

Bacterial Meningitis in Aging Adults

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Bacterial meningitis remains a highly lethal disease in older adults, with mortality rates averaging >20% despite modern antibiotic therapy. In this population, more variable presentations are seen, with fewer patients manifesting fever, neck stiffness, and headache than among younger adults. In addition, many older adults (aged ≥ 60 years) may have other underlying diseases causing symptoms that may be confused with those of meningitis. The spectrum of etiologic bacterial organisms is more broad than that for a younger population, in part because of the increased frequency of severe underlying diseases and in part as a result of immunosenescence. Therapy is complicated by both the range of possible causative organisms and the increasing antibiotic resistance manifested by some. These difficulties, contrasted with the success of vaccination in the pediatric population, highlight the need for improved preventive strategies for older adults. This review outlines some key clinical points in the management of bacterial meningitis in the older adult.

In recent years, bacterial meningitis has radically changed to become a disease largely of adults—in particular, of older adults. This circumstance highlights key problem areas in the management of the disease: (1) recognition of the disease in older patients who present with fewer of the classic symptoms of meningitis or for whom there are other explanations for these symptoms; (2) the greater number of possible causative organisms; (3) the prompt initiation of appropriate therapy against organisms with increasing antibiotic resistance; and (4) the prevention of this disease through effective vaccinations.

EPIDEMIOLOGY

In a summary of bacterial meningitis prior to the widespread use of the *Haemophilus influenzae* vaccine, Gotschlich indicated that of a cohort of 1000 newborns, approximately 1 or 2 would develop neonatal meningitis, 3 or 4 would develop *H. influenzae* meningitis, and 1 would develop either *Streptococcus pneumoniae* or *Neisseria meningitidis* meningitis. Thus, a total of about 6 cases of meningitis would occur in this cohort, and 1 patient would die and 2 patients would have severe neurological

sequelae [1]. Since that time, widespread use of the *H. influenzae* vaccine has markedly changed the demographics of this disease. A comprehensive survey of meningitis in the United States in 1995 showed a marked decrease in the incidence of *H. influenzae* meningitis, to 0.2 per 100,000 persons (0.002 per 1000 persons) and a change in the median age of patients from 15 months to 25 years. Approximately 20% of the cases were projected to involve individuals >60 years of age, as opposed to the 8.6% involving older adults in a similar 1986 survey [2].

Several epidemiological studies indicate that a greater variety of organisms may be responsible for meningitis in the older adult and that viral etiologies are distinctly less common [3–6]. The responsible bacterial organisms include *S. pneumoniae*; *Listeria monocytogenes*; gram-negative bacilli such as *Escherichia coli* and *Klebsiella pneumoniae*; *Streptococcus agalactiae*; and, less commonly, *N. meningitidis* or *H. influenzae* [7, 8]. Table 1 lists the attack and case fatality rates for some of these organisms. In addition, comparative studies reveal significant complication rates of 85% for older adults, versus 41% for a younger group of adults with bacterial meningitis [6].

This increased risk of bacterial meningitis for older adults is likely multifactorial and includes both a greater propensity for underlying acute and chronic diseases and immunosenescence, a decline in immune function related to aging. Many of these epidemiological studies document that pneumonia, diabetes, renal or hepatic failure, or other chronic underlying diseases are associated with bacterial meningitis in older adults, particularly with *S. pneumoniae*, *L. monocytogenes*, and *S. agalactiae*

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Table 1. Data from surveillance studies of bacterial meningitis in older adults (aged >60 years).

Organism	[3] ^a		[4]		[2] ^a	
	AR	CFR	AR	CFR	AR	CFR
<i>Streptococcus pneumoniae</i>	1.5	31	0.5	54	1.9	20
<i>Listeria monocytogenes</i>	0.5	—	0.1	41	0.6	—
<i>Haemophilus influenzae</i>	0.2	—	0.09	24	0.07	—
<i>Neisseria meningitidis</i>	0.1	—	0.2	29	0.1	—
Group B <i>Streptococcus</i>	0.2	51	0.02	23	0.1	18

NOTE. AR, attack rate per 100,000; CFR, case fatality rate (percentage).

^a Incomplete data on CFRs for some organisms.

[5, 6, 9–11]. Gram-negative-rod meningitis is sometimes divided into 2 categories: that resulting from neurosurgical procedures or trauma (direct infection of the meninges) and that from hematogenous spread of these organisms from a distant site of infection, such as the urinary tract or abdomen. Older adults appear to have gram-negative meningitis due to these etiologies more often than other age groups [7, 8, 12].

