Emergency diagnosis and treatment of adult meningitis

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Despite the existence of antibiotic therapies against acute bacterial meningitis, patients with the disease continue to suffer significant morbidity and mortality in both high and low-income countries. Dilemmas exist for emergency medicine and primary-care providers who need to accurately diagnose patients with bacterial meningitis and then rapidly administer antibiotics and adjunctive therapies for this life-threatening disease. Physical examination may not perform well enough to accurately identify patients with meningitis, and traditionally described lumbar puncture results for viral and bacterial disease cannot always predict bacterial meningitis. Results from recent studies have implications for current treatment guidelines for adults with suspected bacterial meningitis, and it is important that physicians who prescribe the initial doses of antibiotics in an emergency setting are aware of guidelines for antibiotics and adjunctive steroids. We present an overview and discussion of key diagnostic and therapeutic decisions in the emergency evaluation and treatment of adults with suspected bacterial meningitis.

Lancet Infect Dis 2007; 7: 191–200

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Introduction

A 25-year-old man presents to the emergency department with a chief complaint of fever, headache, and neck pain. It is a busy Saturday night in your emergency department and you are not made aware of the patient's arrival for 20 min. An experienced member of your nursing staff approaches in the middle of your evaluation of a different patient with potential acute coronary syndrome to ask for an order for an antipyretic agent. When you learn that the patient's temperature is 39·7ºC (103·5ºF), you immediately go to evaluate him. You become concerned about a life-threatening infection of the central nervous system when you find his examination notable for fever, somnolence, photophobia, and neck stiffness.

Many clinicians might feel that the initial medical treatment for a patient like this who presents with classic signs and symptoms of bacterial meningitis may be straightforward. The possibility of bacterial meningitis mandates rapid initiation of stabilising medical treatment and antibiotic administration. However, for the majority of patients who present for emergency evaluation with symptoms that could be caused by meningitis, the most appropriate steps for diagnosis and treatment will not be as immediately apparent.

The topics discussed in this review will focus on decisions that emergency medicine and primary-care physicians have to make when diagnosing and treating adult patients with suspected meningitis. The initial steps in evaluation typically focus on history and physical examination, and we will discuss the literature suggesting that much of this evaluation may not accurately identify meningitis. Decisions regarding neuroimaging before lumbar puncture and the interpretation of lumbar puncture results will be reviewed. Finally, we will examine the empiric treatment of presumptive bacterial meningitis with antibiotics together with adjunctive systemic steroids.

Epidemiology

The estimated incidence of bacterial meningitis per year is 0·6–4 per 100 000 adults in developed countries, and might be up to ten times higher in other parts of the world.[1–6] Meningitis caused by *Haemophilus influenzae* type b has nearly been eliminated in many developed countries since routine childhood vaccination was initiated,[7] and the introduction of conjugate vaccines against seven serotypes of *Streptococcus pneumoniae* has reduced the burden of childhood pneumococcal meningitis substantially.[8,9] In some regions of the world, invasive infections caused by *Neisseria meningitidis* serogroup C have increased over the past 10 years, prompting the introduction of routine immunisation with serogroup C meningococcal polysaccharide–protein conjugate vaccines.[10] The recent approval of a conjugate meningococcal vaccine against serogroups A, C, Y, and W135 might lead to a further decrease in the incidence of this devastating infection.[4,11] As a consequence of these kinds of routine vaccination programmes in developed countries, the age-specific incidence of bacterial meningitis has decreased in children, thus increasing the fraction of patients that are adults.[1,12] In 2005, the Netherlands Reference Laboratory for Bacterial Meningitis received 484 bacterial cerebrospinal fluid isolates from patients with meningitis and 56% were from patients older than 16 years of age.[6] In these adults with community-acquired bacterial meningitis, the most common aetiologic agents now are *S pneumoniae* and *N meningitidis*, which cause 80–85% of all cases.[1,3] This manuscript will focus on the diagnosis and treatment of meningitis, and readers are referred to other resources for details about systemic infections such as meningococcal sepsis.[13,14]

Initial evaluation of meningitis

Patient history, signs, and symptoms

In adult patients diagnosed with meningitis, little is known about the timeframe between the initial onset of symptoms and first consultation with a physician. A recent study provided a systematic assessment of the sequence and development of early symptoms in children and adolescents with meningococcal disease (encompassing the spectrum of disease from sepsis to meningitis) before admission to the hospital.[15] Although limited by the retrospective design, this study showed that classic symptoms of rash, meningismus, and

Headache, fever, stiff neck or Dec LOC in 99% patients

impaired consciousness develop late in the pre-hospital illness, if at all. Early signs before admission in adolescents (ages 15–16 years) with meningococcal disease were leg pain (53%) and cold hands and feet (44%). Studies have not yet been published with similar data for adult patients.

When a patient presents to an emergency department physician, primary-care doctor, neurologist, or infectious disease specialist for an emergent evaluation, the patient history can help to estimate the probability of meningitis. A wide variety of patient complaints may be elicited from patients with meningitis, and a meta-analysis that included 845 patients over a 30-year period showed poor sensitivity and specificity for symptoms such as headache, nausea, and vomiting for the diagnosis of meningitis.[16] This is not surprising since such non-specific symptoms are found in many patients suffering from a wide variety of clinical conditions.

To identify common features that might help to screen for meningitis in an emergency setting, a clinician may look to examine large retrospective studies of patients who were diagnosed with bacterial meningitis. A study from a tertiary hospital with 493 episodes of bacterial meningitis in adults showed that the historical "classic triad" of fever, stiff neck, and alterations in mental status was present in only two-thirds of adults.[2] Fever was the most common finding (present in 95% of patients) and at least one element of the so-called classic triad was found in every single patient with meningitis.[2] Other retrospective analyses of bacterial meningitis found a high incidence of fever (84–97%) associated with lower numbers of patients having the classic triad of symptoms (21–51%),[17,18] or symptoms of fever, stiff neck, and headache (66%).[19] Although a caveat for retrospective studies is that the absence of recorded symptoms does not necessarily mean these were not present, the findings from these large cohorts of patients demonstrate that there are certainly aspects of an initial patient presentation that should make clinicians suspect meningitis. The findings support an intuitive approach to differential diagnosis, but clinicians should be careful to note that signs and symptoms alone do not provide sufficient information to diagnose meningitis. However, one meta-analysis suggests that the absence of fever, neck stiffness, and altered mental status effectively eliminates meningitis as a likely diagnosis with a sensitivity of 99–100%.[16]

A Dutch nationwide prospective study of 696 adults with community-acquired bacterial meningitis found an even lower incidence of 44% for the classic triad of fever, neck stiffness, and change in mental status (defined as a score on the Glasgow Coma Scale of 14 or less).[3] This prospective cohort had a somewhat lower prevalence of fever (77%) in patients diagnosed with bacterial meningitis. However, the researchers did find that 95% of patients with culture-proven bacterial meningitis presented with at least two signs or symptoms of headache, fever, neck stiffness, and alterations in mental status. At least one of these four elements was present in 99% of patients,[3] further supporting the idea that aspects of history and physical examination can be used to heighten suspicion of meningitis even if they cannot alone rule out the diagnosis.

