Initial therapy and prognosis of community-acquired bacterial meningitis in adults

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INTRODUCTION

Bacterial meningitis is a medical emergency, and immediate steps must be taken to establish the specific cause and initiate effective therapy. The mortality rate of untreated disease approaches 100 percent [1], and even with optimal therapy, it is associated with significant morbidity and mortality [2,3].

The presence of bacterial meningitis is suggested by the symptoms of fever, altered mental status, headache, and nuchal rigidity, although one or more of these findings are absent in many patients with bacterial meningitis [4-7]. (See "Clinical features and diagnosis of acute bacterial meningitis in adults".)

The initial therapy and prognosis of community-acquired bacterial meningitis will be reviewed here. The epidemiology, pathogenesis, clinical features, diagnosis, treatment of specific pathogens, and use of dexamethasone in the management of community-acquired bacterial meningitis in adults are discussed separately. (See "Epidemiology of community-acquired bacterial meningitis in adults" and "Pathogenesis and pathophysiology of bacterial meningitis" and "Clinical features and diagnosis of acute bacterial meningitis in adults" and "Treatment of bacterial meningitis caused by specific pathogens in adults" and "Dexamethasone to prevent neurologic complications of bacterial meningitis in adults".)

The management of health care-associated meningitis and ventriculitis is discussed in detail elsewhere. (See "Health care-associated meningitis and ventriculitis in adults: Treatment and prognosis".)

PRETREATMENT EVALUATION

History — If possible, the following historical information should be obtained before antimicrobial therapy of presumed bacterial meningitis is instituted. Some aspects of the history may suggest a potential causative organism. Has the patient had or does the patient have:

- Serious drug allergies
- Recent exposure to someone with meningitis (eg, *Neisseria meningitidis*)
- A recent or current sinusitis or otitis media (eg, *S. pneumoniae*)
- Recent use of antibiotics (drug-resistant *S. pneumoniae*)
- Recent travel such as to the Hajj and Umrah pilgrimage (eg, *N. meningitidis*)
- A history of recent injection drug use (eg, *Staphylococcus aureus*)
- A progressive petechial or ecchymotic rash (eg, *N. meningitidis*)
- A history of recent or remote head trauma (eg, *S. pneumoniae*)
- HIV infection or risk factors (eg, *S. pneumoniae, Listeria monocytogenes*, *Cryptococcus neoformans*)
- Any other immunocompromising conditions

Pretreatment testing — The initial approach to management in a patient with suspected bacterial meningitis includes performance of a lumbar puncture (LP) to determine whether the cerebrospinal fluid (CSF) findings are consistent with the diagnosis (algorithm 1) [8]. An important early decision relates to whether a head computed tomography (CT) should be performed prior to LP.

- Although a screening CT scan is not necessary in the majority of patients, a head CT should be performed **before** LP in adults with suspected bacterial meningitis who have one or more of the following risk factors [8,9]:
    - Immunocompromised state (eg, HIV infection, immunosuppressive therapy, solid organ or hematopoietic cell transplantation)
    - History of central nervous system (CNS) disease (mass lesion, stroke, or focal infection)
    - New-onset seizure (within one week of presentation)
    - Papilledema

- Abnormal level of consciousness
- Focal neurologic deficit

If a head CT is indicated, blood cultures should be obtained immediately, and dexamethasone and empiric antimicrobial therapy should be started once blood cultures have been obtained and prior to head CT. (See "Dexamethasone to prevent neurologic complications of bacterial meningitis in adults".)

If the results of the CT reveal that LP is contraindicated, therapy for bacterial meningitis should be continued (if indicated) or evaluation and treatment for an alternative diagnosis should be undertaken (ie, if the CT suggests a different cause for the patient's clinical presentation).

In one report, adherence to these guidelines in adults with bacterial meningitis identified all patients with major intracranial abnormalities [10].

- In patients **without** any of the risk factors described above, blood cultures and LP may be performed without performing a head CT. Obtaining a head CT scan in patients without an indication has no clinical benefit and delays lumbar puncture [11]. At the time of LP, an opening pressure should be obtained. Once CSF has been obtained (and before results are available), dexamethasone and empiric antimicrobial therapy should be initiated if bacterial meningitis is suspected.

- CSF should be sent for:

  - Cell count and differential
  - Glucose concentration
  - Protein concentration
  - Gram stain and bacterial culture
  - Other appropriate tests, depending upon the level of concern for other etiologies of meningitis or meningoencephalitis

Characteristic findings in bacterial meningitis include a CSF glucose concentration <40 mg/dL, a CSF to serum glucose ratio of ≤0.4, a protein concentration >200 mg/dL, and a white blood cell (WBC) count above 1000/microL, usually composed primarily of neutrophils [2,8,12]. (See "Cerebrospinal fluid: Physiology and utility of an examination in disease states".)

However, the spectrum of CSF values in bacterial meningitis is so wide that the absence of one or more of these findings is of little value (table 1) [4-6]. For example, in a

prospective study of 1412 adults with bacterial meningitis, a CSF WBC >1000/microL was seen in only 66 percent of patients [12]. (See "Clinical features and diagnosis of acute bacterial meningitis in adults", section on 'Cerebrospinal fluid analysis'.)

- Before CSF results are available, it can be difficult to know whether the patient has bacterial or viral meningitis. The decision of which tests to perform on the CSF will depend on patient-specific factors, such as those described above (see 'History' above). In addition to suggesting specific diagnostic tests, we often send an extra tube of CSF if possible to the laboratory to be held for further studies, as the CSF profile and the patient's clinical course may warrant additional testing (see 'Negative CSF culture' below). Selected viruses that can cause meningitis are summarized in the table (table 2). The diagnostic approach to aseptic meningitis is presented separately. (See "Aseptic meningitis in adults".)

The diagnosis of bacterial meningitis is discussed in greater detail separately. (See "Clinical features and diagnosis of acute bacterial meningitis in adults".)

GENERAL PRINCIPLES OF THERAPY

There are a number of general principles of therapy in patients with bacterial meningitis [2,8]. The most important initial issues are avoidance of delay in administering antimicrobial therapy and the choice of drug regimen.

Avoidance of delay — Antimicrobial therapy, along with adjunctive dexamethasone when indicated, should be initiated as quickly as possible after the performance of the lumbar puncture (LP) or, if a CT scan of the head is to be performed before LP, as quickly as possible after blood cultures are obtained (algorithm 1) [2,8]. (See 'Pretreatment testing' above and "Clinical features and diagnosis of acute bacterial meningitis in adults", section on 'Indications for CT scan before LP' and 'When to administer dexamethasone' below.)

Effects of delay — Many studies have shown that a delay in the administration of antimicrobial agents can have adverse effects on mortality and residual neurological deficits [5,13-17]. As an example, in a population-based cohort study of 173 patients with community-acquired bacterial meningitis, a delay in antimicrobial treatment of more than six hours compared to treatment within two hours of admission was associated with an increase in in-hospital mortality (risk ratio [RR] 1.6, 95% CI 0.8-3.2) and unfavorable outcome at discharge (RR 1.5, 95% CI 1.0-2.2) [17]. Longer delays in antibiotic therapy were associated with mortality rates as high as 30 percent.

Causes of delay — Important causes of delay in the initiation of antimicrobial therapy include atypical clinical presentation and delay due to cranial imaging. It is important to note that antimicrobial therapy, along with adjunctive dexamethasone therapy (if indicated), should **not** be delayed if imaging is performed prior to lumbar puncture.

- **Atypical presentation** – In the retrospective study of 119 adults with bacterial meningitis described above, the most dramatic clinical predictor of death was the absence of fever at presentation (OR 39.4, 95% CI 4.3-358.1) [15]. This finding, along with other "atypical features" (eg, lack of headache or neck stiffness), accounts for some of the delay in making the diagnosis and initiating therapy. While a deliberate delay of therapy is never warranted, the diagnosis can be quite challenging in cases with atypical features. Lowering the threshold for initiation of therapy may be prudent, but there is no clear guideline that will identify bacterial meningitis in patients with atypical features without some risk of over-treatment. (See 'Prediction of risk' below.)

- **Delay due to imaging** – An important cause of delayed therapy in patients with suspected bacterial meningitis is performance of a CT scan of the head to exclude an occult mass lesion or other findings that could lead to cerebral herniation during subsequent cerebrospinal fluid (CSF) removal [2,8]. Should LP be delayed by the need for cranial imaging in patients suspected of having bacterial meningitis, blood cultures should be obtained and antimicrobial agents should be administered empirically along with adjunctive dexamethasone (if indicated) just prior to or concomitant with the first antibiotic dose. (See "Dexamethasone to prevent neurologic complications of bacterial meningitis in adults".)

