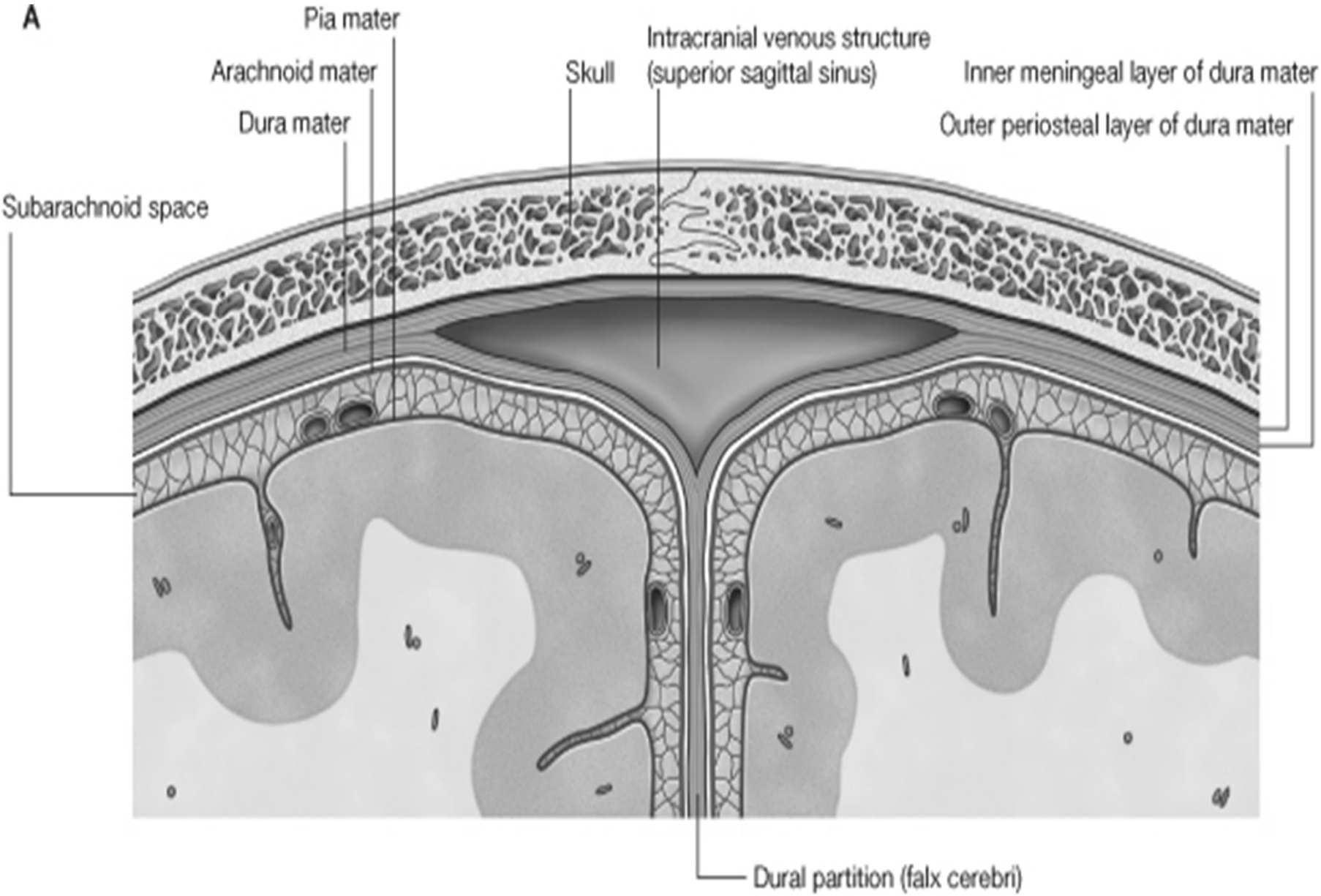
CENTRAL NERVOUS SYSTEM INFECTIONS

❖The term ***central nervous system (CNS) infections*** describes a variety of infections involving the brain and spinal cord and associated tissues, fluids, and membranes, including meningitis, encephalitis, brain abscess, shunt infections, and postoperative infections.