The role of immunosenescence in predisposing patients to bacterial meningitis is not clearly defined, but defects in both humoral and cellular immunity have been noted in older adults and could certainly predispose to infection with this particular range of etiologic organisms [13].

CLINICAL SYMPTOMS

Suspecting bacterial meningitis in the older adult is the initial, major challenge, as there is considerable variability in the clinical findings (table 2). Since febrile responses are often blunted or absent in older adults in general [14], it is not surprising that fever is not a universal symptom, varying in occurrence from 59% in a study by Gorse et al. [6] and 67% in a recent study in Brazil [15] to 100% in other studies [5, 7]. Similarly, headache and nuchal rigidity have been noted in only about 50% of older adults with meningitis, and depressed levels of consciousness such as stupor or coma are often but not universally present [5–7].

An evidence-based review of the clinical examination for identifying adults with meningitis, based on data predominantly from studies of older adults, concluded that no single finding was sufficiently sensitive or specific to prompt a diagnosis. However, 1 of 3 findings—fever, neck stiffness, or altered mental status—was present in virtually all patients with meningitis (sensitivity of 99%–100% for the presence of 1 of these findings); thus, the absence of any of the 3 findings essentially excluded the diagnosis, with a high negative predictive value. The presence of all 3 findings was not common in these patients with meningitis (pooled sensitivity of 46%) [16].

Nuchal rigidity and other signs of meningeal irritation such as Kernig or Brudzinski signs should be sought, but these are not universal findings and may also require interpretation. Neck stiffness was found in 35% of older adults (aged ≥60 years) without meningitis and may be caused by prior cerebrovascular accident, cervical arthritis, Parkinson's disease, or certain drugs [17]. A sometimes helpful clinical sign is that with cervical arthritis, in particular, passive flexion of the neck may elicit resistance more at the extremes of range of motion, whereas with meningeal irritation, resistance may be felt more immediately.

“Jolt” accentuation of headache was purported, in 1 small study [16], to be 97% sensitive for identifying meningitis; this is elicited by asking the patient to rapidly rotate the head horizontally from side to side (2–3 rotations/s). This may be a helpful adjunctive finding, but its sensitivity and specificity for the diagnosis of meningitis require further confirmation.

Thus, in the clinical assessment for possible bacterial meningitis, older adults who present without fever, neck stiffness, or altered mental function probably do not have this disease. Those individuals with 2 or 3 of the 3 classic findings are more likely to have meningitis, but even the presence of all 3 findings is not entirely specific. Headache is present in 21%–81% and nuchal rigidity in 57%–92% [5–7].

DIFFERENTIAL DIAGNOSIS AND INITIAL EVALUATION

Given the lack of specificity or sensitivity of symptoms and signs, the basis for the diagnosis of meningitis is the lumbar puncture (LP), with analysis of the CSF. For other age groups, a major distinction must often be made between viral and bacterial meningitis; however, the former is relatively uncommon in older adults [6]. A more common clinical problem in the geriatric population is distinguishing between bacterial meningitis and infection at another site as the cause of fever and acutely depressed mental function.

In a study of hospitalized patients who had not undergone a neurosurgical procedure, these 2 symptoms, in the absence of others such as meningeal signs or headache, were not due to nosocomially-acquired bacterial meningitis; however, the sample size of 51 patients was too small to allow a firm con-

Table 2. Frequency of signs and symptoms of meningitis in the older adult.

Sign or symptom	Frequency, %
Fever	59–100
Confusion	57–96
Headache	21–81
Nuchal rigidity	57–92

NOTE. Adapted from [5–7].

Table 3. CSF findings indicative of meningitis.

