Meningitis:
Investigating the Infection

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Acute bacterial meningitis is an infection of the central nervous system that results in inflammation of the meninges, the membranes that surround the brain and spinal cord. It occurs in the US with an annual incidence of approximately three cases per 100,000 persons.[1,2]

Overall mortality attributable to bacterial meningitis in various case series has ranged from 15% to 21%.[3-6] Hence, it is extremely important that clinicians be knowledgeable of this condition for a diagnosis to be made and for timely therapy to be instituted.

What causes meningitis?

Neisseria meningitidis and *Streptococcus pneumoniae* are the pathogens that most commonly cause acute community-acquired bacterial meningitis in adults (Table 1). They account for 60% to 88% of culture-positive cases in various case series.[3-6] *Listeria monocytogenes* accounts for an additional 4% to 13% of cases.[3-6] This pathogen causes disease more frequently in patients older than age 50.[5,7]

Other bacteria that have been less frequently implicated as pathogens include streptococci (other than *S. pneumoniae*), Gram-negative bacilli including *Haemophilus influenzae* and *Staphylococcus aureus*.

Patients presenting with meningitis following head trauma or neurosurgery and those with cerebrospinal fluid shunts may have an infection with bacteria other than those mentioned above.

Jack's Case

- Jack, 21, developed a fever and chills.
- Over an eight-hour period, hemorrhagic lesions appeared from head to toe.
- Cerebrospinal fluid analysis yielded a cell count of 485 cells/mm^3 (90% of which were neutrophils), a protein concentration of 1.9 g/L and a glucose concentration of 0.5 mmol/L.
- Bacteria were not observed on gram stain.

What is Jack's diagnosis? For the answer, go to page 90.

Table 1

Common pathogens in bacterial meningitis by age[3-7]

Age	Most common pathogens	Empiric antibiotic therapy
16 to 50	*N. meningitidis, S. pneumoniae*	Vancomycin plus a third-generation cephalosporin*
> 50	*S. pneumoniae, N. meningitidis, L. monocytogenes,* aerobic Gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin*

*Third-generation cephalosporin—either cefotaxime or ceftriaxone
Suggested adult doses: Ampicillin, 12 g/day, divided every 4 hours; cefotaxime, 8 g to 12 g/day, divided every 4-6 hours; ceftriaxone, 4 g/day divided every 12 hours; vancomycin 30 mg to 45 mg/kg/day, divided every 8-12 hours.

Table 2

Physical exam manoeuvres to elicit meningeal irritation[2]

Test name	Clinical manoeuvre
Kernig's sign	With the patient lying supine and the hip flexed at 90°, the knee is passively extended. A positive test is resistance or pain in the lower back or posterior thigh.
Brudzinski's sign	A positive test occurs when passive flexion of the neck in a supine patient results in flexion of the knees and hips.

Jack's Diagnosis

A presumptive diagnosis of meningococcal meningitis with disseminated meningococcemia was made and ceftriaxone, 2 g, intravenously, every 12 hours, was initiated.

Blood cultures and the cerebrospinal fluid both yielded *Neisseria meningitidis* susceptible to penicillin.

Streptococcus pneumoniae and *Neisseria meningitidis* colonize the nasopharynx by attaching to nasopharyngeal epithelial cells. They produce an immunoglobulin A (IgA) protease that allows them to evade mucosal IgA. Transport across epithelial cells occurs via either membrane bound vacuoles or through the tight junctions between cells, resulting in bacteremia. Once they enter the bloodstream, survival of these pathogens is assisted by the presence of a polysaccharide capsule. These bacteria then penetrate the blood brain barrier (BBB) to enter the cerebrospinal fluid (CSF). Here they are able to replicate because of the absence of host humoral immune defenses.

Lysis of bacteria results in the release of cell wall components (teichoic acid, lipopolysaccharide) that elicit the production of inflammatory cytokines and chemokines. These mediators then attract inflammatory cells, alter BBB permeability and alter cerebral blood flow, resulting in meningeal inflammation and the clinical manifestations of meningitis.

How do patients with meningitis present?

The classic triad of signs in meningitis is fever, altered mental status and neck stiffness. The full triad occurs in approximately 44% to 67% of patients with acute bacterial meningitis.[3,4,6] However, the majority of patients will present with at least one of these three findings. In various case series:

- fever has been present in 77% to 97% of patients,
- neck stiffness has been observed in 82% to 88% of patients and
- altered mental status has been documented in 66% to 78% of patients.[3,4,6]

Meningeal irritation may be demonstrated on physical exam by Kernig's and Brudzinski's signs (Table 2).[2] Both of these tests produce pain by stretching inflamed, hypersensitive nerve roots. A petechial or purpuric rash may be observed, most often with infection caused by *N. meningitidis*. On history, headache has been reported in 66% to 87% of patients.[5,6] Nausea and vomiting are also relatively common.[2,5,6] Seizures occur in 5% to 28% of patients.[3-6] Focal neurologic abnormalities, including gaze preference, hemiparesis, aphasia and visual field defects may be present, as may cranial nerve palsies.