❖ CNS infections, such as meningitis, are considered neurologic emergencies that require prompt recognition, diagnosis, and management to prevent death and residual neurologic deficits.

❖ Despite advances in care, the overall mortality of bacterial meningitis remains greater than 20%, and at least 10% to 30% of survivors are afflicted with neurologic impairment, including hearing loss, **hemiparesis, and learning disabilities.**



EPIDEMIOLOGY AND ETIOLOGY:

- Compared with many other types of infections, CNS infections are less common, with 4 to 6 cases of meningitis reported per 100,000 adults annually.

- CNS infections can be caused by bacteria, fungi, mycobacteria, viruses, and spirochetes.

- Bacterial meningitis is the most common cause of CNS infections. An epidemiologic review of bacterial meningitis in 1995 revealed that *Streptococcus pneumoniae (pneumococcus)* was the most common pathogen (47%).

- Non-infectious causes of meningitis include malignancy, medications, autoimmune disease (such as lupus), and trauma.

- Neurosurgical procedures may place patients at risk for meningitis due to bacteria (such as *Staphylococcus aureus,* coagulase-negative staphylococci, and gram-negative bacilli) acquired at the time of surgery or in the postoperative period.

- In addition to bacteria, other pathogens may cause meningitis in at-risk patients. Immunocompromised patients, such as solid-organ transplant patients and patients living with human immunodeficiency virus (HIV) infection, are at risk for fungal meningitis with *Cryptococcus neoformans.*

- Because the treatments for different types of CNS infections are often very different, it is important to pay close attention to patients' risk factors when choosing empirical antimicrobial therapy.

Risk factors:

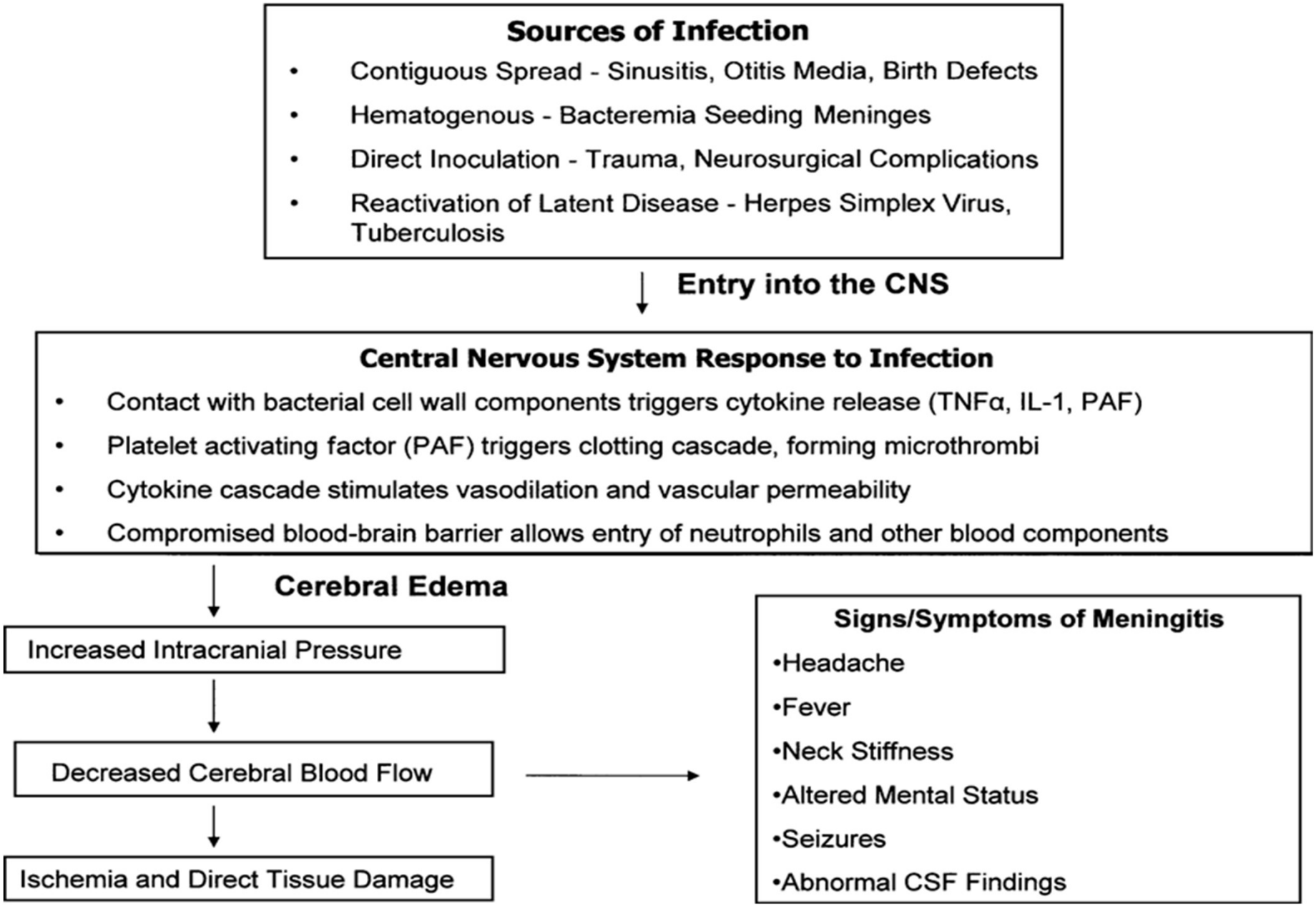
1- *Environmental—recent exposures (such as close contact with* meningitis or respiratory tract infection, contaminated foods), active or passive exposure to cigarette smoke, close living conditions.