Variable	Normal CSF	Findings in meningitis cases		
		Acute bacterial	Viral	Tuberculous
Opening pressure	6–20 cm H ₂ O	Usually elevated	Normal to moderately elevated	Usually elevated
CSF WBCs, cells per mm ³	0–5 (~85% lymphocytes)	Usually several hundred to >60,000 (PMNs predominate)	5 to a few hundred, but may be >1000; lymphocytes predominate but may be >80% PMNs in first few days	Usually 25–100, rarely >500; lymphocytes predominate except in early stages, when PMNs may account for >80% of cells
Protein, mg/dL	18–45	Usually 100–500; occasionally >1000	Frequently normal or slightly elevated; <100; may show greater elevation in severe cases	Nearly always elevated; usually 100–200 but may be much higher if dynamic block
Glucose, mg/dL	45–80, or 0.6 × serum glucose	Usually 5–40, or <0.3 × serum glucose	Usually normal but can be low with mumps, HSV 2	Usually reduced; <45 in 75% of cases
Miscellaneous	For traumatic LP, add 1 WBC and 1 mg/dL protein for each 1000 RBCs	Gram stain positive in ~60–80% ^a	Usually do not need to find specific causal virus	AFB-positive stain in <25%, culture-positive in >2/3 of cases (but may take 4–8 weeks for growth)

NOTE. Adapted from [7, 8, 23]. AFB, acid-fast bacilli; HSV 2, herpes simplex virus type 2; LP, lumbar puncture; PMNs, polymorphonuclear leukocytes.

^a Gram-positive diplococci; gram-negative diplococci; gram-positive rods.

clusion [18]. In deciding whether LP is indicated, one must consider the pretest likelihood of meningitis, and since this is a complex clinical analysis, it is difficult to provide a rigid guideline. Some patients with fever, acutely depressed mental function, and infection at a nonmeningeal site may be treated for the infection and closely observed without LP; however, most patients who develop these symptoms should probably undergo LP if it is safe to do so, particularly if their symptoms began before hospitalization [19].

The cause of depressed mental function in patients with either bacterial meningitis or infection at a remote site is the subject of ongoing investigation. Clearly, bacterial meningitis, with its accompanying vasculitis and interstitial, vasogenic, and cytotoxic cerebral edema, may cause severe brain injury and altered function. Depressed mental function, however, may also be due to increased cytokine levels produced in response to infection of the meninges or infection occurring at a more distant site [8, 20].

The decision to perform LP should be tempered by consideration of the risk of complications from the procedure, particularly cerebral herniation. A careful neurological examination should be performed, including a fundoscopic examination for signs of papilledema. In the absence of papilledema (particularly if venous pulsations are clearly present), focal neurological findings, or rapid neurological progression, the risk of herniation from LP is considered negligible, and LP thus can generally be safely performed [19, 21].

In the older adult, however, fever and altered mental status may also be caused by intracranial mass lesions, with or without accompanying edema, such as brain abscess, tumor, cerebral infarction or hemorrhage, or subdural hematoma. These are

lesions with which herniation may be a significant risk, should LP be attempted. Visualization of the optic fundi may be obscured in the older adult by pupillary constriction or cataract formation; therefore, CT brain scanning should be performed on most such patients prior to LP if the radiological procedure is readily available. Antibiotic therapy should not be delayed for performing CT or LP, however. In a recent outcomes study, outcomes for patients with seizures, hypotension, or severe alterations in mental function were worsened in association with delays in antibiotic therapy for meningitis, and many of these patients were older adults [21]. Empirical antibiotics should be provided, particularly since their use does not seem to affect the results of the CSF examination if the LP is performed within 1–2 h of the antibiotic administration [8, 22].

The findings on testing of the CSF help differentiate bacterial meningitis from other conditions (table 3). A profile of purulence with >500 WBCs, lowered glucose level of less than one-third of the simultaneous peripheral glucose level, and differential count with >85% polymorphonuclear leukocytes is highly suggestive of bacterial meningitis, but patients may not have these classic CSF signs, particularly early in the course of the disease [8, 7, 23]. Newer surrogate markers such as CSF lactate, serum procalcitonin, or cytokine levels are under study as diagnostic aids [24]. Whether these tests have particular relevance to an older adult population is unstudied.

Gram-stained smears are positive in up to 85% of untreated cases and may indicate the identity of the causative organism; however, prior antibiotic therapy may significantly reduce the rate of positivity. *L. monocytogenes* and gram-negative bacilli, more frequent causes of bacterial meningitis in older adults than in younger patients, are less frequently seen on Gram-

stained smears of CSF, and improved, rapid diagnostic tests for these organisms are needed [7, 8, 12].

The use of bacterial antigen detection for diagnosis can be helpful, particularly when a patient has received antibiotics before LP, when bacterial meningitis is suspected but the Gram stain of CSF is unrevealing, and when the CSF is otherwise nondiagnostic. Tests are commercially available for *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type B, *E. coli*, and *S. agalactiae* but not for *L. monocytogenes*. The costs of these tests generally mitigate against their routine use, and their sensitivities range from 50% to 75%, whereas their specificities approach 95%–100%. Thus, a positive test is helpful, but a negative test does not rule out a particular pathogen. It is anticipated that newer diagnostic tests such as PCR or DNA probes will significantly improve our diagnostic abilities [25].

