COMMUNITY-ACQUIRED MENINGITIS
Supporting information

This guideline has been prepared with reference to the following:

McGill F, Heyderman RS, Michael BD et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. J Infect. 2016;72:405-38

http://www.sciencedirect.com/science/article/pii/S0163445316000244

British Infection Society. Early management of suspected bacterial meningitis and meningococcal septicaemia in immunocompetent adults. 3rd ed. 2016. BIS

https://www.britishinfection.org/download_file/view/71/395

Chaudhuri A, Martin PM, Kennedy PG, et al. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. Eur J Neurol 2008;15:649-59

http://onlinelibrary.wiley.com/doi/10.1111/j.1468-1331.2008.02193.x/full

Immediate treatment

The time interval between onset of symptoms (or diagnosis) and initiation of antibiotic treatment affects the outcome?

A systematic review of the literature describing the association between time to antibiotics and death or neurological impairment due to adult community-acquired bacterial meningitis was performed in 2022 (Eisen). A retrospective cohort, multivariable and propensity-score based analyses were performed using individual patient clinical data from Australian, Danish and United Kingdom studies. Individual patient data on 659 subjects were made available for analysis. The risk of death (adjusted odds ratio, aOR) associated with treatment after two hours was 2.29 (95% CI 1.28–4.09) and increased substantially thereafter. Among patients with community-acquired bacterial meningitis, odds of mortality increase markedly when antibiotics are given later than two hours after presentation to the hospital.

Eisen DP, Hamilton E, Bodilsen J et al. Longer than 2 hours to antibiotics is associated with doubling of mortality in a multinational community-acquired bacterial meningitis cohort. Sci Rep. 2022;12:672
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8758708/

Evidence Level: III

What are the causative organisms of meningitis?

Among cases of bacterial meningitis across age groups, the predominant causal organisms in the United States are Streptococcus pneumoniae (58.0%), group B Streptococcus (18.1%), Neisseria meningitidis (13.9%), Haemophilus influenzae (6.7%), and Listeria monocytogenes (3.4%). The relative frequency of different pathogens varies with age, with group B Streptococcus being the most common etiology of meningitis in neonates and L monocytogenes primarily affecting infants and persons over the age of 50 years (Bystritsky, 2022).

The term “aseptic meningitis,” which is often misused interchangeably with viral meningitis, refers to meningitis in which no infectious agent is identified after an initial evaluation for bacterial etiologies. Among cases of aseptic meningitis in high-income countries in which a cause is identified, nonpolio enteroviruses and herpesviruses are the most frequently detected pathogens. In a study of adult immunocompetent patients in Finland presenting with aseptic meningitis, enteroviruses were the causative agent in 26% of cases, herpes simplex virus-2 (HSV-2) in 17%, and varicella-zoster virus (VZV) in 8%. In another study from Spain that included both adults and children with aseptic meningitis, enteroviruses accounted for 44% of cases compared with only 6% attributed to HSV-2 and VZV. Other viral etiologies of meningitis include mumps and measles viruses, arboviruses, and lymphocytic choriomeningitis virus (LCMV). In a large proportion of patients with aseptic meningitis, ranging from 33% to nearly 50% of cases, no etiology may be identified (Bystritsky, 2022).

Bystritsky RJ, Chow FC. Infectious Meningitis and Encephalitis. Neurol Clin. 2022;40:77-91

Evidence Level: IV

These organisms are killed by ceftriaxone or benzylpenicillin?
According to the UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults (McGill et al, 2016), if streptococcus pneumoniae is identified:

- Continue with 2 g ceftriaxone IV 12 hourly or 2 g cefotaxime IV 6-hourly (AR)
- If the pneumococcus is penicillin sensitive (MIC ≤ 0.06 mg/L) any of the following options would be suitable: IV benzylpenicillin 2.4 g 4 hourly, 2 g ceftriaxone IV 12 hourly or 2 g cefotaxime IV 6-hourly (AR).

If N. meningitidis is identified:

- Continue 2 g ceftriaxone IV 12 hourly or 2 g cefotaxime IV 6-hourly (AR)
- 2.4 g benzylpenicillin IV 4-hourly may be given as an alternative (AR)

Benzylpenicillin is a beta-lactam antibiotic which is still effective against s. pneumoniae although resistant strains (or those with reduced susceptibility) have been reported (Tunkel, 2000). Some strains of n. meningitidis also demonstrate reduced susceptibility (Friedland, 1994).