Specific physical examination findings

How good are specific physical examination findings in helping to diagnose patients with suspected meningitis that was based on initial presentation? Although the traditionally described purpuric rash of meningococcal disease would influence a clinician's suspicion for meningitis caused by this pathogen,[15,20] most adults with bacterial meningitis do not present with prominent skin findings—only 11% of cases (30 of 279) had a rash in a large retrospective series[2] and only 26% of cases (176 of 683) had a rash in a prospective study.[3] There are a number of other clinical findings that clinicians are taught in medical school to look for and evaluate in patients with signs and symptoms indicating meningitis, such as Kernig's sign, Brudzinski's sign, and meningismus. Many physicians who use these physical findings in their clinical decision-making might not be aware of the studies suggesting that these findings lack adequate sensitivity to be used in isolation to diagnose or exclude a potentially life-threatening disease.

The presence or absence of meningeal signs such as Kernig's sign, Brudzinski's sign, and nuchal rigidity are physical examination findings often documented when evaluating a patient for possible meningitis. Kernig's sign was first described in the 1880s and was originally done with the patient in the sitting position, but today is frequently done in the supine position. This test involves flexing the hip and extending the knee and a positive result is recorded when pain is elicited in the back and legs. Brudzinski's neck sign is typically done in the supine position where the head is passively flexed and is interpreted as positive when flexion at the hips to lift the legs is elicited in response. Nuchal rigidity is a clinical determination of severe neck stiffness and inability to passively flex and extend the head in a normal fashion.

So is the absence of these meningeal signs sufficient to rule out meningitis? A prospective study with 297 adults evaluated Kernig's sign, Brudzinski's sign, and nuchal rigidity and their relation to meningitis diagnosed by lumbar puncture.[21] This study found that none of these signs accurately identified patients with meningitis. There was no correlation with moderate meningeal inflammation or with microbial evidence of infection (such as positive Gram stain or positive cultures), and Kernig's sign and Brudzinski's sign were found to have poor sensitivity (5%) with high specificity (95%). In this study population, 80 of 297 patients had meningitis, but only 24 had nuchal rigidity (sensitivity 30%). Nuchal rigidity was absent in 148 of the 217 patients without meningitis (specificity 68%). Notably, only three of the

297 patients (1%) had bacterial meningitis by cerebrospinal fluid culture, and nuchal rigidity failed to identify two of these three patients with bacterial meningitis.[21]

The jolt accentuation test is another clinical test for meningeal irritation that was evaluated in a prospective study of 54 patients with headache and fever in an effort to identify those with meningitis.[22] This test is done by having the patient rotate his head in a horizontal fashion at a rate of two to three times per second, and a positive test is the exacerbation of an existing headache. The sensitivity of neck stiffness and Kernig's sign were very poor (15% and 9%, respectively), whereas that of the jolt accentuation was 97% in their small patient cohort with specificity of 60%.[22] Use of the jolt accentuation test has not been evaluated in any larger subsequent studies, but the overall results support that the absence of the traditonally described "meningeal signs" may not be sufficient to rule out meningitis.

Naturally, physicians do not rely on a single test for diagnosis and combine a number of historical and physical examination findings together to form a clinical impression. This approach is supported by the retrospective and prospective studies identifying patient characteristics concerning for meningitis and reveals the limitations of physical examination.[2,3,16–19,21,22] When sufficient suspicion remains after a thorough history and physical examination, clinicians must consider further diagnostic testing.

Diagnostic lumbar puncture

Indications for computed tomography scan before lumbar puncture

Once an initial patient evaluation has been completed with history and physical findings, lumbar puncture is the diagnostic procedure of choice if the diagnosis of bacterial meningitis cannot be ruled out. Characteristic findings in the cerebrospinal fluid are typically used to make the diagnosis of meningitis. In view of the urgent nature of this testing to make the diagnosis of meningitis, one of the issues physicians are faced with in an emergency department setting is whether neuroimaging—either computed tomography (CT) or magnetic resonance imaging (MRI)—is required before lumbar puncture. The possible role of MRI in the acute evaluation of patients with bacterial meningitis is unknown, and the time required to obtain MRI or other high-resolution methods of brain imaging at many centres make this an impractical technique for emergency use. CT scan is, therefore, used for this purpose in most institutions.

One fear that has been discussed in the literature since the first lumbar punctures were done in the late 1800s and early 1900s is the risk of herniation and possible death precipitated by lumbar puncture.[23] Of primary concern is the occult presence of an intracranial mass lesion (such as a tumour or toxoplasmosis lesion) that could possibly lead to brain shift, which may end in herniation and death. Cranial imaging can be considered as a way to evaluate for signs of brain shift as a precaution in selected patients before lumbar puncture. Numerous papers over the past 125 years have tried to establish whether cerebral herniation is caused by lumbar puncture. There are several paediatric studies that show a possible temporal relationship between children with meningitis who had lumbar puncture and subsequently herniated,[24–26] but also reports of patients with meningitis who had brain herniation even in the absence of a lumbar puncture procedure.[24,27] Some reports have noted that a cranial CT may even be normal in some patients when completed just before impending herniation,[25,27] but such cases are difficult to interpret in light of the limitations of CT scan for diagnosing brain herniation, imaging the posterior fossa, and predicting risk of complications after lumbar puncture.

There are several interesting case series that were published before CT scan was available to evaluate for mass lesions or possible signs of increased intracranial pressure. One review of 200 cases of lumbar puncture in patients with known increased intracranial pressure (144 had papilloedema) showed no adverse effect of diagnostic lumbar puncture in 200 patients with verified or suspected brain tumours.[28] Another series of 103 patients with increased intracranial pressure who all had lumbar puncture found only four deaths within 6–40 h after lumbar puncture, but there was no herniation found at autopsy on three and an unclear causal relationship for any of them.[29]

Lumbar puncture completed on 56 patients with papilloedema reported no clinical changes in patient condition in one series,[30] and another series of 70 patients with papilloedema reported one possible complication in a comatose patient with a skull fracture and seizures before lumbar puncture who died 15 h after the procedure was completed.[31] In this same series, 59 patients with increased intracranial pressure but no papilloedema had an 11% incidence of complications within 48 h of lumbar puncture, but all were felt to have not been caused by the lumbar puncture itself.[31] Papilloedema was rare in a large retrospective study including adults with bacterial meningitis (2–4% of patients)[2,19] and in the Dutch Meningitis Cohort,[3] papilloedema was an uncommon finding present in only 13 patients of 386 examined by funduscopy (3%). In this study, unfavourable outcome was defined by a Glasgow Outcome Scale score of 1–4 points at discharge and favourable outcome was defined by a score of 5. Although papilloedema was related to unfavourable outcome (eight of 13 [62%] versus 103 of 373 [35%]; p=0·01), four patients who had papilloedema without any other contraindication to lumbar puncture were reported to have normal CT scans before lumbar puncture was performed (van de Beek D, unpublished data). This might suggest that the risk of acute herniation in the setting of papilloedema or increased intracranial pressure, or both, is perhaps not as high as feared in patients with bacterial