How is meningitis diagnosed?

Meningitis is diagnosed by performing a lumbar puncture (LP). CSF analysis should include the following:

- cell count and differential,
- total protein,
- glucose (with a serum sample sent at the same time for a CSF/serum glucose ratio),
- gram stain and
- culture.

Additional tests may be ordered depending on which pathogens (*i.e.*, tuberculosis, virus, fungi) are in the differential diagnosis. A multitude of non-infectious conditions may cause symptoms compatible with acute bacterial meningitis (Table 3).[8] For patients with a history of malignancy presenting with a clinical pic-

ture of meningitis, it may be prudent to send cerebrospinal fluid for cytology analysis to ensure the process does not represent a carcinomatous meningitis.

In bacterial meningitis, the cerebrospinal fluid will typically have an elevated cell count (neutrophil predominance), elevated protein concentration and reduced glucose concentration. Table 4 summarizes the changes in CSF that occur with bacterial meningitis versus meningitis caused by other pathogens.[1,9,10] A Gram-stain identifies the causative bacterium in 60% to 90% of patients.[7] CSF cultures are positive in 70% to 85% of patients with bacterial meningitis who have not received previous antibiotic therapy.[7]

Computed axial tomographic (CT) scanning of the brain is often performed prior to lumbar puncture to exclude occult intracranial pathology, which could result in brain herniation. Suggested guidelines regarding which patients should receive a CT scan prior to LP are presented in Table 5.[7,11] These guidelines were associated with a negative predictive value of 97% in one study (*i.e.*, their absence predicted a normal scan in 97% [93/96] of patients in this study).[11] However, they have yet to undergo validation in prospective clinical trials.

How is meningitis treated?

Bacterial meningitis is treated with antibiotics. Antibiotic therapy should be initiated as soon as the diagnosis is considered likely. Delaying empiric treatment while awaiting further diagnostic tests (*e.g.*, a CT scan) is not appropriate. The current recommendations for antibiotic therapy are presented in Tables 1 and 6.[7] These recommendations are based on recently published guidelines from the Infectious Diseases Society of America.

Vancomycin is suggested as a component of empiric therapy regimens in the US because of the high prevalence of penicillin-resistant pneumococci in this country. The use of empiric vancomycin in Canada, where the prevalence of penicillin-resistant pneumococci is lower, may be viewed as controversial. However, recent data indicates the current prevalence of penicillin non-susceptiblity among pneumococcal isolates from Canadian hospitals is 15% and this number is on the rise. Ceftriaxone non-susceptibility among the same isolates is 7.7%.[12] Hence, initial treatment with a regimen containing vancomycin should be considered while culture and sensitivity results are pending. The duration of therapy should be guided by the patient's clinical response, but general guidelines are presented in Table 7.[7]

Dexamethasone is also currently recommended in suspected cases of pneumococcal meningitis (0.15 mg/kg, every six hours, for two to four days, first dose 10 to 20 minutes before or concomitant with the first dose of antibiotics).[7] This recommendation is based on the results of a recent randomized, double-blind study of 301 patients that compared adjuvant therapy with dexamethasone to placebo in the treatment of bacterial meningitis.[13] Patients with pneumococcal meningitis who received dexamethasone had both a statistically significant and clinically

Table 3

Differential diagnosis of acute bacterial meningitis[8]

Infectious

- Focal suppurative central nervous system (CNS) infections (*e.g.*, subdural and epidural empyema, brain abscess)
- Fungal CNS infection
- Mycobacterial CNS infection
- Parasitic CNS infection
- Ricketssia (*i.e.*, Rocky Mountain Spotted Fever)
- Viral meningitis/meningoencephalitis

Non-infectious

- Behcet's disease
- Carcinomatous meningitis
- Drug-induced meningitis (*e.g.*, non-steroidal anti-inflammatory drugs, trimethoprim, isoniazid, *etc.*)
- Sarcoidosis
- Subarachnoid hemorrhage
- Systemic lupus erythematosis
- Vasculitis
- Others

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Table 5

Indications for obtaining a head CT scan[7,11]

Indications for CT scan prior to lumbar puncture:

- Age ≥ 60
- Immunocompromised (including patients with HIV and those receiving immunosuppressive therapy)
- History of CNS disease (mass lesion, stroke, focal infections)
- Seizure within one week of presentation
- Papilledema
- Neurologic findings:
  - Abnormal level of consciousness
  - Inability to answer two questions correctly
  - Inability to follow two commands correctly
  - Gaze palsy
  - Abnormal visual fields
  - Facial palsy
  - Arm/leg drift
  - Abnormal language (dysarthria, aphasia)

CT: Computed tomography
CNS: Central nervous system

important reduction in the combined endpoint of death or serious disability (50% relative risk reduction, 26% absolute risk reduction).[13]

It may be prudent to discuss the role of vancomycin and adjunctive dexamethasone with local experts prior to their initiation, as regional differences in opinion regarding the empiric use of these agents may exist.

