ANTIMICROBIAL TREATMENT OF COMMUNITY-ACQUIRED MENINGITIS IN ADULTS

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EPIDEMIOLOGY

Although antimicrobial therapy has transformed the outlook of acute bacterial meningitis from an almost uniformly fatal illness to one in which most patients are cured, there is no room for complacency since the condition still caries an unsettling mortality. The brunt of the disease is borne by children, particularly neonates and toddlers, but, even in adults, a review of cases hospitalised at Massachusetts General Hospital during the 1960s,70s and 80s indicated an overall case fatality rate of 25%.[1] Many of the more serious cases, however, occurred post-neurosurgery or in immuno-compromised individuals and were caused by Gram-negative bacilli or staphylococci. These organisms rarely need to be considered in community-acquired meningitis in immunocompetent adults and, indeed, the leading pathogens in this group have not changed significantly for decades: virtually all cases are caused by *Neisseria meningitidis*, *Streptococcus pneumoniae* or *Listeria monocytogenes*.

PRINCIPLES OF ANTIBIOTIC THERAPY

The primary goal of antibacterial therapy for meningitis is the attainment of adequate concentrations of an appropriate antibiotic within the cerebrospinal fluid (CSF) as rapidly as possible. Whereas it is difficult to determine from retrospective studies any clear correlation between the duration of symptoms and clinical sequelae of bacterial meningitis,[2] there is no doubt that the presence of a deteriorating conscious level or evidence of meningococcal septicaemia is associated with a poor prognosis.[3, 4] Hence, prompt initiation of therapy must be the standard of care in patients with clinically apparent meningitis.

In providing practical guidelines as to what this therapy should comprise, two factors need to be considered: the pharmacokinetic and pharmacodynamic properties of the antibiotic, and the potential for the pathogen to be antibiotic-resistant.

Antibiotic pharmacokinetics pharmacodynamics

To be optimally effective, antibiotics need to enter CSF in adequate concentration and to be bactericidal against the pathogen present (the latter because the CSF is lacking in antibodies and other immune defences). The maximal bactericidal activity of an antibiotic is achieved, at least in experimental pneumococcal and Gram-negative meningitis, when the CSF concentration is at least 10-fold higher than the minimal bactericidal concentration *in vitro*.[5-9] Whether this is strictly applicable to the treatment of meningitis in adults is unclear but it seems prudent to try and achieve such high CSF concentrations if at all possible.

During meningitis, the integrity of the blood brain barrier, which normally limits penetration of non-lipid soluble antibiotics, is disrupted and many antibiotics (including the β-lactams such as penicillins and cephalosporins) can penetrate and achieve therapeutic concentrations within the CSF. Since antibiotic therapy, or the use of dexamethasone, will decrease inflammation and reduce the penetration of antibiotics across the blood brain barrier, intravenous administration of high doses of β-lactam antibiotics needs to be continued throughout the full course of therapy in meningitis. Similar failure of penetration of vancomycin may well explain the poor results obtained with this antibiotic alone as therapy of meningitis in adults.[10]

Altered susceptibility in pathogens

The choice of antibiotic to recommend in the empirical therapy of bacterial meningitis has changed with the development of resistance in the common pathogens.

Penicillin G remains the drug of choice for meningococcal meningitis (and for meningococcaemia without obvious meningitis). Although strains of *N. meningitidis* with reduced susceptibility to penicillin G (minimum inhibitory concentrations (MICs) = 0.1 to 1.0 mg/L) have emerged on several continents,[11-13] these are still rare and most patients with such organisms have been successfully treated with standard doses of penicillin.[14]

Most strains of *S. pneumoniae* remain penicillin-susceptible and for these penicillin G or ampicillin are equally effective and are the drugs of choice. However, the frequency of strains of pneumococci that are either relatively (MICs of penicillin = 0.1 to 1.0 mg/L) or highly (MICs ≥ 2.0 mg/L) penicillin-resistant has increased dramatically.[15, 16] Even pneumococci with intermediate levels of resistance to penicillin may not respond to penicillin or ampicillin therapy.[17] Hence, the potential for failure means that penicillin or ampicillin should not now be used for anyone with pneumococcal meningitis, until the penicillin sensitivity of the isolate is confirmed. Either cefotaxime or ceftriaxone is effective against many penicillin-resistant pneumococci (PRP) but as the MIC of penicillin for pneumococci has risen, resistance to the cephalosporins (and to chloramphenicol, erythromycin and co-trimoxazole) has also emerged and is spreading.[15]