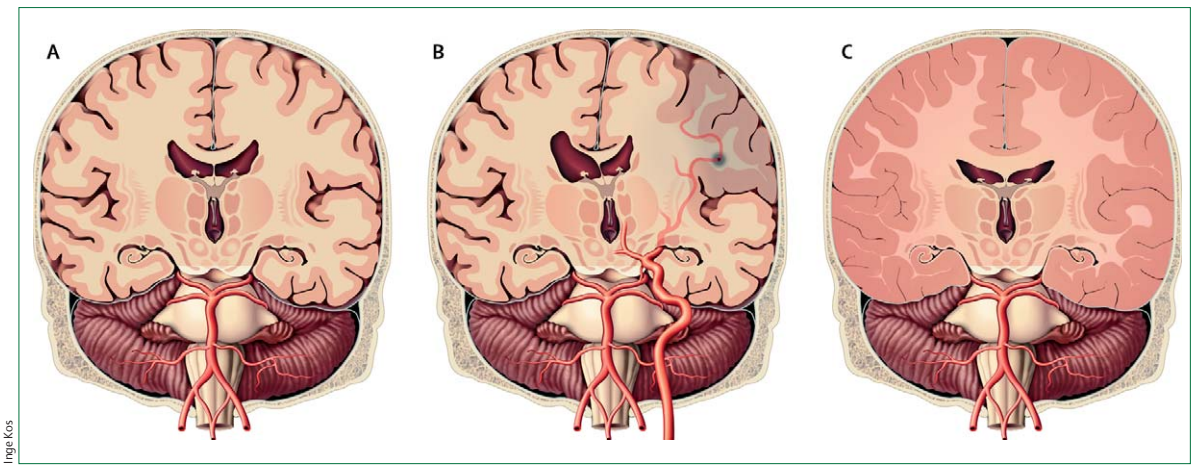

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***Figure 1*: Cranial imaging to evaluate potential contraindications for lumbar puncture should be focused on identifying signs of a focal space-occupying lesion, evidence of brain shift, and/or signs of severe diffuse brain swelling**

(A) Normal brain, (B) meningitis-associated cerebral infarct causing pronounced brain shift, and (C) diffuse brain swelling associated with severe infection. Initial lumbar puncture should not be done when CT findings of significant brain shift are found, and empiric therapy for meningitis should be continued in such patients.

meningitis. Nevertheless, with the low incidence of papilloedema in meningitis, and considering that the funduscopic examination may be challenging to complete in some patients, routine ophthalmological examination might not be required in all patients that are considered for lumbar puncture. However, when papilloedema or other signs concerning for potential brain shift are identified, clinicians should recognise that lumbar puncture could potentially cause or hasten herniation, whether or not there is increased intracranial pressure or papilloedema. Therefore, in patients with suspected bacterial meningitis the interpretation of cranial imaging should be focused on brain shift, which may result from a focal space-occupying lesion or severe diffuse brain swelling as illustrated in figure 1.

Recommendations for cranial CT and fears of herniation are based on the observed clinical deterioration of a few patients in the several to many hours after lumbar puncture and the perceived temporal relationship of lumbar puncture and herniation, but as previously mentioned proving a cause and effect association is very difficult based on the available data. Many of these studies based their diagnosis of herniation on clinical signs alone without a radiographic or pathological confirmation of the diagnosis[25,27,32] and clinicians are left with the realisation that "herniation after lumbar puncture does not necessarily mean herniation caused by lumbar puncture".[33]

With these observations in mind, some authors have attempted to solve this problem in the setting of suspected meningitis.[34,35] There are no unequivocal examples in the literature of patients who were neurologically normal before lumbar puncture who then suffered a devastating insult caused by this diagnostic test.[35] Clinicians should use CT scan to detect evidence of brain shift, since almost all cases of bacterial meningitis have associated increases in cerebrospinal fluid opening pressures and yet herniation remains a rare complication overall.[3,4,27]

Within all of this uncertainty, there remains the issue that there is possibly a small subset of patients whose clinical condition could acutely worsen if lumbar puncture were completed in the emergency department. One set of recommendations for emergency department brain CT scanning before lumbar puncture are based on a prospective study in 2001, which included 301 adult patients with suspected meningitis.[36] Items associated with abnormal CT scan included: age more than 60 years, altered mental status, gaze or facial palsy, abnormal language or inability to answer two questions or follow two commands, immunocompromise, history of central nervous system disease, seizure in past week, visual field abnormalities, and arm or leg drift. In this cohort of patients, if none of these features were present there was a negative predictive value of 97% for an intracranial abnormality, confirming that clinical features can be used to identify patients who are unlikely to have abnormal findings on brain CT. Interestingly, there were a few patients in this study with abnormalities that were missed by these clinical criteria who ultimately underwent lumbar puncture without any apparent complications. It is also important to recognise that this study used CT scan abnormalities as a surrogate marker for increased risk of herniation.

We feel it is reasonable to proceed with lumbar puncture without a CT scan if the patient does not meet any of the following: patients who have new-onset seizures, an immunocompromised state, signs that are suspicious for space-occupying lesions (papilloedema or focal neurological signs [not including cranial nerve palsy]), or moderate-to-severe impairment of consciousness.[4] The classification of patients as low risk for complications after lumbar puncture when they lack

clinical features related to intracranial brain shift appears to be a reasonable approach to this difficult decision.

Interpretation of lumbar puncture results

When lumbar puncture is completed and findings show increased white blood cell counts in the cerebrospinal fluid, confirming a diagnosis of meningitis, many clinicians would like to determine which patients are at risk for the truly life-threatening bacterial meningitis versus those with a typically less concerning viral meningitis. The next topic that physicians evaluating patients in an emergency setting have to consider is whether or not cerebrospinal fluid findings can accurately predict the risk for bacterial disease.

It is important for providers to recognise that there have been several documented cases of bacterial meningitis in the absence of pronounced pleocytosis in the cerebrospinal fluid (ie, less than 100 white blood cells per µL found at the time of lumbar puncture).[2,3,17–19,37] Keeping this in mind, lumbar puncture results might help to risk-stratify patients we are evaluating for potential meningitis. Table 1 reflects a common representation of typical findings in bacterial and viral meningitis that can be found in many textbooks and reference sources.[4,38] Classically described, the white blood cell count in bacterial meningitis is typically greater than 1000 cells per µL, while in viral meningitis it is less than 300 cells per µL—although considerable overlap exists in these categories. The neutrophil count is typically elevated in bacterial meningitis compared with viral meningitis.[39] The measurement of protein and glucose is an important aspect of cerebrospinal fluid analysis to complement the cell counts because abnormal protein and glucose levels are typically found in bacterial disease but are relatively normal in many cases of viral meningitis. Gram stain of cerebrospinal fluid samples, although having reported sensitivities of only 50–90%, can certainly help to make the diagnosis of bacterial disease with a specificity approaching 100%.[2,3,18,40] Adults with pneumococcal meningitis have been found to have positive Gram stains in 81–93% of cases.[37,41] The diagnostic yields from Gram stain and subsequent culture may be decreased when previous antibiotic therapy has been given, although it is unlikely that the other biochemical and cellular abnormalities of cerebrospinal fluid would be affected by previous therapy.[40,42]