  Although commonly performed, a screening CT scan of the head is **not** necessary in the majority of patients. In a study of 549 adults with community-acquired meningitis, 354 (64.8 percent) of patients without an indication underwent cranial imaging with no clinical benefit [11]. Although the use of antimicrobial therapy before LP decreases the yield of CSF Gram stain and culture in bacterial meningitis [18,19], the CSF profile is not affected and can still be utilized by clinicians to formulate their differential diagnosis. This issue is discussed in detail separately. (See "Clinical features and diagnosis of acute bacterial meningitis in adults", section on 'Cerebrospinal fluid examination'.)

Antibiotic regimen

Choice of regimen — Antimicrobial selection must be empiric immediately after CSF is obtained or when lumbar puncture is delayed. In such patients, antimicrobial therapy needs to be directed at the most likely bacteria based upon patient age and underlying comorbid disease

(table 3A-B) [2,8]. Knowledge of local susceptibility patterns also may be important. Empiric regimens are discussed in detail below. (See 'Empiric regimens' below.)

Once the CSF Gram stain results are available, the antimicrobial regimen should be tailored to cover the most likely pathogen. (See 'Regimens based upon Gram stain' below.)

If the CSF findings are consistent with the diagnosis of acute bacterial meningitis but the Gram stain is negative, empiric antimicrobial therapy should be continued. (See 'Empiric regimens' below.)

The antimicrobial regimen should be modified further, when indicated, based on the CSF culture and susceptibility results. (See "Treatment of bacterial meningitis caused by specific pathogens in adults".)

Route of administration — Because of the general limitation in antimicrobial penetration into the CSF, all patients should be treated with intravenous antimicrobial agents. Oral antimicrobial agents should be avoided since the dose and tissue concentrations tend to be considerably lower than with parenteral agents.

Duration — The duration of antimicrobial therapy for bacterial meningitis depends upon the causative pathogen. This is discussed in greater detail separately. (See "Treatment of bacterial meningitis caused by specific pathogens in adults".)

Pharmacologic properties — There are three general requirements of antimicrobial therapy for bacterial meningitis [2,20]: Use of bactericidal drugs effective against the infecting organism; Use of drugs that enter the CSF, since the blood-brain barrier prevents macromolecule entry into the CSF; and Structuring the regimen to optimize bactericidal efficacy based on the pharmacodynamic characteristics of the antimicrobial agent(s).

- **Bactericidal drugs** – Since the CSF is a site of impaired humoral immunity, a fundamental principle of therapy of bacterial meningitis is that antimicrobial agents must achieve a bactericidal effect within CSF to result in optimal microbiologic cure [2,20]. Bactericidal antimicrobial therapy results in optimal microbiologic cure and survival in animals with pneumococcal meningitis [20]. This principle is also supported by clinical observations of poor outcomes in patients receiving bacteriostatic therapy [2,20].

- **Drug entry into CSF** – Antimicrobial penetration into CSF depends to a large extent on the status of the blood-brain barrier and by clearing the antimicrobial via active transport in pumps in the arachnoid villa [20,21]. When the blood-brain barrier is normal, most beta-lactam agents (eg, penicillin) penetrate poorly. However, in the presence of meningeal

inflammation, CSF penetration is enhanced likely as a result of separation of intercellular tight junctions and inhibition of the organic pump, raising the levels of the antimicrobials in the CSF. As inflammation subsides, antimicrobial entry decreases and clearance of the drug increases. Thus, maximal parenteral doses should be continued throughout the course of therapy to maintain adequate CSF concentrations. Antibiotic entry is also enhanced with drugs that have a high lipid solubility, low molecular weight, low protein binding, and low ionization at physiologic pH [20]. (See "Cerebrospinal fluid: Physiology and utility of an examination in disease states", section on 'Blood-brain barrier'.)

There are specific dosing recommendations for the antimicrobial agents used to treat bacterial meningitis in order to attain maximal concentrations in the CSF. In some cases, higher doses of agents are used for bacterial meningitis than for other infections (table 3B).

- **Pharmacodynamics** – For antimicrobial agents that exhibit time-dependent antimicrobial activity (eg, beta-lactams, vancomycin), the bactericidal activity depends upon the time that the agent is above the minimal inhibitory concentration (MIC) as a proportion of the dosing interval [22]. For agents that exhibit concentration-dependent antimicrobial activity (eg, aminoglycosides), killing occurs over a wide range of antimicrobial concentrations and there is a prolonged recovery period (ie, the postantibiotic effect) after drug concentrations fall below the MIC during which regrowth of bacteria is delayed. The CSF pharmacodynamics of fluoroquinolones are more complicated, however, and features of both time dependency and concentration dependency have been described.

When to administer dexamethasone — As part of empiric therapy for adults in the developed world with suspected community-acquired bacterial meningitis in whom the causative organism is not yet known, we recommend administration of dexamethasone. Intravenous administration of glucocorticoids (usually dexamethasone) prior to or at the time of administering antibiotics has been associated with a reduction in the rate of hearing loss, other neurologic complications, and mortality in patients with meningitis caused by *S. pneumoniae,* which is the most common cause of bacterial meningitis in adults in the developed world. The indications for dexamethasone for patients with suspected or confirmed bacterial meningitis in the developing world depend on the patient population and are discussed in detail elsewhere. (See "Dexamethasone to prevent neurologic complications of bacterial meningitis in adults", section on 'Developing regions'.)

Adjunctive dexamethasone should be given shortly before or at the same time as the first dose of antibiotics, when indicated. Dexamethasone should be continued if the CSF Gram stain and/or the CSF or blood cultures reveal *S. pneumoniae*. Rifampin is added to the regimen in

patients with pneumococcal meningitis receiving dexamethasone if susceptibility studies show intermediate susceptibility (minimum inhibitory concentration [MIC] ≥2 mcg/mL) to ceftriaxone and cefotaxime. A detailed discussion on the use of dexamethasone for the management of bacterial meningitis is presented elsewhere. (See "Dexamethasone to prevent neurologic complications of bacterial meningitis in adults".)

EMPIRIC REGIMENS

Factors impacting regimen selection — The empiric approach to antimicrobial selection in patients with suspected bacterial meningitis is directed at the most likely bacteria based on the patient's age and host factors (table 3A-B and table 4) [8,23]. (See 'No known immune deficiency' below and 'Immunocompromised patients' below and 'Beta-lactam allergy' below and 'Empiric treatment during epidemics' below.)

- **Causative organisms** – *S. pneumoniae* followed by *N. meningitidis* are the two most commonly isolated pathogens in community-acquired bacterial meningitis, accounting for 0.306 cases and 0.123 cases per 100,000 people, respectively, in the United States [24]. In a large prospective study of 1412 episodes of community-acquired bacterial meningitis in the Netherlands, *S. pneumoniae* was responsible for 51 percent, *N. meningitidis* for 37 percent, and *L. monocytogenes* for 4 percent of cases [12]. Importantly, in adults, the incidence of bacterial meningitis caused by *L. monocytogenes* rises with increasing age [25]. For this reason, adults >50 years of age should receive an antimicrobial agent with activity against *L. monocytogenes* (eg, ampicillin) as part of the empiric regimen. (See 'No known immune deficiency' below.)

  More detailed discussions of the epidemiology of bacterial meningitis in adults and children are discussed elsewhere. (See "Epidemiology of community-acquired bacterial meningitis in adults", section on 'Incidence' and "Bacterial meningitis in children older than one month: Clinical features and diagnosis", section on 'Epidemiology'.)

- **Efficacy of specific agents** – There have been no randomized trials in adults regarding the empiric therapy of bacterial meningitis. Treatment recommendations are based upon in vitro susceptibility and pharmacodynamic data, randomized trials in children, and accumulated clinical experience.

  Selected third-generation cephalosporins (ie, cefotaxime and ceftriaxone) are the beta-lactams of choice in the empiric treatment of meningitis. These drugs have consistent cerebrospinal fluid (CSF) penetration and potent activity against the major pathogens of

bacterial meningitis, with the notable exceptions of *L. monocytogenes* and some penicillin-resistant strains of *S. pneumoniae* [22]. With the worldwide increase in the prevalence of penicillin-resistant pneumococci, vancomycin should be added to ceftriaxone or cefotaxime as empiric treatment in countries where the prevalence of ceftriaxone resistance is >1 percent (eg, the United States), until culture and susceptibility results are available [2,26,27]. (See "Treatment of bacterial meningitis caused by specific pathogens in adults".)