Cases of pneumococcal meningitis caused by strains with cephalosporin MICs ≥ 1mg/L have failed therapy with standard dosages of cephalosporins[18-21] and recommendations for the treatment of meningitis caused by highly resistant pneumococci have to be made with little more evidence than that obtained from isolated anecdotal reports backed up by results from animal models.[21] The guidelines from the US National Committee for Clinical Laboratory Standards (NCCLS) feels that cephalosporin resistance should be assumed in isolates with MICs of ≥ 0.5 mg/L. In such strains a number of different antibiotics have been studied. Chloramphenicol is not effective, probably because most isolates have relatively high MICs of chloramphenicol and insufficient antibiotic penetrates into the CSF. Vancomycin and ceftriaxone are synergistic in experimental *S. pneumoniae* meningitis, even

for strains resistant to cephalosporins alone,[22] but there are concerns about the penetration of vancomycin into the CSF of adult patients (see above). Ceftriaxone and rifampicin, also effective in animal models,[23] may be a better approach, particularly when dexamethasone is also given.

PRE-HOSPITAL ANTIBIOTICS

The speed with which meningococcal disease (particularly when there is meningococcaemia) may progress has led to a recommendation for patients in whom this diagnosis is suspected to be given antibiotics as soon as possible, preferably by the doctor (usually the general practitioner) who refers the patient to hospital. This advice applies when the patient has fever and a rash suggestive of meningococcaemia and has not been conclusively shown to affect the outcome of any form of bacterial meningitis. Indeed, it has been suggested that initiation of antibiotic therapy of meningococcal disease outside hospital, without facilities for simultaneous resuscitation, may be associated with increased mortality.[24] The recent Consensus Statement of the British Infection Society Working Party[25] considered these data but felt that, with such a devastating disease, the potential benefits of early antibiotics outweighed any caveats and that, for all adult patients with suspected acute bacterial meningitis (whether or not a rash was present), the general practitioner should immediately administer treatment appropriate for meningococcal disease, namely:

- Benzyl penicillin 2 mega units (1.2 g) by iv or im injection;
- For the patient with a clear history of penicillin anaphylaxis, either chloramphenicol 25 mg/kg iv or ceftriaxone (1 g iv) or cefotaxime (1 g iv) should be given, if available;

  and arrange immediate transfer to hospital.

EMPIRICAL ANTIBIOTICS IN HOSPITAL

Once a patient with suspected bacterial meningitis is admitted to hospital, antibiotic therapy must be started at the first opportunity, irrespective of any investigations undertaken. The choice of antibiotics in adults depends upon the presence of clinical signs of meningococcaemia, the age of the patient and knowledge of the resistance pattern of pneumococci in the area of the world from which the patient has come:

- If there is a typical meningococcal rash then, irrespective of age and geographical origin, patients should be given benzylpenicillin, 4 mega units (2.4 g), or ampicillin, 2 g, iv every four hours. Chloramphenicol 25 mg/kg six-hourly iv can be used if there is a clear history of anaphylaxis to β-lactam antibiotics.

For adults without a typical meningococcal rash, then empirical antimicrobial therapy needs to cover not only meningococcal disease but also pneumococcal and (particularly in those over 50 years of age) *L. monocytogenes* meningitis. For areas of the world where pneumococci resistant to cephalosporins are not common, then:

- For adults aged less than 50 years an iv third generation cephalosporin (cefotaxime, 2 g six-hourly, or ceftriaxone, 2 g 12-hourly) should be used;
- Since cephalosporins have no activity against *L. monocytogenes*, for those over 50 years old ampicillin, 2 g iv four-hourly should be added.