There are several problems with using a chart such as table 1 for clinical decisions on individual patients, particularly when determining whether patients require admission or can be discharged home. Much of the data in the literature concerning guidelines for predicting bacterial disease are derived from paediatric patients,[43–47] and the data available for adult patients suggests that using such a strategy would miss a number of patients with bacterial disease.[2,3,17–19,37] One retrospective study found that 5% of cases (27 of 493) with documented bacterial meningitis had a cerebrospinal fluid white blood cell count of less than 100 cells per µL,[2] whereas three other retrospective analyses of bacterial disease found 10–19% of patients with a white blood cell count less than 100 cells per µL—a level many would consider predictive for viral disease.[17–19] A prospective study of 696 patients with bacterial meningitis found that 12% of patients did not have any individual cerebrospinal fluid findings predictive for bacterial meningitis.[3,39] Many studies in adults and paediatric patients have come to the conclusion that in the setting of an elevated white blood cell count in the cerebrospinal fluid, there is no single variable that can reliably rule out bacterial meningitis.[39,43,47–52]

Perhaps clinicians can rely on combinations of cerebrospinal fluid findings to accurately predict bacterial disease? Despite multiple retrospective models using logistic equations and other mathematical model ling,[39,48,53–56] none have yet proved robust enough for widespread clinical practice. The practice guidelines from the Infectious Diseases Society of America suggests that these prediction rules should not be used for clinical decisions in individual patients.[38] One additional aspect of particular importance to physicians working in emergency medicine and other urgent outpatient settings is that all of the studies in adult patients were done on hospitalised populations.[39,48,54,55,57,58] Therefore, in all of the studies evaluating the potential to differentiate bacterial and viral meningitis every patient was admitted to the hospital for observation regardless of whether they received antibiotics or not. One should use appropriate caution when attempting to apply these kinds of decision rules to patients that might be considered candidates for outpatient treatment with suspected viral meningitis. There are no well-designed studies available to assist clinicians with this particular disposition decision, and individual clinicians will have to decide what level of risk is tolerable when diagnosing someone with viral meningitis and considering them as possible candidates for discharge home with outpatient follow-up.

Treatment for suspected bacterial meningitis

Rapid administration of broad-spectrum antibiotics

Bacterial meningitis is a neurological emergency and can lead to substantial morbidity and mortality.[3,4] Recent prospective and retrospective studies document a mortality

	Bacterial meningitis	Viral meningitis
White blood cell count (cells per µL)	1000–10 000 Range <100 to >10 000	<300 Range <100–1000
Neutrophils	>80%	<20%
Protein levels	Elevated	Normal
Glucose levels	Reduced	Normal

See text for discussion of the reasons why these findings may not be adequate to predict the risk of bacterial disease in individual patients.

Table 1: **Classically described cerebrospinal fluid findings in bacterial and viral meningitis**

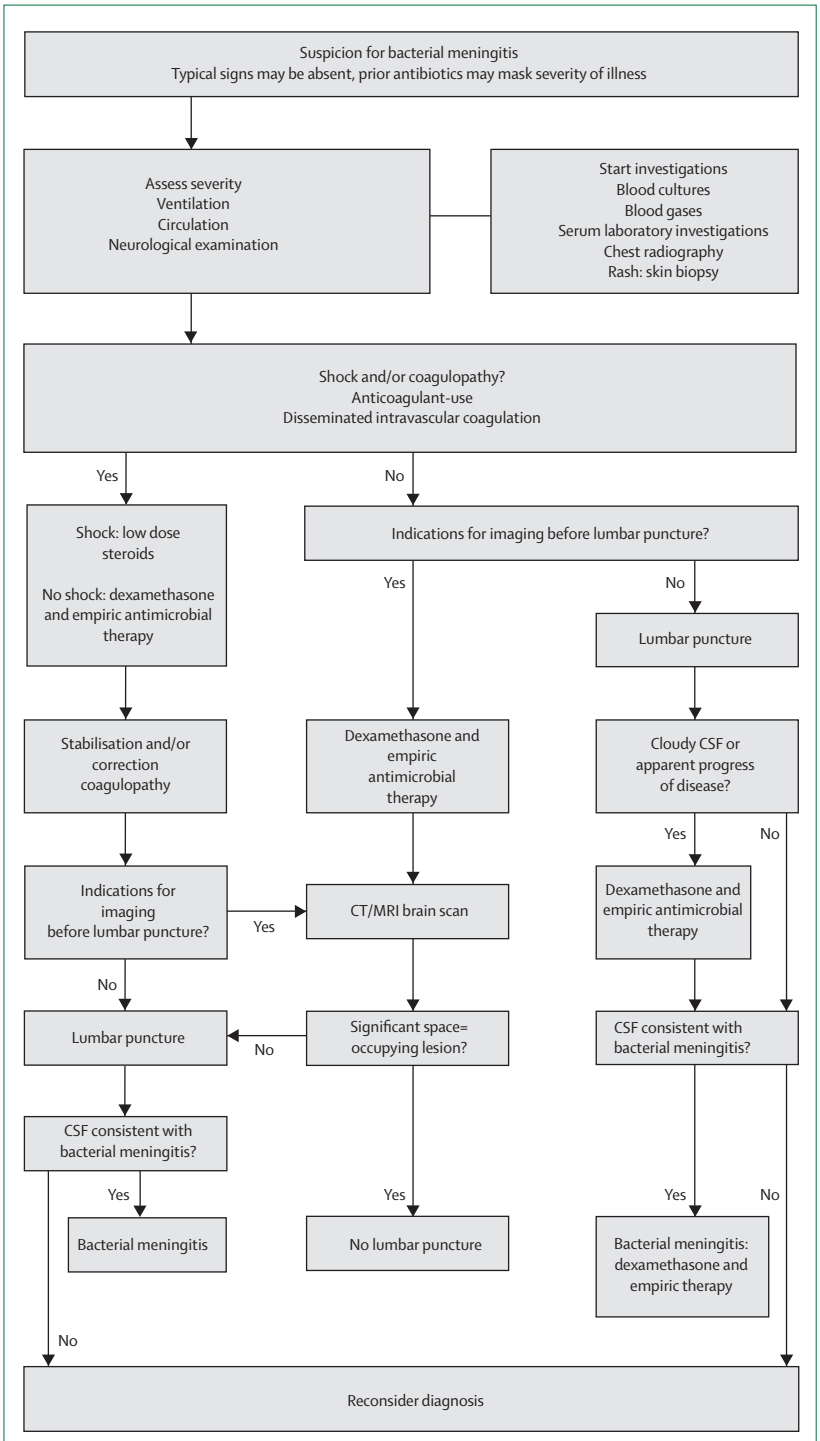

***Figure 2*: Algorithm for the management of patients with suspected community-acquired bacterial meningitis[4]**
This material was previously published as part of an online supplementary appendix to reference 4. Copyright 2006 Massachusetts Medical Society. All rights reserved. CSF=cerebrospinal fluid.

rate of 13–27% despite appropriate antibiotic therapy.[3,17,19,37,59–61] Although there has not yet been a definitive study showing a clear beneficial timeframe for antibiotics, there have been results that suggest worsening patient outcome with increased delays between presentation and antibiotic administration.[59,60,62] Early antibiotic treatment in the emergency department may contribute to increased survival when compared with patients who do not receive antibiotics until after admission to the hospital.[61] Although some guidelines attempt to propose an arbitrary time-based goal for antibiotic administration,[63] others feel that a specific time point has not yet been identified as essential, but instead focus on level of disease severity and antibiotic administration as soon as possible once the diagnosis is considered.[38,60,61]