EMPIRICAL TREATMENT

The increased frequency of resistance of *S. pneumoniae* to penicillin and other antibiotics and the increased frequency of *L. monocytogenes* infection in older adults significantly complicate empirical antibiotic therapy. In a recent nationwide surveillance study, ~25% of strains of *S. pneumoniae* were resistant to penicillin, with 14% demonstrating high-level resistance (≥ 2.0 $\mu\text{g}/\text{mL}$) and 10% demonstrating intermediate resistance (1.2–2.0 $\mu\text{g}/\text{mL}$) [26]. If the Gram stain of CSF is highly suggestive of nonstreptococcal organisms, the use of ceftriaxone or cefotaxime plus ampicillin (to cover *L. monocytogenes*) should provide adequate initial coverage; however, if organisms consistent with *S. pneumoniae* are seen or if the bacterial antigen test is positive for this organism, vancomycin plus ceftriaxone or cefotaxime should be instituted until sensitivity data are available [22].

Penicillin allergy also complicates the decision regarding antibiotic administration. For individuals with such an allergy, vancomycin with rifampin may be the appropriate choice against *S. pneumoniae*, and the addition of trimethoprim-sulfamethoxazole would provide treatment against *L. monocytogenes*, an organism which occasionally is not adequately susceptible to vancomycin [7, 8].

A more problematic scenario is that of CSF findings that are consistent with bacterial meningitis, but with a CSF Gram stain that is unrevealing. Bacterial antigen tests should be performed, but administration of vancomycin, ampicillin, and ceftriaxone or cefotaxime should be instituted until these tests or standard cultures reveal the causative organism, allowing therapy to be narrowed.

SPECIFIC TREATMENT AND ANCILLARY MEASURES

The choice of specific antibiotics should be governed by the degree of penetration of the agent through the blood-brain

Table 4. Antibiotic penetration of CSF.

Excellent ^a	Good ^b (with inflammation)	Poor or negligible ^c
Rifampin	Penicillins	Most 1st- and 2d-generation cephalosporins
TMP-SMZ	3d-generation cephalosporins	Aminoglycosides, tobramycin, gentamicin
Chloramphenicol	Cefuroxime, metronidazole	Vancomycin (variable), erythromycin (variable), tetracyclines (variable)

NOTE. Adapted from [7, 8, 22, 27]. TMP-SMZ, trimethoprim-sulfamethoxazole.

^a >15–20% of serum value.

^b 5–20% of serum value.

^c <1–5% of serum value.

barrier and by the bactericidal effect of the agent(s). The degree of penetration to the CSF and the suggested dosing regimens and indications are listed in tables 4 and 5 [7, 8, 22, 27].

There are few studies of the optimal duration of therapy for bacterial meningitis, particularly for older adults. In general, treatment against *S. pneumoniae* should extend for 10–14 days, whereas treatment against *L. monocytogenes*, *S. agalactiae*, and gram-negative bacilli should be for 14–28 days; *N. meningitidis* meningitis generally can be treated for ≤ 7 days with effective antibiotics [22].

There are no convincing data to support the routine use of corticosteroids such as dexamethasone to decrease the complication rate in the treatment of meningitis in older adults, as there are for the management of *H. influenzae* meningitis in the pediatric age group [28]. However, there are experimental data that would support the use of dexamethasone in the setting of increased intracranial pressure to combat the development or worsening of vasogenic and cytotoxic cerebral edema. If dexamethasone is used in adjunctive therapy for bacterial meningitis, evidence of the penetration and efficacy of the antibiotic therapy—particularly if cell-wall-active agents are used—should be sought, since these drugs depend upon meningeal inflammation to achieve significant levels in the CSF. This may entail the measurement of antibiotic levels in the CSF or, more practically, a repeated assay of the CSF at 24–48 h and perhaps at further intervals to determine improvements in glucose levels and WBC counts as markers of antibacterial efficacy [7, 8].