If the patient is from a part of the world where highly penicillin-resistant (and, therefore, cephalosporin-resistant) pneumococci are common (e.g. Spain, eastern Europe, S Africa and parts of the US), then:

- Vancomycin 500 mg six-hourly (or 1 g 12-hourly)[26] or rifampicin 600 mg 12-hourly iv should be added to the cephalosporin regimen. If dexamethasone is used then the cephalosporin plus rifampicin regimen is recommended.[10, 26] Very high doses of iv cefotaxime (24 g/day) alone have also been used successfully for some cases.[27]
- For patients with β-lactam allergy and no meningococcal rash the recommendations are chloramphenicol plus vancomycin (in the doses given above) for those under 50 years of age. Vancomycin is added since chloramphenicol-resistance is likely to be present in penicillin-resistant pneumococci. For those over 50 years old, high dose co-trimoxazole should also be added, since chloramphenicol and vancomycin have proved unsuccessful in systemic listeriosis,[28] whereas co-trimoxazole has been effective.[29, 30]

SPECIFIC ANTIMICROBIAL THERAPY ONCE PATHOGENS HAVE BEEN IDENTIFIED

If bacteria are visible on Gram stain of the cerebrospinal fluid then the empirical therapy above can be modified:

- If meningococci (Gram-negative diplococci) are seen then benzylpenicillin or ampicillin are the drugs of choice with chloramphenicol for those with a history of β-lactam allergy;
- If Gram-positive diplococci (pneumococci) are reported then a cephalosporin (with or without vancomycin or rifampicin, depending on the area of the world – see above) should be continued;
- If organisms suggestive of *Listeria* (Gram-positive cocco-bacilli) are visible then ampicillin 2 g four-hourly plus gentamicin 5 mg/kg/day, either as a single daily dose or in divided, eight-hourly doses, provides bactericidal activity.[31, 32]

Further and final modification of the antibiotic therapy may be possible if *S. pneumoniae* is cultured and its antimicrobial sensitivity has been determined or if a pathogen other than the 'big three' discussed here is isolated:

- If the pneumococcus is fully sensitive to penicillin then therapy can be changed to benzylpenicillin or ampicillin (in the same dosage as is used for meningococcal disease);
- If it is penicillin resistant but sensitive to a cephalosporin (MIC ≤ 0.5 mg/L [some authorities would suggest ≤ 1.0 mg/L])[33] then any vancomycin or rifampicin can be discontinued and the cephalosporin continued;
- If high level penicillin and cephalosporin resistance is confirmed then vancomycin or rifampicin should be added to the cephalosporin regimen. Another option is to increase the cephalosporin dose to 24 g/day (see above);

- Many other pathogens are rare causes of community-acquired meningitis in adults but the empirical regimens suitable for pneumococcal or listerial infections will often be adequate, at least in the short term. Modifications to the regimen should be discussed with the microbiologist or infectious diseases specialist.

DURATION OF THERAPY

The duration of antibiotic therapy for bacterial meningitis depends on the pathogen isolated and the antibiotic used. There are no comparative clinical data but five days' therapy with any of the commonly used antibiotics is likely to be sufficient for meningococcal disease (whether proven or suspected on the basis of a typical rash).[26, 34] Pneumococcal meningitis has a worse prognosis in adults than in children, the group in which most trials of therapy have been undertaken. Although such trials suggest that seven days' therapy may be sufficient, I personally advocate at least 10 days of antibiotics (and 14 days for penicillin-resistant strains). *Listeria* meningitis should also be treated with an effective regimen for 10-14 days. For culture-negative meningitis without a typical meningococcal rash, therefore, 10-14 days of therapy should be given.

ERADICATION OF MENINGOCOCCI FROM PHARYNX

Most β-lactam antibiotics, even in high dosage, do not reliably eradicate meningococci from the throat: the exception is ceftriaxone. All patients with meningococcal disease, other than those initially treated with ceftriaxone, should, therefore, be given oral rifampicin, 600 mg 12-hourly for 48 hours, or a single dose of 500 mg ciprofloxacin once they are able to eat normally.