Ceftazidime, a third-generation cephalosporin with broad in vitro activity against gram-negative bacteria including *Pseudomonas aeruginosa*, is much less active against penicillin-resistant pneumococci than cefotaxime and ceftriaxone [22]. However, a fourth-generation cephalosporin, cefepime, has been shown to be safe and therapeutically equivalent to cefotaxime for the treatment of bacterial meningitis in infants and children and is a suitable alternative to cefotaxime or ceftriaxone when broad activity against both pneumococcus and gram-negative bacteria, such as *P. aeruginosa,* is needed (eg, for immunocompromised) [28]. (See 'Immunocompromised patients' below.)

Additional information on factors impacting the choice of agent is discussed above. (See 'Antibiotic regimen' above.)

Sporadic community-acquired meningitis — Antimicrobial therapy, along with adjunctive dexamethasone, should be initiated as quickly as possible after the performance of the lumbar puncture (LP) or, if a CT scan of the head is to be performed before LP, as quickly as possible after blood cultures are obtained (algorithm 1) [8,29,30]. This section will review empiric antimicrobial regimens for community-acquired meningitis based upon the patient's age and other host factors.

Antibiotic selection

No known immune deficiency — *S. pneumoniae*, *N. meningitidis*, and, less often, *H. influenzae* and group B *Streptococcus* are the most likely causes of community-acquired bacterial meningitis in otherwise healthy adults up to the age of 60 years [25]. Individuals over aged 50 years are also at increased risk of *L. monocytogenes* meningitis [25,31]. (See "Epidemiology of community-acquired bacterial meningitis in adults", section on 'Incidence' and "Bacterial meningitis in children older than one month: Clinical features and diagnosis", section on 'Epidemiology'.)

Such patients, without evidence of renal insufficiency, should be treated empirically with the following regimen until culture and susceptibility data are available (table 3A-B) [8,26,27]:

- Ceftriaxone – 2 g intravenously (IV) every 12 hours.

  Or

  Cefotaxime (where available) – 2 g IV every four to six hours.

  plus

- In countries with ceftriaxone resistance rates >1 percent, vancomycin – 15 to 20 mg/kg IV every 8 to 12 hours (not to exceed 2 g per dose or a total daily dose of 60 mg/kg; adjust dose to achieve vancomycin serum trough concentrations of 15 to 20 mcg/mL). Countries with resistance rates >1 percent include the United States, Canada, China, Croatia, Greece, Italy, Mexico, Pakistan, Poland, Spain, and Turkey [27].

  plus

- In adults >50 years of age, ampicillin – 2 g IV every four hours.

A third-generation cephalosporin (eg, ceftriaxone, cefotaxime) should be continued even if in vitro tests demonstrate *S. pneumoniae* with reduced susceptibility to third-generation cephalosporins (minimum inhibitory concentration ≥1 mcg/mL), since they may provide synergy with vancomycin in this setting [22].

Immunocompromised patients — For immunocompromised hosts, empiric antibiotic coverage must be directed against *L. monocytogenes* in addition to standard coverage for *S. pneumoniae,* regardless of age [20]. Such patients include those who are immunocompromised due to underlying conditions (eg, AIDS, lymphoma), as well as those receiving immunosuppressive agents such as cytotoxic chemotherapy, systemic glucocorticoids, and/or biologic immunomodulators (eg, TNF inhibitors). A more detailed discussion of risk factors for *Listeria* is found elsewhere. (See "Epidemiology and pathogenesis of Listeria monocytogenes infection", section on 'Predisposing conditions'.)

In addition to *Listeria* coverage, immunocompromised patients warrant expanded gram-negative coverage to include *P. aeruginosa*. Although it is unclear if all immunocompromised hosts need such coverage, we typically use the fourth-generation cephalosporin cefepime or an antipseudomonal carbapenem in our initial regimen, instead of a third-generation cephalosporin that does not have activity against *Pseudomonas*. Antipseudomonal coverage is particularly important for those with neutropenia or impaired mucosal barriers (eg, from chemotherapy or severe burns), as well as for those at increased risk of nosocomial exposure. (See "Epidemiology, microbiology, and pathogenesis of Pseudomonas aeruginosa infection", section on 'Epidemiology'.)

An appropriate regimen for immunocompromised patients with normal renal function is (table 3A-B):

- Vancomycin – 15 to 20 mg/kg IV every 8 to 12 hours (not to exceed 2 g per dose or a total daily dose of 60 mg/kg; adjust dose to achieve vancomycin serum trough concentrations of 15 to 20 mcg/mL).

  plus

- Ampicillin – 2 g IV every four hours.

  plus either

- Cefepime – 2 g IV every eight hours.

  or

- Meropenem – 2 g IV every eight hours. If meropenem is used, initial treatment with ampicillin is not required, as meropenem has activity against *Listeria*. However, if *Listeria* is identified as the causative agent, the regimen should be modified to include ampicillin or penicillin (usually in combination with gentamicin). (See "Treatment and prevention of Listeria monocytogenes infection", section on 'Alternatives to ampicillin or penicillin'.)

Beta-lactam allergy — The approach to therapy in patients with beta-lactam allergies is challenging given the importance of early initiation of therapy and the crucial role of beta-lactam antibiotics in the treatment of bacterial meningitis. The choice of regimen must balance efficacy with the risk and severity of an allergic reaction. (See "Penicillin allergy: Immediate reactions" and "Penicillin allergy: Delayed hypersensitivity reactions" and "Cephalosporin hypersensitivity: Clinical manifestations and diagnosis".)

Initial regimen

- **Patients without severe beta-lactam allergy** – In general, most patients who are labeled as allergic to penicillin are able to receive a cephalosporin such as ceftriaxone (or cefepime if immunocompromised) (table 3B and table 4). More detailed information on penicillin allergy is found elsewhere. (See "Penicillin allergy: Immediate reactions" and "Penicillin allergy: Immediate reactions", section on 'Immediate versus delayed reactions'.)

  Meropenem should be used instead of ceftriaxone in patients with isolated mild hives to a cephalosporin without other signs of anaphylaxis (especially if the reaction occurred in

childhood and/or >10 years ago) or mild delayed-type reactions to cephalosporins (table 3B and table 4).

- **Patients with severe beta-lactam allergy** – When there is concern for a severe allergy to a penicillin or a cephalosporin (eg, anaphylaxis, Stevens Johnson syndrome/toxic epidermal necrolysis [SJS/TEN], drug reaction with eosinophilia and systemic symptoms [DRESS], acute generalized exanthematous pustulosis [AGEP]), an appropriate initial regimen for patients with normal renal function includes (table 3B and table 4):

  - Vancomycin – 15 to 20 mg/kg IV every 8 to 12 hours (not to exceed 2 g per dose or a total daily dose of 60 mg/kg; adjust dose to achieve vancomycin serum trough concentrations of 15 to 20 mcg/mL).

    plus

  - Moxifloxacin – 400 mg IV once daily. In immunocompromised patients, aztreonam should be added to treat *Pseudomonas* as long as the patient does not have a serious allergy (eg, anaphylaxis, SJS/TEN, DRESS, AGEP) to aztreonam itself or an immediate or IgE-mediated allergy (eg, anaphylaxis, angioedema, hives/urticaria) to ceftazidime. Ceftazidime and aztreonam share an R1 side chain group, and cross-reactivity between the two drugs is possible. (See "Immediate cephalosporin hypersensitivity: Allergy evaluation, skin testing, and cross-reactivity with other beta-lactam antibiotics", section on 'Carbapenems and monobactams'.)

- **Patients who require *Listeria* coverage** – If *Listeria* coverage is required (patients >50 years of age and/or immunocompromised hosts), trimethoprim-sulfamethoxazole can be initiated (5 mg/kg [based on the trimethoprim component] IV every eight hours in patients with normal renal function) instead of ampicillin (table 3B and table 4). However, there are limited data on the preferred dosing interval, and in case reports, the dose of trimethoprim-sulfamethoxazole has been administered anywhere from every 6 to every 12 hours [8].

  If meropenem is used instead of a cephalosporin, additional treatment for *Listeria* is not required as meropenem has activity against *Listeria*. (See "Treatment and prevention of Listeria monocytogenes infection", section on 'Alternatives to ampicillin or penicillin'.)

Continuing antibiotics — After the initial dose of an antibiotic is administered, the regimen may be able to be modified. As examples:

- Patients with a severe immediate allergy (eg, anaphylaxis) to a penicillin or cephalosporin may be able to tolerate meropenem, because rates of cross-reactivity between either penicillins or cephalosporins and carbapenems (eg, meropenem) are <1 percent. However, in this setting, it should be administered via a test dose procedure. Because test dosing can introduce unnecessary delay in initiation of antibiotics, it is reasonable to administer moxifloxacin for the initial dose in an emergency room setting, and then transition to meropenem while awaiting the final culture results. Test dose protocols are reviewed separately. (See "Choice of antibiotics in penicillin-allergic hospitalized patients", section on 'Test dose procedure (graded challenge)'.)