PREVENTION

Since a significant number of cases of bacterial meningitis in older adults are caused by *S. pneumoniae*, prevention of this form should be a high priority for clinicians. Surveys from 1993 showed that fewer than one-third of patients for whom *S. pneumoniae* vaccine was indicated had received it. Whether this vaccine can adequately prevent invasive forms of *S. pneu-*

Table 5. Recommended antibiotic therapy for bacterial meningitis in older adults.

Organism, MIC	Antibiotic (total daily dose)
Unknown (suspected diagnosis) ^a	Cefotaxime (8–12 g) or ceftriaxone (4 g) plus ampicillin (12 g)
<i>Streptococcus pneumoniae</i>	
≤0.1 µg/mL	Penicillin G (20–24 million units)
0.1–1.0 µg/mL	Cefotaxime (8–12 g) or ceftriaxone (4 g)
≥1.0 µg/mL	Vancomycin (2 g) plus ceftriaxone (4 g)
<i>Listeria monocytogenes</i>	Ampicillin (12 g) plus an aminoglycoside: gentamicin, tobramycin (3–5 mg/kg)
<i>Neisseria meningitidis</i>	Penicillin G (20–24 million units) or ampicillin (12 g)
<i>Haemophilus influenzae</i>	Cefotaxime (8–12 g) or ceftriaxone (4 g)
Enterobacteriaceae (gram-negative bacilli)	Cefotaxime (8–12 g) or ceftriaxone (4 g) ^b
<i>Staphylococcus aureus</i> (methicillin-susceptible)	Nafcillin or oxacillin (8–12 g)
<i>Staphylococcus aureus</i> (methicillin-resistant)	Vancomycin (2 g)

NOTE. Adapted from [7, 8, 22].

^a Add vancomycin if highly penicillin-resistant *Streptococcus pneumoniae* is the suspected pathogen.

^b Ceftazidime (6 g/day) or Cefepime (4 g/day) if *P. aeruginosa* is the suspected or proven pathogen.

moniae disease has been controversial, but the vaccine does appear to be at least partially effective (56%–81% for invasive disease, including meningitis) and to be both safe and well-tolerated. Thus, increased utilization of pneumococcal vaccine is a major health care goal of the Centers for Disease Control and Prevention (Atlanta) and a number of other agencies, with an aim to achieve 60% vaccination rates among eligible persons and 80% among institutionalized older adults [29].

The development of an improved pneumococcal vaccine is also a major goal, and a protein conjugate vaccine using elements of the capsule of *S. pneumoniae* is currently licensed for administration to infants. Early test results suggest improved protection in the pediatric population, and it is hoped that similar results may be obtained among older adults and immunocompromised individuals [29].

H. influenzae is an uncommon cause of meningitis in the older adult, and since the vaccine protects against only type B, the use of this vaccine in the geriatric population would not be expected to have a significant impact. Similarly, *N. meningitidis* vaccine is available and utilized for outbreaks of invasive disease or to protect some travelers and longer-term visitors and residents in areas where the disease is highly endemic. However, there are no recommendations for its routine use in the older-adult population [30]. Vaccination is recommended, however, for those individuals who have had prior serious infections with this organism and those with complement deficiencies.

Current preventive efforts against *L. monocytogenes* focus on decreasing exposure to this pathogen by improving food safety and awareness. Research efforts toward the development of an *S. agalactiae* vaccine are under way and are largely directed toward its use to prevent perinatal transmission of this organism and subsequent invasive disease in the neonate. No trials

involving older adults, including those with risk factors such as diabetes or renal failure, have been reported [31].

FUTURE ENDEAVORS

Future improvements in the management of bacterial meningitis in older adults should probably focus on three areas. First, improved diagnostic testing would be beneficial. Meningeal imaging that could reliably document the presence of meningitis would help delineate those patients who require LP. Alternatively, a serum test for a marker unique to bacterial meningitis could also be helpful. Improved, rapid diagnostic CSF tests could lead to more targeted and effective antibiotic therapy.

Second, improved antibiotic regimens may be needed. High-dose quinolone therapy may be useful, since these drugs do seem to achieve significant CSF levels and may be valuable in treatment against resistant organisms such as *S. pneumoniae*. Clinical trials are needed. The use of dexamethasone or other agents to decrease the adverse effects of meningitis holds the promise of altering the significant complication rate of this disease among older adults. The results of a large European multicentered trial are pending. Third, improved prevention strategies are essential. The successes of *H. influenzae* vaccination in the pediatric population could be repeated and substantially decrease the incidence of bacterial meningitis among older adults.

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