REFERENCES

1. Durand ML, Calderwood SB, Weber DJ *et al*. Acute bacterial meningitis in adults: a review of 493 episodes. *N Engl J Med* 1993; 328:21-8.
2. Radetsky M. Duration of symptoms and outcome in bacterial meningitis: an analysis of causation and the implications of a delay in diagnosis. [Review]. *Pediatr Infect Dis J* 1992; 11: 694-8.
3. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. *Ann Intern Med* 1998; 129:862-9.
4. Schutte C-M, van der Meyden CH. A prospective study of Glasgow Coma Scale (GCS), age, CSF-neutrophil count and CSF-protein and glucose levels as prognostic indicators in 100 adult patients with meningitis. *J Infect* 1998; 37:112-5.
5. Schaad UB, McCracken GH, Loock CA *et al*. Pharmacokinetics and bacteriologic efficacy of moxalactam, cefotaxime, cefoperazone and rocephin in experimental bacterial meningitis. *J Infect Dis* 1981; 143:156-63.
6. McCracken GH, Nelson JD, Grimm L. Pharmacokinetics and bacteriological efficacy of cefoperazone, cefuroxime, ceftriaxone, and moxalactam in experimental *Streptococcus pneumoniae* and *Haemophilus influenzae* meningitis. *Antimicrob Agents Chemother* 1982; 21:262-7.
7. Schaad UB, McCracken GH, Threlkeld N *et al*. Clinical evaluation of a new broad-spectrum oxa-beta-lactam antibiotic, moxalactam, in neonates and infants. *J Pediatr* 1981; 98:129-36.
8. Decazes JM, Ernst JD, Sande MA. Correlation of *in vitro* time-kill curves and kinetics of bacterial killing in CSF during ceftriaxone therapy of experimental *Escherichia coli* meningitis. *Antimicrob Agents Chemother* 1983; 24:463-7.
9. Täuber MG, Doroshow CA, Hackbarth CJ *et al*. Antibacterial activity of beta-lactam antibiotics in experimental meningitis due to *Streptococcus pneumoniae*. *J Infect Dis* 1984; 149:568-74.
10. Viladrich PF, Gudiol F, Linares J *et al*. Evaluation of vancomycin for therapy of adult pneumococcal meningitis. Antimicrob *Agents Chemother* 1991; 35:2467-72.
11. Saez-Nieto JA, Lujan R, Berron S *et al*. Epidemiology and molecular basis of penicillin-resistant *Neisseria meningitidis* in Spain: a 5-year history (1985-1989). [Review]. *Clin Infect Dis* 1992; 14:394-402.
12. Woods CR, Smith AL, Wasilauskas BL *et al*. Invasive disease caused by *Neisseria meningitidis* relatively resistant to penicillin in North Carolina. *J Infect Dis* 1994; 170:453-6.
13. Sutcliffe EM, Jones DM, el-Sheikh S *et al*. Penicillin-insensitive meningococci in the UK. *Lancet* 1988; 1:657-8.
14. Jones DM, Sutcliffe EM. Meningococci with reduced susceptibility to penicillin. *Lancet* 1990; 335:863-4.
15. Leggiadro RJ. Penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*: an emerging microbial threat. *Pediatrics* 1994; 93:500-3.
16. Johnson AP, Livermore DM, Woodford N *et al*. High-level β-lactam resistance in strains of *Streptococcus pneumoniae* isolated in the UK. *J Antimicrob Chemother* 1998; 42:115-6.
17. Viladrich PF, Gudiol F, Linares J *et al*. Characteristics and antibiotic therapy of adult meningitis due to penicillin-resistant pneumococci. *Am J Med* 1988; 84:839-46.
18. Bradley JS, Connor JD. Ceftriaxone failure in meningitis caused by *Streptococcus pneumoniae* with reduced susceptibility to beta-lactam antibiotics. *Pediatr Infect Dis J* 1991; 10:871-3.
19. Sloas MM, Barrett FF, Chesney PJ *et al*. Cephalosporin treatment failure in penicillin- and cephalosporin-resistant *Streptococcus pneumoniae* meningitis. *Pediatr Infect Dis J* 1992; 11:662-6.
20. Friedland IR, Klugman KP. Failure of chloramphenicol therapy in penicillin-resistant pneumococcal meningitis. *Lancet* 1992; 339:405-11.
21. Friedland IR, McCracken GH, Jr. Management of infections caused by antibiotic-resistant *Streptococcus pneumoniae*. *N Engl J Med* 1994; 331:377-82.
22. Friedland IR, Paris M, Ehrett S *et al*. Evaluation of antimicrobial regimens for treatment of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis. *Antimicrob Agents Chemother* 1993; 37:1630-6.
23. Paris MM, Hickey SM, Uscher MI *et al*. Effect of dexamethasone on therapy of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis. *Antimicrob Agents Chemother* 1994; 38:1320-4.
24. Sørensen HT, Møller-Petersen J, Krarup HB *et al*. Early treatment of meningococcal disease. *BMJ* 1992; 305:774.
25. Begg N, Cartwright KAV, Cohen J *et al*. Consensus statement on diagnosis, investigation, treatment and prevention of acute bacterial meningitis in immunocompetent adults. *J Infect* 1999; 39:1-15.
26. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. *N Engl J Med* 1997; 336(10):708-16.
27. Viladrich PF, Cabellos C, Pallares R *et al*. High doses of cefotaxime in treatment of adult meningitis due to *Streptococcus pneumoniae* with decreased susceptibilities to broad spectrum cephalosporins. *Antimicrob Agents Chemother* 1996; 40: 218-20.
28. Dryden MS, Jones NF, Phillips I. Vancomycin therapy failure in *Listeria monocytogenes* peritonitis in a patient on continuous ambulatory peritoneal dialysis. *J Infect Dis* 1991; 164:1239-40.
29. Levitz RE, Quintilani R. Trimethoprim-sulfamethoxazole for bacterial meningitis. *Ann Intern Med* 1984; 100:881-90.
30. Friedrich LV, White RL, Reboli AC. Pharmacodynamics of trimethoprim-sulfamethoxazole in *Listeria* meningitis: a case report. *Pharmacother* 1990; 10(4):301-4.
31. Tunkel AR, Wispelwey B, Scheld WM. Bacterial meningitis: recent advances in pathophysiology and treatment. *Ann Intern*