  Fluoroquinolones are not recommended as part of standard therapy unless unusual conditions, such as severe drug allergies or highly resistant organisms, are present. Although moxifloxacin has activity against drug-resistant pneumococcus and meningococcus, and fluoroquinolones achieve reasonably high CSF concentrations [8,20], these agents have not been extensively studied and there is only limited evidence of efficacy in animal models and in humans [20,22]. (See "Treatment of bacterial meningitis caused by specific pathogens in adults", section on 'Alternative agents'.)

- If an organism is suspected (eg, based on Gram strain) and the most appropriate treatment could not be initiated (eg, immediate reaction to cephalosporin) the patient should optimally be desensitized to the most effective beta-lactam if a drug allergy specialist is available and the type of past allergy is amenable to desensitization. However, the alternative regimen must be used until the desensitization can be performed. Desensitization protocols involve specialized knowledge and some risk and should be performed by drug allergy specialists. Following completion of treatment for bacterial meningitis, patients who have undergone desensitization should be referred for formal allergy assessment of their beta-lactam allergy label. This should ideally occur >6 weeks after completion of treatment. (See "Rapid drug desensitization for immediate hypersensitivity reactions".)

  Recommended treatment regimens for specific pathogens are discussed in detail separately. (See "Treatment of bacterial meningitis caused by specific pathogens in adults", section on 'Regimens in patients with drug allergies'.)

Empiric treatment during epidemics — Epidemics of meningitis due to *N. meningitidis* are reported almost every year from sub-Saharan Africa. The empiric therapy recommended by the World Health Organization for meningococcal meningitis during epidemics is one or two intramuscular injections of long-acting chloramphenicol (oily suspension), although intramuscular ceftriaxone is an acceptable alternative. This is discussed in detail separately. (See

"Treatment and prevention of meningococcal infection", section on 'Considerations during epidemics in resource-limited settings'.)

TAILORING THERAPY

Directed therapy against a specific organism is recommended when the clinical presentation and results of the cerebrospinal fluid Gram stain are unequivocal (table 3C) or once the culture results are available (table 3D) [32]. For patients with negative CSF culture, therapy is individualized depending on the remainder of the evaluation and clinical status.

Regimens based upon Gram stain — Rather than empiric therapy, intravenous antimicrobial therapy should be directed at the presumed pathogen if the Gram stain is diagnostic (table 3B-C) [5]. If the CSF findings are consistent with the diagnosis of acute bacterial meningitis but the Gram stain is negative, empiric antimicrobial therapy should be continued. If indicated, antimicrobial therapy should then be modified once the cerebrospinal fluid (CSF) culture and in vitro susceptibility studies are available (table 3B, 3D). In addition, resistance patterns at a given hospital should be taken into account when choosing an empiric regimen.

- If gram-positive cocci are seen on the Gram stain of a patient with community-acquired meningitis, *S. pneumoniae* should be the suspected pathogen. Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone) should be administered. However, in the setting of neurosurgery or head trauma within the past month, a neurosurgical device, or a CSF leak, *S. aureus* and coagulase-negative staphylococci are more common, and therapy with vancomycin is warranted [28].

- If gram-negative cocci are seen, *N. meningitidis* is the probable pathogen.

- Gram-positive bacilli suggest *L. monocytogenes*.

- Gram-negative bacilli usually represent Enterobacteriaceae (eg, *Klebsiella* spp, *E. coli*) in cases of community-acquired meningitis.

Additional information on regimens for patients with beta- lactam allergies is discussed above. (See 'Beta-lactam allergy' above.)

Positive CSF culture — Directed therapy against a specific organism is recommended when the cultures are already positive [32]. If, on the other hand, empiric therapy is begun, the regimen should be adjusted, if necessary, once the culture results are available (table 3D). Recommended dosages for use in patients with normal renal and hepatic function are shown in the table (table 3B). The recommended treatment regimens for specific pathogens are

discussed in detail separately. (See "Treatment of bacterial meningitis caused by specific pathogens in adults".)

Negative CSF culture — Cessation of antimicrobial therapy is **not** recommended in patients who have received prior or are receiving concurrent antimicrobial therapy with a negative CSF culture and who are suspected of having bacterial meningitis based on clinical and laboratory findings (eg, CSF pleocytosis). The choice of antimicrobial regimen and duration of administration should be individualized based on risk factors and likely infecting pathogens.

In patients in whom the diagnosis of community-acquired bacterial meningitis is uncertain (eg, possible viral meningitis), additional assessment is warranted. Review CSF parameters (eg, glucose, protein, WBC count); review or request CSF PCR analysis for viruses that may cause meningitis (table 2); and assess for alternative diagnoses. If the CSF PCR is positive for a viral etiology, then antibiotics can be discontinued.

Some clinicians calculate a risk score that has been used to identify patients at zero risk for having bacterial meningitis [33]. The following high-risk findings are considered:

- Host factors (eg, age >60 years, or intravenous drug use, or immunosuppressed)
- Exam (Glasgow Coma scale<15, or vesicular or petechial rash, or aphasia, or focal motor deficits, or cranial nerve palsy, or seizure within one week
- CSF analysis (CSF glucose <45mg/dL, or CSF protein >100mg/dL or serum WBC >12,000/mm^3)

If none of these are present, it would be appropriate to discontinue antibiotics with careful monitoring.

In a case-control study in 111 patients with intracranial hemorrhage, the cell index had good discrimination capacity in identifying patients with culture confirmed cases [34]. Despite these findings, any decisions to discontinue antibiotics should be made with appropriate consultation.

Infections of CSF shunts and other devices are discussed separately. (See "Infections of cerebrospinal fluid shunts".)

SUPPORTIVE CARE

Fluid management — Careful management of fluid and electrolyte balance is important, since both over- and under-hydration are associated with adverse outcomes.

A meta-analysis evaluated three randomized controlled trials of treatment of differing volumes of fluid (maintenance versus restricted fluid) given in the initial management of bacterial meningitis [35]. The largest trial was conducted in a setting with a high mortality rate. There was no significant difference between the two groups in number of deaths or acute severe or mild to moderate neurologic sequelae. However, when neurologic sequelae were defined further, there was a statistically significant difference in favor of the maintenance fluid group in regard to spasticity (relative risk [RR] 0.50, 95% CI 0.27-0.93), seizures at both 72 hours (RR 0.59, 95% CI 0.42-0.83) and 14 days (RR 0.19, 95% CI 0.04-0.88), and chronic severe neurologic sequelae at three months follow-up (RR 0.42, 95% CI 0.20-0.89). Thus, there is evidence that the use of intravenous maintenance fluids is preferred to restricted fluid intake in the first 48 hours in settings with high mortality rates and when patients present late. There is insufficient evidence to guide practice in other settings.

Reduction of intracranial pressure — Patients with bacterial meningitis who have elevations of intracranial pressure (ICP) and who are stuporous or comatose may benefit from insertion of an ICP monitoring device [36,37]. Pressures exceeding 20 mmHg are abnormal and should be treated; there is also rationale for treating smaller pressure elevations (ie, above 15 mmHg) to avoid larger elevations that can lead to cerebral herniation and irreversible brainstem injury. (See "Evaluation and management of elevated intracranial pressure in adults", section on 'ICP monitoring'.)

Methods to reduce ICP include elevating the head of the bed to 30° and hyperventilation to maintain $PaCO_2$ between 27 and 30 mmHg. Another method that has been evaluated for reducing ICP is oral administration of the hyperosmolar agent, glycerol. However, a randomized trial in adults with bacterial meningitis in Malawi (a resource-poor country with high HIV prevalence) was stopped early because planned interim analysis demonstrated increased mortality by day 40 in the glycerol group (63 versus 49 percent) [38]. The reason for this finding is unclear but might relate to an increased incidence of seizures in the patients who received glycerol. Another possible reason could be a rebound increase in ICP as the drug is eliminated, although ICP was not monitored in this trial. In contrast with this trial involving adults, some studies using glycerol have shown promising results in children with bacterial meningitis, although further data are needed before it can be recommended. (See "Bacterial meningitis in children: Dexamethasone and other measures to prevent neurologic complications", section on 'Glycerol'.)

In a study of 15 patients with bacterial meningitis in whom intracranial pressure was monitored, pressure was significantly lowered by a broad range of measures that utilized unconventional volume-targeted intracranial pressure management [39]. These included sedation,

glucocorticoids, normal fluid and electrolyte homeostasis, blood transfusion, albumin infusion, decrease of mean arterial pressure, treatment with a prostacyclin analog, and eventually thiopental, ventriculostomy, and dihydroergotamine. In those not surviving their episode of bacterial meningitis, mean intracranial pressure was significantly higher. However, given that this was not a comparative trial, the results must be interpreted with caution.

