum
Leptospira spp.

Yeasts, protozoa and helminths

Cryptococcus neoformans
Naegleria fowleri
Angiostrogylus cantonensis
Strongyloides stercoralis

* An exhaustive list of causes would include pathogens not prevalent in Australia. Non-infectious causes are rare and are not relevant to this exercise.

This list is not meant to reflect the local epidemiology of the disease; nevertheless, the most frequent bacterial causes are similar to elsewhere in the country and the world, namely *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B. Less common bacteria — which are more likely to be found in cases in the very young, very old or immunocompromised — are *Listeria monocytogenes*, Group B streptococcus (neonates) and *Escherichia coli*. Also, it is worth noting that several of the other potential causative agents listed above cause non-meningitic disease in the NT at a higher rate than elsewhere in the country and therefore we need to be aware of these as possible causes. These include TB, melioidosis, salmonella, strongyloides, cryptococcus, syphilis, rickettsia and leptospirosis. Meningitis is a well described manifestation of TB infection and there have been documented reports of melioid and salmonella meningitis in remote communities in Australia.^{6,7}

The most likely viral causes are the enteroviruses (such as Echo and Cocksackie viruses).^{5,8} The yeast *Cryptococcus neoformans* can also cause meningitis, mainly, but not exclusively, in the immunocompromised.⁸

Table 2 (opposite) gives a summary of the potential causes of non-viral acute meningitis in the NT with recommended treatments.

As can be seen from the list in table 2, treatment with ceftriaxone and penicillin covers all the main six bacterial causes and five out of the other 13 causes in the list.

Table 2: Potential causes of acute meningitis in the NT with a list of first-line treatments*

Agent	First line antibiotic	With penicillin allergy	Reference/comments
Main recognised causes			
Haemophilus influenzae	Ceftriaxone or cefotaxime		Antibiotic Guidelines (ABGs)9, Mandell5
Neisseria meningitidis	Benzylpenicillin or ampicillin	Ceftriaxone	Mandell5, ABGs9, Meningococcal guidelines10
Streptococcus pneumoniae	Ceftriaxone or cefotaxime		The addition of empirical vancomycin in areas of increased resistance is recommended, but is currently not applicable in the NT. ABGs
Listeria monocytogenes	Benzylpenicillin or ampicillin	Co-trimoxazole	ABGs9, Mandell5
Streptococcus agalactiae (Group B strep)	Benzyl penicillin or ampicillin	Vancomycin	Ceftriaxone acceptable in penicillin allergy. Mandell5
Escherichia coli	Ceftriaxone or cefotaxime		Mandell5
Other potential causes in NT1			
Salmonella spp.	Ceftriaxone or cefotaxime		Price et al11
Burkholderia pseudomallei	Co-trimoxazole and one of: Ceftazidime Imipenem Meropenem		ABGs9
Mycobacterium tuberculosis	Isoniazid Ethambutol Rifampicin Pyrazinamide		ABGs9
Treponema pallidum	Benzylpenicillin	Doxycycline	ABGs9
Cryptococcus neoformans	Amphotericin and flucytosine		ABGs9
Strongyloides stercoralis	Invermectin or albendazole or thiabendazole		ABGs9
Orientia tsutsugamushi	Doxycycline		ABGs9
Leptospira spp.	Benzyl penicillin or doxycycline	Doxycycline	ABGs9
Other bacterial causes			
Staphylococcus epidermidis	Vancomycin		Mandell5
Klebsiella pneumoniae	Ceftriaxone or cefotaxime		Brooks12
Pseudomonas aeruginosa	Ceftazidime		Mandell5
Nocardia spp	Co-trimoxazole		Brooks12
Enterococcus faecalis	Ceftriaxone or cefotaxime		Mandell5

* The risk here is theoretical and not based on any epidemiological study and therefore the organisms are not listed in any order.