A prospective study involving 156 patients with pneumococcal meningitis who were admitted to the intensive care unit found that a delay of more than 3 h after presentation to the hospital for receiving antibiotics was independently associated with 3-month mortality.[64] Future prospective studies will be needed to confirm whether this or another timeframe is found to be important for patients in all clinical settings. Whereas some publications advise community physicians to give parenteral antibiotics before transferring patients with suspected meningococcal meningitis to the hospital,[63,65] conflicting studies make this recommendation difficult to endorse with available retrospective data.[66–69] Until prospective data are available to support this practice,[70] we suggest rapid administration of antibiotic therapy in the emergency department (figure 2 and table 2). Several studies have identified sources of delay in antibiotic administration, the most important of which include waiting for CT scan, laboratory studies, or admission to the hospital.[36,59,73] It is important to remember that the recommendations for CT scan include the caveat that patients who undergo CT first should have blood cultures and antibiotics started before ordering the CT scan.[4]

When initial choice of antibiotics is considered, practice guidelines and expert opinions recommend broad-spectrum coverage until bacterial identification can be obtained.[4,38,63,71] The choice of initial antimicrobial therapy must be based on the most common bacteria causing the disease according to the patient's age and the clinical setting, and local patterns of antimicrobial susceptibility.[72] Empirical coverage with a third-generation cephalosporin (cefotaxime or ceftriaxone) at appropriate doses for meningitis is recommended, based on a broad spectrum of activity and excellent penetration into the cerebrospinal fluid during inflammatory conditions.[74] The increasing prevalence of multidrug-resistant *S pneumoniae* in many parts of the world (as high as 35% in parts of the USA)[75,76] has led most experts to recommend the addition of vancomycin to initial empirical therapy in adult patients.[4,38,63] Additionally, patients over the age of 50 years should have ampicillin added to the above antibiotics for additional coverage of *Listeria monocytogenes*, which has a higher incidence in this age group.[3,4,38,63] Table 2 summarises these recommendations.

Systemic steroid therapy to treat inflammation in suspected bacterial meningitis

Inflammation from any source in the central nervous system is poorly tolerated, and such inflammatory responses within the enclosed spaces of the brain and spinal cord have been shown to lead to destructive secondary effects in basic science models.[77–80] In the case of bacterial meningitis, the cerebrospinal fluid is effectively sterilised a few hours after beginning appropriate antimicrobial therapy, and Gram stain and culture are often negative within hours of antibiotic administration.[40,42] The intense inflammatory response to bacterial infection within the enclosed spaces of the brain and spinal cord is thought to lead to significant morbidity and mortality despite effective antibiotic therapy.[77] Therefore, pharmacological attempts to modulate this inflammatory response may be an essential component of a successful strategy to treat this life-threatening disease, and dexamethasone is the only currently accepted adjunctive therapy for the treatment of patients with bacterial meningitis that has proven clinical efficacy. Several other adjunctive therapies have been described, which have been reviewed elsewhere.[81]

An important aspect of treatment for patients with suspected bacterial meningitis that emergency physicians must be familiar with is the use of intravenous dexamethasone to be given at the time of the first dose of antibiotics. For adult patients, there are several published studies in the literature that support the use of dexamethasone for bacterial meningitis,[81–83] including a prospective, randomised, double-blind multicentre, placebo-controlled trial of 301 adults with bacterial meningitis.[84] Dexamethasone (10 mg) or placebo was administered 15–20 min before or with the first dose of antibiotic and was given every 6 h for 4 days. The primary outcome measure was the score on the Glasgow Outcome Scale at 8 weeks after admission (a score of 5, indicating favourable outcome, versus a score of 1–4, indicating an unfavourable outcome). In this study, treatment with dexamethasone was associated with a reduction in the risk of an unfavourable outcome (relative risk [RR] 0·59; 95% CI 0·37–0·94) and with a reduction in mortality (RR 0·48; 0·24–0·96). In patients with pneumococcal meningitis, mortality was reduced from 34% to 14%, a result of reduced mortality from systemic causes.[82] The benefits of adjunctive dexamethasone therapy were not undermined by increased neurological disability in patients who survived or by any steroid-induced complications.

A meta-analysis of 623 adult patients with bacterial meningitis showed an overall decrease in mortality and neurological sequelae by the use of adjunctive dexamethasone.[82] A larger systematic review in the Cochrane Database including 1800 adults and children also demonstrates a substantial reduction in fatality, hearing loss, and neurological sequelae with steroid use in bacterial meningitis.[85] Current practice guidelines and expert opinions recommend that dexamethasone be initiated with dosing every 6 h for 4 days in adult patients with suspected bacterial meningitis.[4,38,63] Whereas some clinicians may consider discontinuing steroids if subsequent culture results suggest a pathogen other than *S pneumoniae*,[38] we feel strongly that the current evidence shows that all patients with bacterial meningitis should receive steroids for the recommended 4-day course regardless of ultimate microbial diagnosis.[4,83] Patients with septic shock and adrenal insufficiency benefit from steroid therapy in physiological doses and longer duration; however, in those with no evidence of relative adrenal insufficiency, therapy with high-dose steroids might be detrimental.[86,87] There are no controlled studies of the effects of steroid therapy in a substantial number of patients with both meningitis and septic shock and, therefore, high-dose steroid therapy in that group cannot be unequivocally recommended, but the use of lower doses seems reasonable at present.[4,83,88]

One concern for steroid use is that by reducing inflammation there is a possibility that steroids may decrease permeability of the blood–brain barrier and impede penetration of antibiotics into the cerebrospinal fluid.[89] Animal studies suggest that although ceftriaxone levels are not affected, cerebrospinal fluid vancomycin levels are lower in dexamethasone-treated animals.[90] In human studies, treatment failure in patients with drug-resistant pneumococci treated with vancomycin and dexamethasone has also been described,[91] although treatment with dexamethasone did not reduce vancomycin levels in the cerebrospinal fluid in a study of children with bacterial meningitis.[92] Vancomycin as single-agent antimicrobial therapy is not currently recommended because of concerns about its efficacy against pneumococcus,[89] and even when used in combination with a third generation cephalosporin it is recommended that patients with pneumococcal meningitis should be carefully observed throughout therapy.[4]

Another concern that has been raised for steroid therapy is a possible association with long-term cognitive difficulties.[84] In animal studies of bacterial meningitis, corticosteroids aggravated hippocampal apoptosis and increased the development of learning deficiencies.[93] In a

Patient characteristics	Initial intravenous therapy*
Adults younger than 50 years	Ceftriaxone 2 g intravenous or cefotaxime 2 g intravenous plus vancomycin 1 g intravenous† plus dexamethasone 10 mg intravenous‡
Adults 50 years old or more (or other risk factors present)§	Ceftriaxone 2g intravenous or cefotaxime 2 g intravenous plus vancomycin 1 g intravenous† plus dexamethasone 10 mg intravenous‡ plus ampicillin 2 g intravenous§