In a prospective intervention-control comparison study of adult patients with acute bacterial meningitis, 53 patients were treated with conventional intensive care and 52 patients were given ICP-targeted treatment in the neuro-intensive care unit [40]. ICP-targeted treatment included cerebrospinal fluid (CSF) drainage using external ventricular catheters (48 patients), osmotherapy (21 patients), hyperventilation (13 patients), external cooling (9 patients), high doses of methylprednisolone (3 patients), and deep barbiturate sedation (2 patients), aiming to keep the ICP <20 mmHg and cerebral perfusion pressure of >50 mmHg. Mortality was significantly lower in the intervention group (10 versus 30 percent). However, this was not a randomized controlled trial and controls were identified retrospectively. Additional data are therefore needed.

Induced hypothermia — There has been interest in evaluating induced hypothermia in patients with severe meningitis since there is evidence that it is beneficial in patients with global cerebral hypoxia following cardiac arrest (see "Initial assessment and management of the adult post-cardiac arrest patient", section on 'Temperature management'). However, more data are needed before therapeutic hypothermia can be recommended in patients with severe bacterial meningitis.

In an open-label multicenter randomized trial in 49 intensive care units in France, 98 comatose patients were randomly assigned to undergo induced hypothermia with a loading dose of 4°C cold saline and cooling to 32 to 34°C for 48 hours or standard care [41]. The trial was stopped early because of concerns about excess mortality in the induced hypothermia group compared with the control group (51 versus 31 percent; RR 1.99, 95% CI 1.05-3.77). At three months, 86 percent of patients in the hypothermia group had an unfavorable outcome (defined as a Glasgow Coma Scale score of 1 to 4) compared with 74 percent of those in the control group (RR 2.17, 95% CI 0.78-6.01). After adjustment for age, Glasgow Coma Scale score at inclusion, and the presence of septic shock at inclusion, mortality remained higher in the induced-hypothermia group, although the difference was not statistically significant (hazard ratio 1.76; 95% CI 0.89-3.45). The authors concluded that moderate hypothermia did not improve outcomes in patients with severe bacterial meningitis and that it may be harmful.

In a study of therapeutic hypothermia in adults with community-acquired bacterial meningitis, the incidence of hospital mortality (20 versus 49 percent) and adverse neurologic outcome (ie, a

Glasgow outcome score 1 to 3; 44 versus 66 percent) were significantly lower in patients treated with therapeutic hypothermia [42]. However, the number of enrolled patients was small, and outcomes in this study of the 41 enrolled patients were compared with historical controls.

REPEAT CSF ANALYSIS

There is limited utility to routine repeat lumbar puncture (LP) to assess the response to therapy in adults with bacterial meningitis. This was illustrated in a review of 165 adults with meningitis who underwent an end-of-treatment LP [43]. Wide ranges of glucose and protein concentrations and cell counts were found at the end of treatment in patients who were ultimately shown to be cured without further therapy. In addition, repeat cerebrospinal fluid (CSF) examination failed to detect relapse in the two patients who relapsed following treatment, and the CSF test results led to unnecessary testing in 13 patients with abnormal CSF findings at the end of therapy. The authors concluded that clinical signs of improvement were a better indicator of response to therapy than the results of CSF analysis after treatment had been completed.

Although not routinely recommended, there are settings in which repeat LP should be performed in patients with bacterial meningitis [8]:

- When there is no evidence of improvement by 48 hours after the initiation of appropriate therapy
- Two to three days after the initiation of therapy of meningitis due to microorganisms resistant to standard antimicrobial agents (eg, penicillin-resistant pneumococcal infection), especially for those who are not responding as expected.
- Persistent fever for more than eight days without another explanation

Repeat CSF cultures should be sterile. For patients in whom repeat cultures are positive despite appropriate therapy with parenteral antibiotic therapy, administration of intrathecal (or intraventricular) antibiotics may be considered [44].

PROGNOSIS

There is an appreciable mortality rate associated with bacterial meningitis even with the administration of appropriate antibiotics.

Mortality — Despite the decreased mortality of meningitis with the advent of effective antibiotics, mortality from meningitis still remains significant. The global burden of disease study in 2016 documented that meningitis caused 318,000 deaths and 21,866,000 disability-adjusted life years annually in the world [45].

The mortality rate of bacterial meningitis increases linearly with increasing age. In a United States population-based surveillance study between 2003 and 2007, the case-fatality rate in adults was 16.4 percent; among patients between 18 and 34 years of age, the case-fatality rate was 8.9 percent compared with 22.7 percent in patients ≥65 years of age [46]. The overall case-fatality rate did not change significantly between 1998 to 1999 and 2006 to 2007.

Outcomes also vary depending upon the organism. The following observations from different time periods illustrate the range of findings:

- In a review of 493 episodes of bacterial meningitis in 445 adults seen at a single center in the United States from 1962 to 1988, the overall mortality rate was 25 percent and did not vary over the course of the study [6]. The mortality rate was higher with health care-associated compared with community-acquired infection (35 versus 25 percent) and was higher with infection due to *S. pneumoniae* and *L. monocytogenes* compared with *N. meningitidis* (28 and 32 versus 10 percent).

- In a series of 248 patients seen in 1995 in acute care hospitals in 22 counties in four states in the United States, the mortality rate was highest with *S. pneumoniae* and *L. monocytogenes* (21 and 15 percent, respectively) and lowest with *N. meningitidis* (3 percent) [47].

- A report from the Netherlands evaluated 696 cases of community-acquired acute bacterial meningitis seen between 1998 and 2002 [48]. The overall mortality rate was significantly higher with pneumococcal compared with meningococcal meningitis (30 versus 7 percent). In addition, an unfavorable outcome was six times more common with pneumococcal meningitis, even after adjustment for other clinical predictors.

Mortality rates of bacterial meningitis may be elevated in settings with a high prevalence of HIV infection. In a cohort study of patients undergoing lumbar puncture in Botswana, among whom 72 percent had documented HIV infection, the 10-week and 1-year mortality rates among the 238 patients with culture-confirmed pneumococcal meningitis were 47 percent and 49 percent, respectively [49]. The median CD4 count was 136 cells/microL and 45 percent of the cohort was on antiretroviral therapy.

The use of adjunctive dexamethasone is associated with a reduction in mortality in selected patients with bacterial meningitis. This is discussed in detail separately. (See "Dexamethasone to prevent neurologic complications of bacterial meningitis in adults".)

Neurologic complications — Neurologic complications are not uncommon in adults with bacterial meningitis. In a review of 493 episodes of bacterial meningitis in adults, for example, 28 percent of community-acquired episodes resulted in one or more neurologic complications [6]. The neurologic complications of bacterial meningitis include:

- Impaired mental status
- Increased intracranial pressure and cerebral edema
- Seizures
- Focal neurologic deficits (eg, cranial nerve palsy, hemiparesis)
- Cerebrovascular abnormalities
- Sensorineural hearing loss
- Intellectual impairment

These are discussed in detail separately. (See "Neurologic complications of bacterial meningitis in adults".)

Prediction of risk — Baseline features can be used to estimate the individual patient's risk for an adverse outcome. A prognostic model was derived from a cohort of 176 adults and then validated in another cohort of 93 patients [5]. In-hospital mortality was 27 percent, and 9 percent had a neurologic deficit at discharge. Three baseline clinical features (hypotension, altered mental status, and seizures) were independently associated with an adverse outcome (defined as in-hospital death or neurologic deficit at discharge) and stratified the patients into three risk groups:

- Low risk (no clinical risk factors) – 9 percent adverse outcome
- Intermediate risk (one clinical risk factor) – 33 percent adverse outcome
- High risk (two or three risk factors) – 56 percent adverse outcome

An additional risk factor for an adverse outcome in this report was advancement from low or intermediate risk to high risk in the emergency department prior to the administration of antibiotics. Although this finding supports the recommendation to avoid delays in antimicrobial therapy in patients with suspected bacterial meningitis, it is also consistent with the hypothesis that severely ill patients at the start may have an adverse outcome regardless of the timing of initial therapy [50].

In a review and external validation study of nine risk scores developed to predict outcomes in patients with bacterial meningitis, pneumococcal meningitis, and invasive meningococcal disease, none could be recommended for use in managing individual patients [51].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bacterial meningitis in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Bacterial meningitis (The Basics)")
- Beyond the Basics topics (see "Patient education: Vaccines for adults (Beyond the Basics)" and "Patient education: Vaccines for children age 7 to 18 years (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Overview** – Community-acquired bacterial meningitis is a medical emergency. The most important initial management issues are avoiding a delay in administering antimicrobial therapy and choosing an effective drug regimen. The mortality rate of untreated disease approaches 100 percent and, even with optimal therapy, there can be a high failure rate. (See 'General principles of therapy' above and 'Prognosis' above.)