Who should receive meningitis prophylaxis?

Secondary attack rates of between two to four cases/1,000 have been reported among close contacts of patients with meningococcal meningitis.[9] Close contacts include household contacts within the seven days prior to diagnosis of the patient and people exposed to oral secretions from the patient (includes kissing). Prophylactic therapy is recommended for these individuals.

Suggested regimens for prophylaxis include:

- rifampin, 600 mg, orally, every 12 hours, for four doses in adults (and children older than 12 years) and 10 mg/kg every 12 hours, for four doses in children older than one year;
- ciprofloxacin (adults only), 500 mg, orally, as a single dose, or
- ceftriaxone, 250 mg, intramuscularly, one dose (children younger than 15 years, 125 mg, intramuscularly, for one dose).

No prophylactic therapy is recommended for adult close contacts of patients with other types of bacterial meningitis or viral meningitis.

Table 4

Cerebrospinal fluid (CSF) analysis in meningitis[1,9,10]

Etiology	Cell count Normal=Up to 4 cells/mm^3, lymphocytes	Protein Normal=0.1 g/L to 0.4 g/L	Glucose Normal=2.3 mmol/L to 4.5 mmol/L
Bacterial	< 100 cells/mm^3 to > 10,000 cells/mm^3 (usual is 1,000 cells/mm^3 to 5,000 cells/mm^3); neutrophil predominance	Increased	Decreased (less than 2.2 mmol/L or CSF/serum glucose ratio of < 0.4
Viral	10 cells/mm^3 to 1,000 cells/mm^3; lymphocyte predominance	Normal or slightly increased	Normal
Tuberculosis	10 cell/mm^3 to 1,000 cells/mm^3; lymphocyte predominance	Increased	Decreased (approximately 1.6 mmol/L to 2.5 mmol/L)
Fungal	10 cells/mm^3 to 1,000 cells/mm^3; lymphocyte predominance	Increased	Decreased

CSF: Cerebrospinal fluid

Table 6

Antibiotic therapy for bacterial meningitis[7]

Empiric antibiotic therapy—Gram stain known, culture pending

Gram stain	Likely pathogen	Empiric antibiotic therapy
Gram-positive cocci	*S. pneumoniae*	Vancomycin plus a third-generation cephalosporin*
Gram-negative cocci	*N. meningitidis*	Third-generation cephalosporin*

Specific antibiotic therapy for common pathogens once culture complete

Pathogen	Antibiotic therapy
S. pneumoniae	
Penicillin MIC:	
< 0.1 µg/ml	Penicillin G or ampicillin
0.1-1 µg/ml	Third-generation cephalosporin*
≥ 2 µg/ml	Vancomycin plus a third-generation cephalosporin*
N. meningitidis	
Penicillin MIC	
< 0.1 µg/ml	Penicillin G or ampicillin
0.1-1 µg/ml	Third-generation cephalosporin*
L. monocytogenes	Ampicillin or penicillin G
S. agalactiae	Ampicillin or penicillin G
E. coli and other enterobacteriaceae	Third-generation cephalosporin*

MIC: Minimum inhibitory concentration
*Third-generation cephalosporin—either cefotaxime or ceftriaxone
Suggested adult doses: Ampicillin, 12 g/day, divided every 4 hours; cefotaxime, 8 g to 12 g/day, divided every 4-6 hours; ceftriaxone, 4 g/day divided every 12 hours; penicillin G, 24 mU, divided every 4 hours; vancomycin 30 mg to 45 mg/kg/day, divided every 8-12 hours.

Table 7

Duration of antibiotic therapy[7]

Pathogen	Duration of therapy
S. pneumoniae	10 to 14 days
N. meningitidis	7 days
L. monocytogenes	≥ 21 days
Aerobic gram-negative bacilli	21 days
S. agalactiae	14 to 21 days

Can bacterial meningitis be prevented?

Vaccination against *Haemophilus influenzae* Type b has resulted in a dramatic reduction in the number of cases of meningitis caused by this pathogen.[14] Both pneumococcal and meningococcal C conjugate vaccines are now available and these vaccines have been added to the immunization schedule in certain provinces. The use of these vaccines may ultimately reduce the number of cases of meningitis caused by *S. pneumoniae* and *N. meningitidis* serogroup C.

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