2- *Recent infection in the patient—respiratory infection, otitis* media, sinusitis, mastoiditis.

3- *Immunosuppression—anatomic or functional asplenia, sickle* cell disease, alcoholism, cirrhosis, immunoglobulin or complement deficiency, cancer, HIV/AIDS, debilitated state of health.

4- *Surgery, trauma—neurosurgery, head trauma, CSF shunt,* cochlear implant.

Pathophysiology of bacterial meningitis.



CLINICAL PRESENTATION AND DIAGNOSIS:

General

- Evaluate patient risk factors and recent exposures.
- Evaluate other possible causes: space-occupying lesion (which may or may not be malignant), drug-induced CNS disease, autoimmune disease, and trauma.

Signs and Symptoms:

- Headache (87%)
- Nuchal rigidity (stiff neck) (83%)
- Fever (77%)
- Nausea (74%)
- Altered mental status (i.e., confusion, lethargy, and obtundation).
- Focal neurologic defects (including positive **Brudzinski's sign and Kernig's sign) (33%)**
- Seizures
- Malaise, restlessness
- Photophobia
- Skin lesions (diffuse petechial rash) .
- Signs and symptoms in neonates, infants, and young children: nonspecific findings, such as altered feeding and sleep patterns, vomiting, irritability, lethargy, bulging fontanel, seizures, respiratory distress, and petechial/purpuric rash.
- Predictors of an unfavorable outcome: seizures, focal neurologic findings, altered mental status, papilledema, hypotension, septic shock, and pneumococcal meningitis.

Laboratory Tests:

- CSF examination via lumbar puncture.
- Computed tomographic scan (CT) should be performed before LP if there is a question of a CNS mass to avoid potential for brain herniation.

Central Nervous System Response to Infection (Cerebrospinal Fluid Findings)

	Normal CSF	Bacterial Infection	Viral Infection	Fungal Infection	Tuberculosis
WBC (mm^3, $\times 10^9/L$)	Less than 5 (less than 0.005)	1000–greater than 5000 (1.0–greater than 5.0)	100–1000 (0.1–1)	100–400 (0.1–0.4)	50–500 (0.05–0.5)
WBC differential (%, predominant cell type)	Greater than 85% monocytes	At least 80% PMNs	50% lymphocytes (PMNs early)	Greater than 50% lymphocytes	Greater than 80% lymphocytes (PMNs early)
Protein (mg/dL, mg/L)	20–45 (200–450)	Greater than 100 (greater than 1000)	50–100 (500–1000)	100–200 (1000–2000)	40–150 (400–1500)
Glucose (mg/dL, mmol/L); CSF: serum glucose ratio	45–80 (2.5–4.44) At least 0.6 serum glucose	5–40 (0.28–2.22) less than 0.4 serum glucose	30–70 (1.67–3.89) 0.6 serum glucose	Less than 30–70 (less than 1.67–3.89) less than 0.4 serum glucose	Less than 30–70 (less than 1.67–3.89) less than 0.4 serum glucose
CSF stain	Negative	Positive Gram stain (60%–90%)	Negative	Positive India ink stain (*Cryptococcus*)	Positive acid-fast bacilli stain