- **Pretreatment evaluation** – The initial evaluation should include two sets of blood cultures and a lumbar puncture (LP) (algorithm 1). An important early decision relates to whether a head CT should be performed prior to LP. (See 'Pretreatment testing' above.)

  If possible, crucial information (eg, serious drug allergies, recent exposure to an individual with meningitis) should also be obtained before antibiotic treatment of presumed bacterial meningitis is instituted. (See 'History' above.)

- **Empiric antimicrobial therapy** – We recommend that antimicrobial therapy be initiated immediately after the performance of the LP or, if a CT scan is going to be performed before the LP, immediately after blood cultures are obtained (**Grade 1B**). (See 'Avoidance of delay' above.)

  The approach to regimen selection in patients with suspected bacterial meningitis is directed at the most likely bacteria based on the patient's age and other host factors (table 3A-B and table 4). (See 'Avoidance of delay' above and 'Empiric regimens' above.)

- **When to administer** dexamethasone – For adults in resource-rich settings with suspected community-acquired bacterial meningitis due to an unknown organism, we recommend administration of dexamethasone in addition to antimicrobial therapy (**Grade 1B**). Adjunctive dexamethasone should be given shortly before or at the same time as the first dose of antibiotics, when indicated. Dexamethasone should be only continued if the CSF Gram stain and/or the CSF or blood cultures reveal *S. pneumoniae*.

  The indications for dexamethasone for patients with suspected or confirmed bacterial meningitis in resource-limited settings depend on the patient population and are discussed in detail elsewhere. (See 'When to administer dexamethasone' above and "Dexamethasone to prevent neurologic complications of bacterial meningitis in adults".)

- **Tailoring therapy** – Once the CSF Gram stain results are available, the antimicrobial regimen should be tailored to cover the most likely pathogen. If the CSF findings are consistent with the diagnosis of acute bacterial meningitis but the Gram stain is negative, empiric antibiotic therapy should still be continued. (See 'Regimens based upon Gram stain' above.)

  The antibiotic regimen should be modified further, when indicated, based on the CSF culture and susceptibility results. (See "Treatment of bacterial meningitis caused by specific pathogens in adults".)

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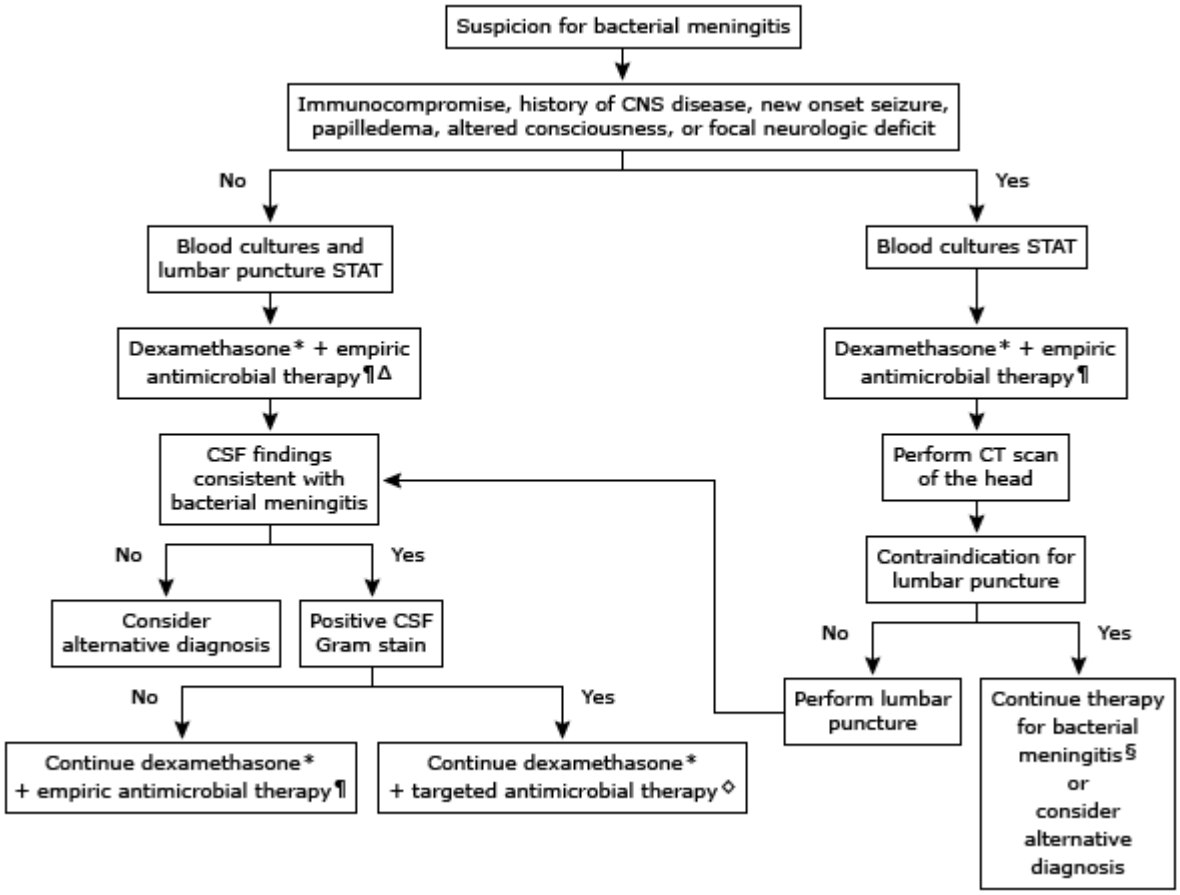
Topic 1290 Version 53.0

GRAPHICS

Management algorithm for adults with suspected bacterial meningitis



"STAT" indicates that the intervention should be done emergently.

CNS: central nervous system; CSF: cerebrospinal fluid; CT: computed tomography.

* Refer to UpToDate topic review on dexamethasone to prevent neurologic complications of bacterial meningitis in adults for specific recommendations.

¶ Refer to UpToDate table on recommendations for empiric antimicrobial therapy for purulent meningitis based on patient age and specific predisposing condition.

Δ Administer dexamethasone and antibiotic therapy immediately after CSF is obtained.

◇ Refer to UpToDate table on recommendations for antimicrobial therapy in adults with presumptive pathogen identification by positive Gram stain.

§ If the diagnosis of bacterial meningitis is likely.

Graphic 50114 Version 5.0

Typical cerebrospinal fluid findings in central nervous system infections*

	Glucose (mg/dL)		Protein (mg/dL)		Total white blood cell (cells/microL)		
	<10¶	10 to 40Δ	100 to 500◇	50 to 300§	>1000	100 to 1000	
More common	Bacterial meningitis	Bacterial meningitis	Bacterial meningitis	Viral meningitis Nervous system Lyme disease (neuroborreliosis) Encephalitis Neurosyphilis TB meningitis¥	Bacterial meningitis	Bacterial or viral meningitis TB meningitis	Ea ba me Vir me Ne TB me
Less common	TB meningitis Fungal meningitis	Neurosyphilis Some viral infections (such as mumps and LCMV)		Early bacterial meningitis	Some cases of mumps and LCMV	Encephalitis	En

TB: tuberculosis; LCMV: lymphocytic choriomeningitis virus.

* It is important to note that the spectrum of cerebrospinal fluid values in bacterial meningitis is so wide that the absence of one or more of these findings is of little value. Refer to the UpToDate topic reviews on bacterial meningitis for additional details.

¶ <0.6 mmol/L.

Δ 0.6 to 2.2 mmol/L.

◇ 1 to 5 g/L.

§ 0.5 to 3 g/L.

¥ Cerebrospinal fluid protein concentrations may be higher in some patients with tuberculous meningitis; concentrations >500 mg/dL are an indication of blood-brain barrier disruption or increased intracerebral production of immunoglobulins, and extremely high concentrations, in the range of 2 to 6 g/dL, may be found in association with subarachnoid block.