Friedland IR, McCracken GH. Management of infections caused by antibiotic-resistant streptococcus pneumoniae. N Engl J Med 1994;331:377-82

McGill F, Heyderman R, Michael B et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. J Infect. 2016;72:405-38
http://www.sciencedirect.com/science/article/pii/S0163445316000244

Tunkel AR, Scheld WM. Acute meningitis. In: Mandell GL, Bennett JE, Dolin R (eds). Mandell, Douglas and Bennett's Principles and practice of infectious diseases, 5th ed. Philadelphia: Churchill Livingstone, 2000. p.981

Evidence Level: III

Dexamethasone, given parenterally to patients with severe meningitis
i) Reduces mortality or the incidence of neurological complication?
ii) Reduces recovery time?
A randomised trial in 301 patients (de Gans, 2002) compared 157 given dexamethasone 10 mg with the first dose of antibiotic (or 15-20 minutes before) with 144 given placebo. The treatment group had reduced mortality (RR 0.48, 95% CI 0.24-0.96) and reduced incidence of complications (RR 0.59, 95% CI 0.37-0.94) in the form of seizures or cardiorespiratory failure. Neurologic sequelae however, including hearing loss, were not affected.
A post hoc multivariate analysis of data from the European Dexamethasone Study (Weisfelt, 2006) showed that absence of dexamethasone treatment was an independent predictor of mortality (p=0.05).
A 2016 meta-analysis of ten RCTs (including 2,459 patients) comparing dexamethasone with placebo found that dexamethasone was not associated with a significant reduction in follow-up mortality (P=0.14) and severe neurological sequelae (P=0.42). However, dexamethasone seemed to reduce hearing loss among survivors (P=0.03). No significant difference was found between these two groups in adverse events.

de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. N Engl J Med 2002;347:1549-56
http://www.nejm.org/doi/full/10.1056/NEJMoa021334

Shao M, Xu P, Liu J et al. The role of adjunctive dexamethasone in the treatment of bacterial meningitis: an updated systematic meta-analysis. Patient Prefer Adherence. 2016;10:1243-9
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4951054/

Weisfelt M, van de Beek D, de Gans J. Dexamethasone treatment in adults with pneumococcal meningitis: risk factors for death. Eur J Clin Microbiol Infect Dis 2006;25:73-8

Evidence Level: I

For a maximum of how many days should IV dexamethasone be continued?
The RCT by de Gans (2002) recommends 4 days, advice repeated in a later review by the same team (van de Beek, 2006).

de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. N Engl J Med 2002;347:1549-56 http://www.nejm.org/doi/full/10.1056/NEJMoa021334#t=articleTop

van de Beek D, de Gans J. Dexamethasone in adults with community-acquired bacterial meningitis. Drugs 2006;66:415-27

Evidence Level: II

What is the efficacy of aciclovir against herpes simplex?
Aciclovir is a selective inhibitor of the replication of herpes simplex virus (HSV) types 1 and 2 (average median effective concentrations: 0.04 and 0.10 g per millilitre, respectively) and is the treatment of choice for infections caused by these organisms (Hayden, 2000; Whitley, 1992). In a randomised trial comparing aciclovir with vidarabine in 208 patients with HSV encephalitis, aciclovir reduced mortality to 19-28%, compared with 50-54% for vidarabine (Whitley, 1986).

Hayden FG. Antiviral drugs (other than antiretrovirals). In: Mandell GL, Bennett JE, Dolin R (eds). Mandell, Douglas and Bennett's Principles and practice of infectious diseases, 5th ed. Philadelphia: Churchill Livingstone, 2000. p.462

Whitley RJ, Gnann JW. Acyclovir: a decade later. N Engl J Med 1992;327:782-9

Whitley RJ, Alford CA, Hirsch MS, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med 1986;314:144-9

Evidence Level: II

The presence of polymorphs in the cerebrospinal fluid is indicative of bacterial meningitis?
Typical CSF findings in patients with bacterial meningitis include a percentage of polymorphs (neutrophils) in excess of 80% (Tunkel, 2000; Begg, 1999). These findings are diagnostic in 90% of cases (Pollard, 1998; Tunkel, 1995), the remaining 10% presenting with a predominance of lymphocytes. Normal CSF white cell count is in the range 1000-5000/mL.