Changes for the 4th edition

In developing these guidelines, an important consideration has been deciding what level of treatment is appropriate in the bush given the remoteness and lengthy transit times to secondary centres. Specifically, is pre-hospital treatment (as recommended in other guidelines) sufficient or should early hospital treatment be started prior to transfer? Transit times to hospital from diagnosis depend on a multitude of things and can vary from 30 minutes to 12 hours; indeed, in some circumstances evacuation is not possible for several days. Usually, though, the transit time to a secondary centre (including the logistics) is 3–6 hours. Hence, even though in some circumstances what would be referred to as ‘pre-hospital’ treatment (in other guidelines) would be appropriate care, in other cases, and I would argue most others, it would be prudent to administer ‘early hospital’ treatment.

In reviewing the guidelines the following literature has been consulted:

ABG Writing group. Therapeutic Guidelines Antibiotic version 11. 2000. Therapeutic Guidelines Limited. Melbourne.⁹

Communicable Disease Network Australia. Guidelines for the early clinical and public health management of Meningococcal disease in Australia. 2001. Commonwealth Department of Health and Aged Care, Canberra.¹⁰

Chin J.(Ed) Control of Communicable Diseases Manual. 2000. American Public Health Association.¹³

Mandell GL, Bennett JE, Dolin R. (Eds) Principles and Practice of Infectious Diseases. 2000. Churchill Livingstone, New York.⁵

Brooks GF, Butel JS, Morse SA.(Eds) Jawetz, Melnick and Adelburg’s Medical Microbiology. 2001. McGraw Hill, New York.¹²

Beaman MH, Wesselingh SL. Acute community-acquired meningitis and encephalitis. Med J Aust 2002; 176:389–96.⁸

Discussion via e-mail with Dr John Ferguson at Hunter Health who is revising the Central Nervous System chapter of ABGs for the twelfth edition.

Discussion with colleagues.

Other articles as appear in the reference list.

Changes to the third edition of the CARPA STM

1. In the first table of symptoms and signs delete ‘headache’ from the bottom of the first column entitled ‘in children under 2 years’ and insert ‘headache’ to the top of the second column entitled ‘in older children or adults’.

Justification: I’m sure this just corrects a formatting error from the previous edition.

2. In the second table in the second column entitled ‘or any adult who:’ add ‘is very unwell’.
Justification: Meningitis should be on the list of causes of ‘being very unwell’ in adults just as in children, because specific signs may be masked or difficult to elicit in the obtunded patient. In addition, meningococcal (or pneumococcal) septicaemia is not covered elsewhere in the manual, and treatment of these conditions as presumptive meningitis would be appropriate (see below).

3. In the list of things under ‘If out bush, do the following:’, add ‘— take a throat swab’. This may require reference to an additional paragraph in ‘How to do some lab tests’. [Editor: This is now covered in the CRANA Clinical Procedures Manual] There should also be a proviso: ‘Treat the patient even if you cannot do a throat swab’, as with blood cultures.

Justification: In the case of meningococcal or Hib disease there is often throat carriage and isolation from the throat is possible. It is easier to do than blood cultures and the swabs are likely to be easily available. However, national meningococcal guidelines state that the sensitivity of throat swabs done in hospital is not diminished after pre-hospital treatment with parenteral antibiotics, so on those grounds it would do no harm to wait until arrival in hospital.

Nevertheless, in the remote setting with a greater possibility of delay before microbiological assessment, one would think the more sites cultured the better. The editors may not think the potential benefits here outweigh the work involved in explaining the technique.

4. Treatment for all ages should be: Ceftriaxone 50 mg/kg up to 2 g im/iv and benzylpenicillin 60 mg/kg up to 1.8 g im/iv. The third edition suggests benzylpenicillin only for those under three months and at 30 mg/kg. New doses will mean a new table for benzylpenicillin.

Justification: There are several points to consider here:

i. Version 11 of the Therapeutic Guidelines: Antibiotic suggests:

- pre-hospital treatment with benzylpenicillin (60 mg/kg) or ceftriaxone (50 mg/kg)
- empirical early hospital treatment of ceftriaxone 60 mg/kg (or cefotaxime) and benzylpenicillin 60 mg/kg (or amoxy/ampicillin), with the proviso ‘penicillin may be omitted in patients aged between 3 months and 15 years because it is added to cover *Listeria* . . .’

ii. National meningococcal guidelines suggest:

- pre-hospital treatment with benzylpenicillin (30–60 mg/kg) in cases of suspect meningococcal disease with ceftriaxone as an ‘acceptable alternative’
- early hospital treatment is the same as recommended in the ABGs above.