Graphic 76324 Version 11.0

Differential diagnosis of selected causes of aseptic meningitis

Viral

- Adenovirus
- Arboviruses
- Coxsackieviruses types A and B
- Cytomegalovirus
- Echoviruses
- Encephalomyocarditis virus
- Epstein-Barr virus
- Herpes simplex virus types 1 and 2
- Human herpes virus 6 (in children)
- Human Parechovirus
- Human immunodeficiency virus
- Influenza A and B
- Lymphocytic choriomeningitis virus
- Measles
- Mumps
- Parainfluenza
- Poliovirus
- Rotavirus
- Rubella
- Toscana virus
- Varicella-zoster virus

Bacterial

- *Actinomyces* spp
- Bacterial endocarditis
- *Borrelia burgdorferi* (Lyme disease)
- *Borrelia recurrentis* (relapsing fever)
- *Brucella* spp
- *Chlamydia* spp
- *Leptospira* spp
- *Mycobacterium tuberculosis*
- *Mycoplasma hominis*
- *Mycoplasma pneumoniae*
- *Nocardia* spp
- Parameningeal bacterial infection (epidural, subdural abscess)
- Partially treated bacterial meningitis
- *Rickettsia* spp
- *Spirillum minor* (rat bite fever)
- *Treponema pallidum* (syphilis)
- *Ureoplasma ureolyticum*

Fungal

- *Aspergillus* spp
- *Blastomyces dermatitidis*
- *Candida* spp
- *Coccidioides immitis*
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*
- *Sporothrix schenckii*

Parasitic

- *Angiostrongylus cantonensis*
- *Taenia solium* (cysticercosis)
- *Toxoplasma gondii*

- *Trichinella spiralis*

Drug

- Anti-CD3 monoclonal antibody
- Azathioprine
- lbuprofen
- Other NSAIDs
- Pyridium (phenazopyridine)
- Trimethoprim-sulfamethoxazole

Malignancy

- Leukemia
- Lymphoma
- Metatstatic carcinomas and adenocarcinomas

Autoimmune

- Behçet disease
- Sarcoidosis
- Systemic lupus erythematosus
- Vogt-Koyanagi-Harada syndrome

Other

- Epidermoid cyst
- Postvaccination

NSAIDs: nonsteroidal anti-inflammatory drugs.

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

Graphic 79745 Version 5.0

Recommendations for empiric antimicrobial therapy for purulent meningitis based on patient age and specific predisposing condition*

Predisposing factor	Common bacterial pathogens	Antimicrobial therapy
Age		
<1 month	*Streptococcus agalactiae*, *Escherichia coli*, *Listeria monocytogenes*	Ampicillin plus cefotaxime; OR ampicillin plus an aminoglycoside
1 to 23 months	*Streptococcus pneumoniae*, *Neisseria meningitidis*, *S. agalactiae*, *Haemophilus influenzae*, *E. coli*	Vancomycin plus a third-generation cephalosporin¶ Δ ◇
2 to 50 years	*N. meningitidis*, *S. pneumoniae*	Vancomycin plus a third-generation cephalosporin¶ Δ ◇
>50 years	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, aerobic gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin¶ Δ
Head trauma		
Basilar skull fracture	*S. pneumoniae*, *H. influenzae*, group A beta-hemolytic streptococci	Vancomycin plus a third-generation cephalosporin¶ Δ
Penetrating trauma	*Staphylococcus aureus*, coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin plus cefepime; OR vancomycin plus ceftazidime; OR vancomycin plus meropenem
Postneurosurgery	Aerobic gram-negative bacilli (including *P. aeruginosa*), *S. aureus*, coagulase-negative staphylococci (especially *S. epidermidis*)	Vancomycin plus cefepime; OR vancomycin plus ceftazidime; OR vancomycin plus meropenem
Immunocompromised state	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, aerobic gram-negative bacilli (including *P. aeruginosa*)	Vancomycin plus ampicillin plus cefepime; OR vancomycin plus meropenem§

* For recommended doses, refer to the UpToDate content on treatment of bacterial meningitis in children and adults.

¶ Ceftriaxone or cefotaxime.

Δ Some experts would add rifampin if dexamethasone is also given.

◇ Add ampicillin if meningitis caused by *Listeria monocytogenes* is suspected.

§ Meropenem provides sufficient coverage for *Listeria* when used as part of an initial regimen. However, if *Listeria* is identified, the patient should generally be switched to a regimen that includes ampicillin. Refer

to the UpToDate topic that discusses treatment of *Listeria* for a discussion of regimen selection.

Graphic 71968 Version 12.0

Recommended intravenous dosages of antimicrobial therapy for adults with bacterial meningitis who have normal renal and hepatic function

Antimicrobial agent	Dose (adult)
Amikacin	5 mg/kg every 8 hours*
Ampicillin	2 g every 4 hours
Aztreonam	2 g every 6 to 8 hours
Cefepime	2 g every 8 hours
Cefotaxime	2 g every 4 to 6 hours
Ceftazidime	2 g every 8 hours
Ceftriaxone	2 g every 12 hours
Chloramphenicol	1 to 1.5 g every 6 hours¶
Ciprofloxacin	400 mg every 8 to 12 hours
Gentamicin	1.7 mg/kg every 8 hours*
Meropenem	2 g every 8 hours
Moxifloxacin	400 mg every 24 hoursΔ
Nafcillin	2 g IV every 4 hours
Oxacillin	2 g IV every 4 hours
Penicillin G potassium	4 million units every 4 hours
Rifampin	600 mg every 24 hours◇
Tobramycin	1.7 mg/kg every 8 hours*
Trimethoprim-sulfamethoxazole (cotrimoxazole)	5 mg/kg every 8 hours§ ¥
Vancomycin	15 to 20 mg/kg every 8 to 12 hours‡†

IV: intravenously; MRSA: methicillin-resistant *Staphylococcus aureus*; IDSA: Infectious Diseases Society of America.

* Dose based on ideal body weight or dosing weight except in underweight patients. A calculator for ideal body weight and dosing weight is available in UpToDate. Dosage and interval must be individualized to produce a peak serum concentration of 7 to 9 mg/L and trough <1 to 2 mg/L for gentamicin or tobramycin and a peak of 25 to 40 mg/L and trough <4 to 8 mg/L for amikacin. For additional information, refer to the UpToDate topic on aminoglycosides.

¶ The higher dose is recommended for patients with pneumococcal meningitis.

Δ No data on optimal dosage needed in patients with bacterial meningitis.

◇ For the treatment of MRSA meningitis, the IDSA suggests a rifampin dose of 600 mg orally once daily or 300 to 450 mg twice daily.[1]

§ Dosage is based on the trimethoprim component.

¥ We administer trimethoprim-sulfamethoxazole at a dose of 5 mg/kg (based on the trimethoprim component) IV every 8 hours in patients with normal renal function. However, there are limited data on the preferred dosing interval, and in case reports, the dose of trimethoprim-sulfamethoxazole has been administered anywhere from every 6 to every 12 hours. For the treatment of MRSA meningitis, the IDSA suggests a trimethoprim-sulfamethoxazole dose of 5 mg/kg (based on the trimethoprim component) intravenously twice or three times daily.[1]

‡ For treatment of meningitis due to pathogens other than *S. aureus*, the vancomycin dose should not exceed 2 g per dose or a total daily dose of 60 mg/kg. Adjust dose to achieve vancomycin serum trough concentrations of 15 to 20 mcg/mL.[1]

† For treatment of meningitis due *S. aureus*, a vancomycin loading dose (20 to 35 mg/kg) is appropriate;[2] within this range, we use a higher dose for critically ill patients. The loading dose is based on actual body weight, rounded to the nearest 250 mg increment and not exceeding 3000 mg. The initial maintenance dose and interval are determined by nomogram (typically 15 to 20 mg/kg every 8 to 12 hours for most patients with normal renal function). Subsequent dose and interval adjustments are based on AUC-guided or trough-guided serum concentration monitoring. Refer to the UpToDate topic on vancomycin dosing for a sample nomogram and discussion of vancomycin monitoring.

Reference:

1. *Liu C, Bayer A, Cosgrove SE, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children: Executive Summary. Clin Infect Dis 2011; 52:285.*
2. *Rybak MJ, Le J, Lodise TP, et al. Therapeutic Monitoring of Vancomycin for Serious Methicillin-Resistant Staphylococcus Aureus Infections: A Revised Consensus Guideline and Review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2020; 77:835.*

Graphic 60707 Version 15.0

Choice of empiric antibiotics in adults with possible community-acquired bacterial meningitis with reported past hypersensitivity reactions to beta-lactam antibiotics