Med 1990; 112:610-23.
[32] Scheld WM, Fletcher DD, Funk FN *et al.* Response to therapy in an experimental rabbit model of meningitis due to *Listeria monocytogenes*. *J Infect Dis* 1979; 140:287-94.
[33] Tan TQ, Schutze GE, Mason EO *et al*. Antibiotic therapy and acute outcome of meningitis due to *Streptococcus pneumoniae* considered intermediately susceptible to broad-spectrum cephalosporins. *Antimicrob Agents Chemother* 1994; 38: 918-23.
[34] O'Neill PO. How long to treat bacterial meningitis. *Lancet* 1993; 341:530.

MRCP (UK) PART 2 EXAMINATION

We wish to give you notice of changes to the MRCP(UK) Part 2 Examination in 2001 and how it will affect the arrangements for both the Written and Clinical components of the Examination. This applies to the MRCP(UK) General Medicine Examination only.

The Part 2 Written Examination will become free standing. Candidates who pass the Part 2 Written Examination will be entitled to up to three attempts at the new style clinical examination called PACES (Practical Assessment of Clinical Examination Skills) without re-entering the Part 2 Written Examination.

PACES will replace the current Oral and Clinical Examination. This was first announced in December 1999. It will be held three times a year in UK centres and, at the same diets as at present, in overseas centres. Candidates can choose when they wish to enter PACES but the three attempts allowed under the new Regulations must be made within a period of two years after passing the Part 2 Written Examination.

Success in PACES will lead to the award of the MRCP(UK) Diploma. Those failing PACES three times will be required to resit and pass the Part 2 Written Examination provided they remain eligible to do so (i.e are within seven years of having passed the Part 1 Examination), before re-entering PACES.

Information explaining PACES is available on the websites of the three Royal Colleges of Physicians and more details will be issued shortly. New application forms for the 'free standing' Part 2 Written Examination and PACES will be available shortly from all three Royal Colleges. The amended MRCP(UK) Examination Regulations will be available later this year.

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An announcement about the arrangements for the MRCP(UK) Paediatric/MRCPCH Examination in 2001 will be made shortly.

Dr K.M. Cochran
Chairman
MRCP(UK) Policy Committee
26 July 2000