*Clinicians should use local patterns of infection to guide initial antibiotic therapy as appropriate for each institution, which may differ from these recommendations. †Vancomycin provides coverage for resistant *S pneumoniae*. ‡Dexamethasone should be administered before or at the same time as the first dose of antibiotics and is recommended every 6 h over the first 4 days of treatment. §Ampicillin provides coverage for *L monocytogenes*. This should also be considered as additional coverage for younger patients with risk factors such as alcohol abuse, immunocompromise, recent head injury, or cerebrospinal fluid leak.[71,72]

Table 2: **Recommended emergency department initial dose of empiric therapy for adults with suspected bacterial meningitis**

Panel: Emergency diagnosis and treatment of meningitis

- Physical examination alone may not perform well enough to accurately diagnose or rule out meningitis
- Lumbar puncture results must be interpreted with care when attempting to differentiate viral versus bacterial disease
- Systemic steroids (dexamethasone, 10 mg intravenously) are an important adjunctive treatment for adult patients with suspected bacterial meningitis and should be given with the first dose of antibiotics in the emergency department
- Prospective studies are needed to evaluate the diagnostic accuracy of signs, symptoms, and cerebrospinal fluid results in patients with suspected bacterial meningitis

Search strategy and selection criteria

In addition to reviewing recently published practice guidelines and their reference lists (see references 38, 63, 65, and 95), PubMed and Cochrane Database electronic resources were searched for published studies (as of September, 2006) on the topics of diagnosis and treatment of meningitis in adult patients. Search terms included combinations of "meningitis", "diagnosis", "lumbar puncture", "practice guideline", "antibiotics", "steroids", "dexamethasone", "epidemiology", and "emergency". We identified additional articles by searching the reference lists of existing articles. Only English language papers were reviewed.

long-term follow-up of the European trial that evaluated the effect of adjunctive dexamethasone therapy in adults with bacterial meningitis,[84] neuropsychological outcomes were evaluated in patients who survived pneumococcal or meningococcal meningitis.[94] In 87 of 99 eligible patients, 46 (53%) of whom were treated with dexamethasone and 41 (47%) of whom received placebo, no significant differences in outcome were found between patients in the dexamethasone and placebo groups (median time between meningitis and testing was 99 months).[94] These results show that adjunctive dexamethasone treatment for meningitis is not associated with an increased risk for long-term cognitive impairment in adult patients with bacterial meningitis.

Available data suggests that the timing of steroid initiation is crucial and that it needs to be administered just before or at the same time as antibiotic therapy. This recommendation is based on the treatment algorithm used by the large randomised study of adult patients who all received steroids or placebo before antibiotics,[84] a regimen specifically chosen after data from paediatric patients found beneficial effects only in those subsets of patients who received steroids before antibiotics.[83–85,95,96] Keeping this in mind, it is essential that emergency physicians understand the importance of this timing since they are most often the physicians prescribing that initial dose of antibiotics. If steroids are not given before or with the first dose of antibiotics in the emergency setting, the window of opportunity no longer exists to initiate this valuable adjunctive treatment after admission to the hospital. Therefore, emergency physicians should strongly consider administering 10 mg of dexamethasone intravenously any time they are giving antibiotics for suspected bacterial meningitis. This therapy should be initiated at the time of first antibiotic administration and continued every 6 h for 4 days.

Risk classification

Risk classification is important for establishing the level of care that a patient will require in the hospital, particularly to determine which patients should be managed in an intensive care unit or high-dependency unit. In patients with bacterial meningitis, deterioration can occur rapidly and this is difficult to predict.[4] The most important factors for unfavourable outcome in adults with bacterial meningitis are those indicative of systemic compromise (ie, tachycardia, low blood pressure, positive blood culture, elevated erythrocyte sedimentation rate, or a reduced platelet count), a low cerebrospinal fluid leucocyte count, a low level of consciousness, and those indicative for infection with *S pneumoniae* (ie, advanced age, presence of otitis or sinusitis, presence of pneumonia, and an immunocompromised state).[3,37] In the Dutch Meningitis Cohort, the odds of an unfavourable outcome were six times higher for patients infected with *S pneumoniae* when compared with patients infected with *N meningitidis*, even after adjustment for other clinical predictors.[3] Several other prognostic factors have been described: seizures, infection by antibiotic-resistant *S pneumoniae*, and delays in antibiotic administration.[59,60,64] Intensive care unit admission criteria have been published previously.[4]

Conclusions

The information reviewed in this manuscript is intended to help emergency physicians and primary-care providers who are faced with difficult diagnostic and therapeutic decisions on patients with signs and symptoms concerning for bacterial meningitis (panel). Understanding the available literature regarding these topics will assist clinicians in their approach to patient care for a potentially life-threatening infection, and a previously published algorithm for the management of patients with suspected community-acquired bacterial meningitis is presented in figure 2 to help guide decision-making.[4]

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

MTF received faculty funding support from the Brooks Scholars in Academic Medicine award at the Wake Forest University School of Medicine. DvdB received funding support from the Meningitis Research Foundation, UK, and Meerwaldt Foundation, Netherlands; and is supported by a personal grant of the Netherlands Organization for Health Research and Development (ZonMw), Netherlands; NWO-Rubicon grant 2006 (019.2006.1.310.001) and NWO-Veni grant 2006 (916.76.023).

References

1 Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. *N Engl J Med* 1997; **337:** 970–76.

2 Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. *N Engl J Med* 1993; **328:** 21–28.

3 van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med* 2004; **351:** 1849–59.

4 van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. *N Engl J Med* 2006; **354:** 44–53.

5 Gjini AB, Stuart JM, Lawlor DA, et al. Changing epidemiology of bacterial meningitis among adults in England and Wales 1991–2002. *Epidemiol Infect* 2006; **134:** 567–69.

6 Netherlands Reference Laboratory for Bacterial Meningitis. Bacterial meningitis in The Netherlands: Annual report 2005. Amsterdam: University of Amsterdam, 2006.

7 Peltola H. Worldwide *Haemophilus influenzae* type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. *Clin Microbiol Rev* 2000; **13:** 302–17.

8 Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003; **348:** 1737–46.

9 Kyaw MH, Lynfield R, Schaffner W, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N Engl J Med* 2006; **354:** 1455–63.

10 Snape MD, Pollard AJ. Meningococcal polysaccharide–protein conjugate vaccines. *Lancet Infect Dis* 2005; **5:** 21–30.

11 Bilukha OO, Rosenstein N. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2005; **54:** 1–21.

12 Bonthius DJ, Karacay B. Meningitis and encephalitis in children. An update. *Neurol Clin* 2002; **20:** 1013–38, vi-vii.

13 Brandtzaeg P, van Deuren M. Meningococcal infections at the start of the 21st century. *Adv Pediatr* 2005; **52:** 129–62.

14 Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. *N Engl J Med* 2001; **344:** 1378–88.

15 Thompson MJ, Ninis N, Perera R, et al. Clinical recognition of meningococcal disease in children and adolescents. *Lancet* 2006; **367:** 397–403.

16 Attia J, Hatala R, Cook DJ, Wong JG. The rational clinical examination. Does this adult patient have acute meningitis? *JAMA* 1999; **282:** 175–81.