The rationale for the addition of high dose benzylpenicillin is firstly that it is the treatment of choice for meningococcal disease and secondly that it covers *Listeria*. In addition, because the guideline is written to be used in the remote setting, it was thought appropriate that it cover the ‘early hospital treatment’ recommendations of both the reference guidelines. Editors and reviewers may think otherwise. To be consistent with the ABGs we could omit penicillin in immunocompetent patients between three months and 15 years old, but given the underlying risk of immunocompromise in this middle group and the possibility of meningococcal disease it seems both simpler and more appropriate to recommend a blanket treatment with both antibiotics.

5. The recommendation for the use of ceftriaxone in patients with penicillin allergy should be commensurate with that mentioned elsewhere in the manual and should override this one. My recommendation is the following. After ‘If a previous severe reaction to penicillin has occurred:’ insert ‘do not give the benzyl penicillin and discuss with the doctor before giving the ceftriaxone.’ Omit the recommendation about vancomycin and chloramphenicol.

Justification: I note that other guidelines vary in their recommendation in this regard and that the ABGs (V11) recommendation is contradictory (i.e. in some instances ceftriaxone is the recommended substitute, while in other situations cephalosporins are contraindicated). There is recent evidence to suggest that the risk of giving cephalosporins to patients who have IgE hypersensitivity to penicillin is a lot less than previously estimated.^{14,15} For most of the potential aetiological agents for which penicillin is the first line treatment, ceftriaxone has been recommended as an appropriate substitute. The exception here is *Listeria*, for which cotrimoxazole is recommended, and this is not usually available in the parenteral form in the bush. As such a reasonable approach in patients with penicillin allergy is simply to omit the penicillin but continue with the ceftriaxone. However, it may depend on the severity of the allergy and the particular patient circumstances, so it was thought that the guideline need not be proscriptive but to suggest discussing with a medical officer.

6. Under public health considerations the fifth point where it says ‘CDC or your own health. . .’ after rifampicin add ‘, ciprofloxacin or ceftriaxone’.

Justification: These are now standard as options for prophylaxis against meningococcal disease.¹⁰

Other issues

While responding to a possible case of meningitis health practitioners may need to be aware of other possible diagnoses. The price of having a simplified treatment manual for use in the bush is the loss of detail which is required to cover other possible explanations for the group of symptoms and signs with which patients may present. Future editors of the manual might keep these in mind if they feel further expansion is necessary. The following are areas of interest.

Encephalitis

Encephalitis may present in a similar fashion to meningitis. Most of the causes are viral, and presumptive treatment with acyclovir is not feasible in the bush setting. Non-viral causes include Treponema, Cryptococcus, Mycobacteria, melioidosis and Listeria; most of these usually have a subacute or chronic course.⁸ Listeria is covered by empirical anti-meningitis treatment.

Brain abscess

There is much overlap between the symptoms and signs of meningitis and those of a brain abscess. Causative organisms vary and usually differ from those of meningitis. Nevertheless, empirical treatment for brain abscess, according to the ABGs V11⁹, does include the two antibiotics recommended for meningitis in this guideline and the third (metronidazole) could be given if the clinical situation was suggestive and there was a prolonged delay getting to hospital. This needs to be kept in mind.

Meningococcal septicaemia

Meningococcal disease often presents as overwhelming sepsis rather than meningitis and for this reason the treatment of anyone who becomes suddenly very unwell with empirical anti-meningitis antibiotics is appropriate. Whether a statement needs to be made to this effect in the guideline is up to the editors.

Acknowledgments

The authors would like to acknowledge Prof Bart Currie, Dr Jim Burrow and Dr Keith Edwards for their help in reviewing the guideline and document.

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