Treatment:

Goals of Therapy:

The treatment goals for CNS infections are to :

1-Prevent death and residual neurologic deficits.

2-Eradicate or control causative microorganisms.

3-Ameliorate clinical signs and symptoms, and identify measures to prevent future infections (such as vaccination and suppressive therapy).

- Supportive care, consisting of hydration, electrolyte replacement, antipyretics, antiemetics, analgesics, antiepileptic drugs, and wound care (for surgical wounds), is an important adjunct to antimicrobial therapy, particularly early in the treatment course.

Treatment Principles:

- Prompt initiation of intravenous high-dose cidal antimicrobial therapy directed at the most likely pathogen(s) is essential.

- Initiation of antibiotic therapy as soon as possible after bacterial meningitis.

- If dexamethasone is to be used, it should be administered prior to or at the same time as the first dose of antibiotic therapy.

- Use of bactericidal antibiotics.

- Ability of antibiotics to reach and achieve effective concentrations at the infection site is the key to treatment success.

- In general, low-molecular-weight lipophilic antibiotics that are un-ionized at physiologic pH and not highly protein bound penetrate best into CSF and other body tissues and fluids.

- Sulfonamides, trimethoprim, chloramphenicol, rifampin, and most antitubercular drugs achieve therapeutic CSF levels even without meningeal inflammation.

- Most β- lactams and related antibiotics (i.e., carbapenems and monobactams), vancomycin, quinolones, acyclovir, linezolid, and colistin achieve therapeutic CSF levels in the presence of meningeal inflammation.

- Amino-glycosides, first-generation cephalosporins, second-generation cephalosporins (except cefuroxime), clindamycin, and amphotericin do not achieve therapeutic CSF levels, even with inflammation, but clindamycin does achieve therapeutic brain tissue levels.

Empirical Antimicrobial Therapy:

- In most patients, a diagnostic lumbar puncture will be performed before beginning antibiotics, but this never should delay initiation of antimicrobials.

- Empirical therapy should be directed **at the most likely pathogen(s)** for a specific patient, taking into account age, risk factors for infection (including underlying disease and immune dysfunction, vaccine history, and recent exposures), CSF Gram stain results, CSF antibiotic penetration, and local antimicrobial resistance patterns.

- Increasing **pneumococcal resistance** to penicillin G has changed empirical treatment regimens to the combination of a **third-generation cephalosporin plus vancomycin**.

- Recognition of relative and high-level resistance to **N. meningitidis** in the laboratory, as well as in clinical treatment failures, has led to greater use of **third-generation cephalosporins** for empirical therapy of meningococcal meningitis.

- Now, treatment of suspected or proven β-lactamase-mediated **Hib meningitis** requires a *third-generation cephalosporin*.

- Increasing rates of **methicillin-resistant *S. aureus*** and coagulase-negative staphylococci require the use of **vancomycin** for empirical therapy when these pathogens are suspected.

- The adjunctive agent dexamethasone has been shown to improve outcomes in selected patient populations with meningitis.

- Dexamethasone inhibits the release of proinflammatory cytokines and limits the CNS inflammatory response stimulated by infection and antibiotic therapy.

- Dexamethasone should be administered before the initiation of antibiotics to reduce neurologic deficits (primarily by reducing hearing loss).

- The American Academy of Pediatrics recommends dexamethasone (0.15 mg/kg intravenously every 6 hours for 2 to 4 days) for infants and children at least 6 weeks of age with Hib meningitis and consideration of dexamethasone in pneumococcal meningitis.