17 Sigurdardottir B, Bjornsson OM, Jonsdottir KE, Erlendsdottir H, Gudmundsson S. Acute bacterial meningitis in adults. A 20-year overview. *Arch Intern Med* 1997; **157:** 425–30.

18 Pizon AF, Bonner MR, Wang HE, Kaplan RM. Ten years of clinical experience with adult meningitis at an urban academic medical center. *J Emerg Med* 2006; **30:** 367–70.

19 Hussein AS, Shafran SD. Acute bacterial meningitis in adults. A 12-year review. *Medicine (Baltimore)* 2000; **79:** 360–68.

20 Riordan FA, Thomson AP, Sills JA, Hart CA. Who spots the spots? Diagnosis and treatment of early meningococcal disease in children. *BMJ* 1996; **313:** 1255–56.

21 Thomas KE, Hasbun R, Jekel J, Quagliarello VJ. The diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity in adults with suspected meningitis. *Clin Infect Dis* 2002; **35:** 46–52.

22 Uchihara T, Tsukagoshi H. Jolt accentuation of headache: the most sensitive sign of cerebrospinal fluid pleocytosis. *Headache* 1991; **31:** 167–71.

23 Cushing H. Some aspects of pathological physiology of intracranial tumors. *Boston Med Surg J* 1909; **141:** 71.

24 Rennick G, Shann F, de Campo J. Cerebral herniation during bacterial meningitis in children. *BMJ* 1993; **306:** 953–55.

25 Shetty AK, Desselle BC, Craver RD, Steele RW. Fatal cerebral herniation after lumbar puncture in a patient with a normal computed tomography scan. *Pediatrics* 1999; **103:** 1284–87.

26 Horwitz SJ, Boxerbaum B, O'Bell J. Cerebral herniation in bacterial meningitis in childhood. *Ann Neurol* 1980; **7:** 524–28.

27 Oliver WJ, Shope TC, Kuhns LR. Fatal lumbar puncture: fact versus fiction—an approach to a clinical dilemma. *Pediatrics* 2003; **112:** e174–76.

28 Masson CB. The dangers of diagnostic lumbar puncture in increased intracranial pressure due to brain tumor, with a review of 200 cases in which lumbar puncture was done. *Res Nerv Ment Dis Proc* 1927; **8:** 422.

29 Schaller WF. Propriety of lumbar puncture in intracranial hypertension. *J Neurol Psychopath* 1933; **14:** 116.

30 Sencer W. The lumbar puncture in the presence of papilledema. *J Mt Sinai Hosp N Y* 1956; **23:** 808–15.

31 Korein J, Cravioto H, Leicach M. Reevaluation of lumbar puncture; a study of 129 patients with papilledema or intracranial hypertension. *Neurology* 1959; **9:** 290–97.

32 Winkler F, Kastenbauer S, Yousry TA, Maerz U, Pfister HW. Discrepancies between brain CT imaging and severely raised intracranial pressure proven by ventriculostomy in adults with pneumococcal meningitis. *J Neurol* 2002; **249:** 1292–97.

33 Evans RW. Complications of lumbar puncture. *Neurol Clin* 1998; **16:** 83–105.

34 van Crevel H, Hijdra A, de Gans J. Lumbar puncture and the risk of herniation: when should we first perform CT? *J Neurol* 2002; **249:** 129–37.

35 Archer BD. Computed tomography before lumbar puncture in acute meningitis: a review of the risks and benefits. *CMAJ* 1993; **148:** 961–65.

36 Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med* 2001; **345:** 1727–33.

37 Weisfelt M, van de Beek D, Spanjaard L, Reitsma JB, de Gans J. Clinical features, complications, and outcome in adults with pneumococcal meningitis: a prospective case series. *Lancet Neurol* 2006; **5:** 123–29.

38 Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004; **39:** 1267–84.

39 Spanos A, Harrell FE Jr, Durack DT. Differential diagnosis of acute meningitis. An analysis of the predictive value of initial observations. *JAMA* 1989; **262:** 2700–07.

40 Zunt JR, Marra CM. Cerebrospinal fluid testing for the diagnosis of central nervous system infection. *Neurol Clin* 1999; **17:** 675–89.

41 Weisfelt M, de Gans J, van der Poll T, van de Beek D. Pneumococcal meningitis in adults: new approaches to management and prevention. *Lancet Neurol* 2006; **5:** 332–42.

42 Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. *Pediatrics* 2001; **108:** 1169–74.

43 Negrini B, Kelleher KJ, Wald ER. Cerebrospinal fluid findings in aseptic versus bacterial meningitis. *Pediatrics* 2000; **105:** 316–19.

44 Oostenbrink R, Moons KG, Twijnstra MJ, Grobbee DE, Moll HA. Children with meningeal signs: predicting who needs empiric antibiotic treatment. *Arch Pediatr Adolesc Med* 2002; **156:** 1189–94.

45 Nigrovic LE, Kuppermann N, Malley R. Development and validation of a multivariable predictive model to distinguish bacterial from aseptic meningitis in children in the post-*Haemophilus influenzae* era. *Pediatrics* 2002; **110:** 712–19.

46 Freedman SB, Marrocco A, Pirie J, Dick PT. Predictors of bacterial meningitis in the era after *Haemophilus influenzae*. *Arch Pediatr Adolesc Med* 2001; **155:** 1301–06.

47 Graham AK, Murdoch DR. Association between cerebrospinal fluid pleocytosis and enteroviral meningitis. *J Clin Microbiol* 2005; **43:** 1491.

48 Hoen B, Viel JF, Paquot C, Gerard A, Canton P. Multivariate approach to differential diagnosis of acute meningitis. *Eur J Clin Microbiol Infect Dis* 1995; **14:** 267–74.

49 Ratzan KR. Viral meningitis. *Med Clin North Am* 1985; **69:** 399–413.

50 Jaeger F, Leroy J, Duchene F, et al. Validation of a diagnosis model for differentiating bacterial from viral meningitis in infants and children under 3·5 years of age. *Eur J Clin Microbiol Infect Dis* 2000; **19:** 418–21.

51 Oostenbrink R, Moons KG, Derksen-Lubsen AG, Grobbee DE, Moll HA. A diagnostic decision rule for management of children with meningeal signs. *Eur J Epidemiol* 2004; **19:** 109–16.

52 Bonsu BK, Harper MB. Differentiating acute bacterial meningitis from acute viral meningitis among children with cerebrospinal fluid pleocytosis: a multivariable regression model. *Pediatr Infect Dis J* 2004; **23:** 511–17.

53 Leblebicioglu H, Esen S, Bedir A, Gunaydin M, Sanic A. The validity of Spanos' and Hoen's models for differential diagnosis of meningitis. *Eur J Clin Microbiol Infect Dis* 1996; **15:** 252–54.

54 McKinney WP, Heudebert GR, Harper SA, Young MJ, McIntire DD. Validation of a clinical prediction rule for the differential diagnosis of acute meningitis. *J Gen Intern Med* 1994; **9:** 8–12.

55 Baty V, Viel JF, Schuhmacher H, Jaeger F, Canton P, Hoen B. Prospective validation of a diagnosis model as an aid to therapeutic decision-making in acute meningitis. *Eur J Clin Microbiol Infect Dis* 2000; **19:** 422–26.