Begg N, Cartwright KA, 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

Pollard AJ, Faust SN, Levin M. Meningitis and meningococcal septicaemia: extended review. J R Coll Physicians Lond 1998;32:319-28

Tunkel AR, Scheld WM. Acute bacterial meningitis. Lancet 1995;346:1675-80

Tunkel AR, Scheld WM. Acute meningitis. In: Mandell GL, Bennett JE, Dolin R (eds). Mandell, Douglas and Bennett's Principles and practice of infectious diseases, 5th ed. Philadelphia: Churchill Livingstone, 2000. p.975

Evidence Level: IV

Lymphocytes in the cerebrospinal fluid predominate in:

- **i) part-treated bacterial meningitis**
- **ii) cerebral abscess**
- **iii) paradural pyogenic collections**
- iv) **non-pyogenic forms (e.g. listeria, TB, syphilis, leptospirosis, borrelia, cryptococcus and herpes simplex?**

Lymphocytes normally predominate in partially-treated bacterial meningitis (Begg, 1999), cerebral abscess (Mendelow, 1993), and non-pyogenic forms of the disease (Mendelow, 1993; Connolly, 1990; Corey, 1986). The picture may be obscured in approximately 10% of cases that do not conform to the usual pattern (Pollard, 1998; Tunkel, 1995). In early tuberculous meningitis, a retrospective review of 52 patients has shown that the CSF showed polymorphs in 14 (27%) cases, contrary to normal expectations (Kennedy, 1979).

Begg N, Cartwright KA, 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

Connolly KJ, Hammer SM. The acute aseptic meningitis syndrome. Infect Dis Clin North Am 1990;4:599-622

Corey L, Spear PG. Infections with herpes simplex viruses (second of two parts). N Engl J Med 1986;314:749-57

Kennedy DH, Fallon RJ. Tuberculous meningitis. JAMA 1979;241:264-8

Mendelow AD. Raised intracranial pressure, cerebral oedema, hydrocephalus, and intracranial tumours. In: Walton J (ed). Brain's Diseases of the nervous system, 10th ed. Oxford: OUP, 1993. p177

Pollard AJ, Faust SN, Levin M. Meningitis and meningococcal septicaemia: extended review. J R Coll Physicians Lond 1998;32:319-28

Tunkel AR, Scheld WM. Acute bacterial meningitis. Lancet 1995;346:1675-80

Evidence Level: IV

No cellular reaction in the cerebrospinal fluid means that the meningitis does not have a bacterial aetiology?

The British Infection Society consensus statement advises that treatment should never be withheld or delayed because of a "normal" CSF (Begg, 1999). A study of 120 patients in west Gloucestershire (Wylie, 1997) included 9 (8%) whose CSF showed no abnormality on initial examination, but who were later confirmed as having meningococcal disease. The CSF is also usually normal in meningococcal septicaemia (Begg, 1999).

A meta-analysis of 33 studies (Sakushima, 2011) found that the pooled test characteristics of CSF lactate were sensitivity 0.93 (95% CI: 0.89-0.96), specificity 0.96 (95% CI: 0.93-0.98), likelihood ratio positive 22.9 (95% CI: 12.6-41.9), likelihood ratio negative 0.07 (95% CI: 0.05-0.12), and diagnostic odds ratio 313 (95% CI: 141-698). Pretreatment with antibiotics lowered the sensitivity 0.49 (95% CI: 0.23-0.75). CSF lactate of around 35 mg/dl (34-36 mg/dl) had higher sensitivity and specificity than those of around 27 mg/dl (26-28 mg/dl). The authors concluded that "CSF lactate of 35 mg/dl could be optimal cut-off value for distinguishing bacterial meningitis from aseptic meningitis."

Begg N, Cartwright KA, 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

Sakushima K, Hayashino Y, Kawaguchi T, et al. Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: a meta-analysis. J Infect 2011;62:255-62

Wylie PAL, Stevens D, Drake W, et al. Epidemiology and clinical management of meningococcal disease in west Gloucestershire: retrospective, population based study. BMJ 1997;315:774-9
http://www.bmj.com/content/315/7111/774

Evidence Level: I

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