Past beta-lactam reaction	Initial regimen	Comments
Mild cutaneous reactions to a penicillin (eg, mild drug eruptions, with or without pruritus, immediate or delayed), including isolated mild hives to a penicillin without other signs of anaphylaxis, especially if the reaction occurred in childhood and/or >10 years ago.	▪ Ceftriaxone or cefotaxime **plus** ▪ Vancomycin	If *Listeria* coverage is required (eg, patients >50 years of age and/or immunocompromised hosts), trimethoprim-sulfamethoxazole should be initiated. Immunocompromised patients generally require expanded gram-negative coverage (eg, cefepime or meropenem instead of ceftriaxone or cefotaxime).* If meropenem is used, it provides sufficient coverage for *Listeria* when used as part of an initial empiric regimen.
Isolated mild hives to a cephalosporin without other signs of anaphylaxis (especially if the reaction occurred in childhood and/or >10 years ago) Or Mild delayed type reactions to cephalosporins.	▪ Meropenem **plus** ▪ Vancomycin	Meropenem provides sufficient coverage for *Listeria* and *Pseudomonas aeruginosa* when used as part of an initial empiric regimen.*
Severe immediate allergy (eg, anaphylaxis) to a penicillin and/or cephalosporin Or SJS/TEN, DRESS, or AGEP with any beta-lactam other than aztreonam.	▪ Moxifloxacin¶ **plus** ▪ Vancomycin	If *Listeria* coverage is required (eg, patients >50 years of age and/or immunocompromised hosts), trimethoprim-sulfamethoxazole should be initiated. Immunocompromised patients generally require expanded gram-negative coverage.* If expanded gram-negative coverage is required, aztreonam should be added as long as there

		is no history of serious allergy (eg, anaphylaxis, SJS/TEN, DRESS, AGEP) to aztreonam itself or an immediate or IgE-mediated allergy to ceftazidime.
Other uncommon forms of hypersensitivity	**Initial regimen**	**Comments**
Interstitial nephritis[Δ], or drug-induced liver disease[Δ◇], or drug-induced cytopenia[Δ], or serum sickness[Δ]	▪ Ceftriaxone or cefotaxime **plus** ▪ Vancomycin	If *Listeria* coverage is required (eg, patients >50 years of age and/or immunocompromised hosts), trimethoprim-sulfamethoxazole should be initiated. Immunocompromised patients generally require expanded gram-negative coverage (eg, cefepime or meropenem instead of ceftriaxone or cefotaxime).* If meropenem is used, it provides sufficient coverage for *Listeria* when used as part of an initial empiric regimen.

This table discusses empiric antibiotic selection for the initial regimen in patients with a beta-lactam allergy. Once the organism is identified, therapy should then be tailored to the best available agent. If the most appropriate treatment was not initiated due to a beta-lactam allergy, the patient should be managed in conjunction with a drug allergy specialist to see if the type of past allergy is amenable to rechallenge or desensitization.

IV: intravenous; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis; DRESS: drug reaction with eosinophilia and systemic symptoms; AGEP: acute generalized exanthematous pustulosis.

* Refer to the topic that discusses initial selection of antibiotics for treatment of bacterial meningitis for a more detailed discussion of which patients require expanded gram-negative coverage and regimen selection in this setting.

¶ Patients with a severe immediate allergy (eg, anaphylaxis) to a penicillin or cephalosporin can usually tolerate meropenem, because cross-reactivity rates between penicillins or cephalosporins and carbapenems for patients with proven immediate allergy are <1%. However, in such patients, meropenem should be administered using a test dose procedure. Thus, to avoid delays in initiating treatment, it is reasonable to administer moxifloxacin for the initial dose in an emergency room setting, and then transition to meropenem while awaiting the final culture results. Test dose protocols are reviewed in the topic that discusses the use of antibiotics in penicillin-allergic hospitalized patients.

Δ Interstitial nephritis, drug-induced liver disease, drug-induced cytopenias, and serum sickness (as well as serum sickness-like reactions) tend to be drug specific. This type of reaction to a penicillin in the past would not necessitate avoidance of cephalosporins.

◇ Commonly implicated drugs are amoxicillin-clavulanate in North America and flucloxacillin in Europe.

Graphic 120657 Version 3.0

Recommendations for antimicrobial therapy of bacterial meningitis in adults with presumptive pathogen identification by positive Gram stain*

Microorganism	Recommended therapy	Alternative therapies
Streptococcus pneumoniae	Vancomycin plus a third-generation cephalosporin¶ Δ	Fluoroquinolone◇
Neisseria meningitidis	Third-generation cephalosporin¶	Chloramphenicol, fluoroquinolone, aztreonam
Listeria monocytogenes	Ampicillin§ or penicillin G§	Trimethoprim-sulfamethoxazole
Haemophilus influenzae	Third-generation cephalosporin¶	Chloramphenicol, cefepime, meropenem, fluoroquinolone

* For recommended dosages, refer to the UpToDate table on recommended intravenous dosages of antimicrobial therapy for adults with bacterial meningitis.

¶ Ceftriaxone or cefotaxime.

Δ Some experts would add rifampin if dexamethasone is also given.

◇ Moxifloxacin is recommended given its excellent cerebrospinal fluid penetration and in vitro activity against *Streptococcus pneumoniae*, although there are no clinical data available. If used, many authorities would combine moxifloxacin with vancomycin or a third-generation cephalosporin (cefotaxime or ceftriaxone).

§ Addition of an aminoglycoside should be considered.

Graphic 75922 Version 6.0

Recommendations for specific antimicrobial therapy of bacterial meningitis in adults based on isolated pathogen and susceptibility testing*

Microorganism, susceptibility	Standard therapy	Alternative therapies¶
Streptococcus pneumoniae		
Penicillin MIC		
≤0.06 mcg/mL	Penicillin G or ampicillin	Third-generation cephalosporin[Δ] chloramphenicol
≥0.12 mcg/mL		
Third-generation cephalosporin[Δ] MIC <1 mcg/mL	Third-generation cephalosporin[Δ]	Cefepime, meropenem
Third-generation cephalosporin[Δ] MIC ≥1 mcg/mL	Vancomycin plus a third-generation cephalosporin[Δ ◇]	Fluoroquinolone[§]
Neisseria meningitidis		
Penicillin MIC		
<0.1 mcg/mL	Penicillin G or ampicillin	Third-generation cephalosporin[Δ] chloramphenicol
0.1 to 1.0 mcg/mL	Third-generation cephalosporin[Δ]	Fluoroquinolone, meropenem, chloramphenicol
Listeria monocytogenes	Ampicillin[¥] or penicillin G[¥]	Trimethoprim-sulfamethoxazole
Streptococcus agalactiae (group B *Streptococcus*)	Ampicillin or penicillin G	Third-generation cephalosporin[Δ]
Escherichia coli and other Enterobacteriaceae[‡]	Third-generation cephalosporin[Δ]	Aztreonam, fluoroquinolone, meropenem, trimethoprim-sulfamethoxazole, ampicillin
Pseudomonas aeruginosa[‡]	Cefepime or ceftazidime	Aztreonam, ciprofloxacin, meropenem
Acinetobacter baumannii	Meropenem	Colistin (usually formulated as colistimethate sodium)[†] or polymyxin B[†]
Haemophilus influenzae		
Beta-lactamase negative	Ampicillin	Third-generation cephalosporin[Δ] cefepime, fluoroquinolone, aztreonam, chloramphenicol

Beta-lactamase positive	Third-generation cephalosporin[Δ]	Cefepime, fluoroquinolone, aztreonam, chloramphenicol
Staphylococcus aureus		
Methicillin susceptible	Nafcillin or oxacillin	Vancomycin, meropenem, linezolid, daptomycin**
Methicillin resistant	Vancomycin[¶¶]	Trimethoprim-sulfamethoxazole, linezolid, daptomycin**
Staphylococcus epidermidis	Vancomycin[¶¶]	Linezolid
Enterococcus species		
Ampicillin susceptible	Ampicillin plus gentamicin	–
Ampicillin resistant	Vancomycin plus gentamicin	–
Ampicillin and vancomycin resistant	Linezolid	–

MIC: minimum inhibitory concentration.

* For recommended dosages, refer to the UpToDate table on the recommended intravenous doses of antimicrobial therapy for adults with bacterial meningitis.

¶ There may not be clinical data to support all recommendations for alternative antibiotics in patients with bacterial meningitis, but specific agents are recommended based on cerebrospinal fluid (CSF) penetration in experimental animal models and in vitro activity against the offending organism.

Δ Ceftriaxone or cefotaxime.

◇ Consider addition of rifampin if the MIC of ceftriaxone is >2 mcg/mL.

§ Moxifloxacin is recommended given its excellent CSF penetration and in vitro activity against *Streptococcus pneumoniae*, although there are no clinical data available. If used, many authorities would combine moxifloxacin with vancomycin or a third-generation cephalosporin (cefotaxime or ceftriaxone).

¥ Addition of an aminoglycoside should be considered.

‡ Choice of a specific antimicrobial regimen must be guided by in vitro susceptibility test results.

† Should be administered not only by the intravenous route but also by the intraventricular or intrathecal route.

** Daptomycin has poor central nervous system penetration and is generally not recommended; if used because other alternatives are not available, it should be combined with rifampin therapy.

¶¶ Consider addition of rifampin.

Reference:

1. *van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in the treatment of bacterial meningitis. Lancet 2012; 380:1693.*

Graphic 81209 Version 18.0