56 Brivet FG, Ducuing S, Jacobs F, et al. Accuracy of clinical presentation for differentiating bacterial from viral meningitis in adults: a multivariate approach. *Intensive Care Med* 2005; **31:** 1654–60.

57 Karandanis D, Shulman JA. Recent survey of infectious meningitis in adults: review of laboratory findings in bacterial, tuberculous, and aseptic meningitis. *South Med J* 1976; **69:** 449–57.

58 Bernit E, de Lamballerie X, Zandotti C, et al. Prospective investigation of a large outbreak of meningitis due to echovirus 30 during summer 2000 in Marseilles, France. *Medicine (Baltimore)* 2004; **83:** 245–53.

59 Proulx N, Frechette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. *QJM* 2005; **98:** 291–98.

60 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:** 862–69.

61 Miner JR, Heegaard W, Mapes A, Biros M. Presentation, time to antibiotics, and mortality of patients with bacterial meningitis at an urban county medical center. *J Emerg Med* 2001; **21:** 387–92.

62 Bryan CS, Reynolds KL, Crout L. Promptness of antibiotic therapy in acute bacterial meningitis. *Ann Emerg Med* 1986; **15:** 544–47.

63 Heyderman RS. Early management of suspected bacterial meningitis and meningococcal septicaemia in immunocompetent adults—second edition. *J Infect* 2005; **50:** 373–74.

64 Auburtin M, Wolff M, Charpentier J, et al. Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: the PNEUMOREA prospective multicenter study. *Crit Care Med* 2006; **34:** 2758–65.

65 Heyderman RS, Lambert HP, O'Sullivan I, Stuart JM, Taylor BL, Wall RA. Early management of suspected bacterial meningitis and meningococcal septicaemia in adults. *J Infect* 2003; **46:** 75–77.

66 Cartwright K, Strang J, Gossain S, Begg N. Early treatment of meningococcal disease. *BMJ* 1992; **305:** 774.

67 Sorensen HT, Moller-Petersen J, Krarup HB, Pedersen H, Hansen H, Hamburger H. Early treatment of meningococcal disease. *BMJ* 1992; **305:** 774.

68 Hahne SJ, Charlett A, Purcell B, et al. Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review. *BMJ* 2006; **332:** 1299–303.

69 Harnden A, Ninis N, Thompson M, et al. Parenteral penicillin for children with meningococcal disease before hospital admission: case-control study. *BMJ* 2006; **332:** 1295–98.

70 Sorensen HT, Steffensen FH, Schonheyder HC, Nielsen GL, Olsen J. Clinical management of meningococcal disease. Prospective international registration of patients may be needed. *BMJ* 1998; **316:** 1016–17.

71 Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. *N Engl J Med* 1997; **336:** 708–16.

72 van de Beek D, de Gans J, Spanjaard L, Vermeulen M, Dankert J. Antibiotic guidelines and antibiotic use in adult bacterial meningitis in The Netherlands. *J Antimicrob Chemother* 2002; **49:** 661–66.

73 Talan DA, Guterman JJ, Overturf GD, Singer C, Hoffman JR, Lambert B. Analysis of emergency department management of suspected bacterial meningitis. *Ann Emerg Med* 1989; **18:** 856–62.

74 Kearney BP, Aweeka FT. The penetration of anti-infectives into the central nervous system. *Neurol Clin* 1999; **17:** 883–900.

75 Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *N Engl J Med* 2000; **343:** 1917–24.

76 Jacobs MR, Bajaksouzian S, Zilles A, Lin G, Pankuch GA, Appelbaum PC. Susceptibilities of *Streptococcus pneumoniae* and *Haemophilus influenzae* to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 US Surveillance study. *Antimicrob Agents Chemother* 1999; **43:** 1901–08.

77 Koedel U, Scheld WM, Pfister HW. Pathogenesis and pathophysiology of pneumococcal meningitis. *Lancet Infect Dis* 2002; **2:** 721–36.

78 Fitch MT, Doller C, Combs CK, Landreth GE, Silver J. Cellular and molecular mechanisms of glial scarring and progressive cavitation: in vivo and in vitro analysis of inflammation-induced secondary injury after CNS trauma. *J Neurosci* 1999; **19:** 8182–98.

79 Lazar DA, Fitch MT, Silver J, Kliot M. Cellular and molecular mechanisms mediating injury and recovery in the nervous system. In: Winn HR, ed. Youmans neurological surgery 5th edn. Philadelphia, PA: WB Saunders, 2004: 195–213.

80 Fitch MT, Silver J. Beyond the glial scar: cellular and molecular mechanisms by which glial cells contribute to CNS regenerative failure. In: Tuszynski MH, Kordower JH, eds. CNS regeneration: basic science and clinical advances. San Diego, CA: Academic Press, 1999: 55–88.

81 van de Beek D, Weisfelt M, de Gans J, Tunkel AR, Wijdicks EF. Drug insight: adjunctive therapies in adults with bacterial meningitis. *Nat Clin Pract Neurol* 2006; **2:** 504–16.

82 van de Beek D, de Gans J, McIntyre P, Prasad K. Steroids in adults with acute bacterial meningitis: a systematic review. *Lancet Infect Dis* 2004; **4:** 139–43.

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

84 de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002; **347:** 1549–56.

85 van de Beek D, de Gans J, McIntyre P, Prasad K. Corticosteroids in acute bacterial meningitis. *Cochrane Database Syst Rev* 2003; **3:** CD004405.

86 Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ* 2004; **329:** 480.

87 Cronin L, Cook DJ, Carlet J, et al. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med* 1995; **23:** 1430–39.

88 Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; **288:** 862–71.

89 Chowdhury MH, Tunkel AR. Antibacterial agents in infections of the central nervous system. *Infect Dis Clin North Am* 2000; **14:** 391–408, ix.

90 Cabellos C, Martinez-Lacasa J, Martos A, et al. Influence of dexamethasone on efficacy of ceftriaxone and vancomycin therapy in experimental pneumococcal meningitis. *Antimicrob Agents Chemother* 1995; **39:** 2158–60.

91 Viladrich PF, Gudiol F, Linares J, et al. Evaluation of vancomycin for therapy of adult pneumococcal meningitis. *Antimicrob Agents Chemother* 1991; **35:** 2467–72.

92 Klugman KP, Friedland IR, Bradley JS. Bactericidal activity against cephalosporin-resistant *Streptococcus pneumoniae* in cerebrospinal fluid of children with acute bacterial meningitis. *Antimicrob Agents Chemother* 1995; **39:** 1988–92.

93 Leib SL, Heimgartner C, Bifrare YD, Loeffler JM, Tauber MG. Dexamethasone aggravates hippocampal apoptosis and learning deficiency in pneumococcal meningitis in infant rats. *Pediatr Res* 2003; **54:** 353–57.

94 Weisfelt M, Hoogman M, van de Beek D, de Gans J, Dreschler WA, Schmand BA. Dexamethasone and long-term outcome in adults with bacterial meningitis. *Ann Neurol* 2006; **60:** 456–68.

95 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.

96 McIntyre PB, Berkey CS, King SM, et al. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. *JAMA* 1997; **278:** 925–31.