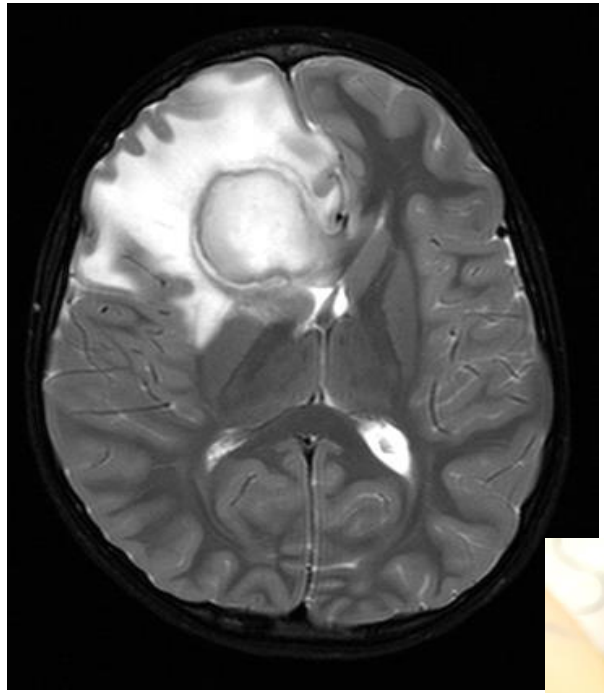
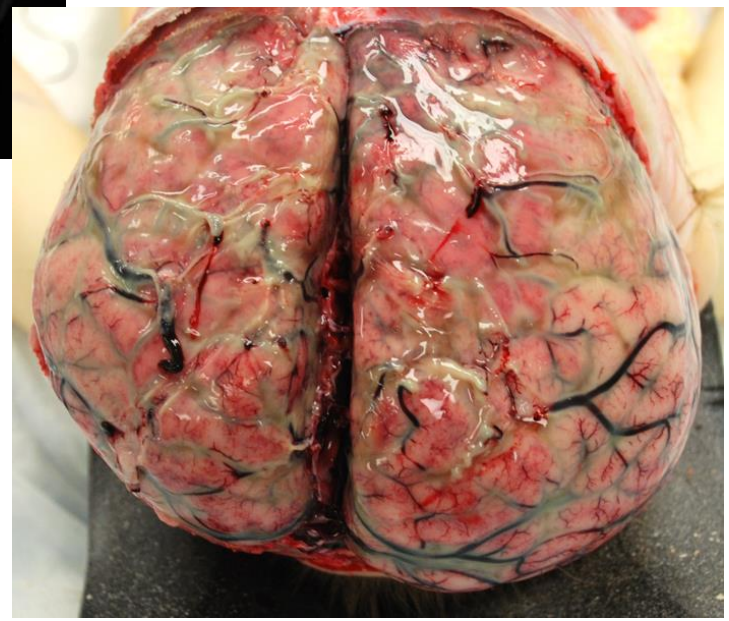
Microbiology of the central nervous system





Anas Abu-Humaidan
M.D. Ph.D.

Lecture 4

How is viral meningitis different from bacterial meningitis?

- The term **aseptic meningitis** encompasses broad differential diagnoses related to inflammation of the meninges not due to pyogenic bacteria. Although viral pathogens are the most common etiology, many different causes – both infective and non-infective – can be responsible for aseptic meningitis.

- The spectrum of non-infectious causes may include druginduced (e.g. amoxicillin, nonsteroidal anti-inflammatory medications or trimethoprimsulfamethoxazole), neoplastic, neurosarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, or vasculitis (e.g. Kawasaki disease) (during the nonwinter months).

How is viral meningitis different from bacterial meningitis?

- Viral meningitis (aseptic meningitis) has **similar symptoms to bacterial meningitis** (headache, fever, and signs of meningeal irritation), but **rarely** produces **focal neurological defects** and profound alterations in conciousness.

- **Enteroviruses** are the **leading cause** of viral meningitis, e.g. echoviruses, Coxsackie viruses, enteroviruses 70 and 71.

- Incidence is not clear but **seasonal variations** are found. (In temperate climates, there is a substantial increase in cases during the nonwinter months).

Acute Meningitis	
Common	Less Common
Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71) Varicella-zoster virus Herpes simplex virus 2 Epstein-Barr virus Arthropod-borne viruses HIV	Herpes simplex virus 1 Human herpesvirus 6 Cytomegalovirus Lymphocytic choriomeningitis virus Mumps

Specific viral presentations

- **Enterovirus**— in neonates, fever is accompanied by vomiting, anorexia, rash, and upper respiratory tract symptoms. In older children and adults, symptoms are milder with fever, headache, neck stiffness, and photophobia

- **Mumps virus**— CNS symptoms usually occur 5 days after the onset of parotitis.

- **VZV meningitis** is associated with a characteristic, diffuse vesicular rash.

- **Herpesviruses**— HSV- 2 meningitis presents with classical symptoms.

Acute Meningitis	
Common	Less Common
Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71) Varicella-zoster virus Herpes simplex virus 2 Epstein-Barr virus Arthropod-borne viruses HIV	Herpes simplex virus 1 Human herpesvirus 6 Cytomegalovirus Lymphocytic choriomeningitis virus Mumps

Enteroviral meningitis in Northern Jordan: prevalence and association with clinical findings

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Affiliations + expand

PMID: 11782931 DOI: 10.1002/jmv.2133

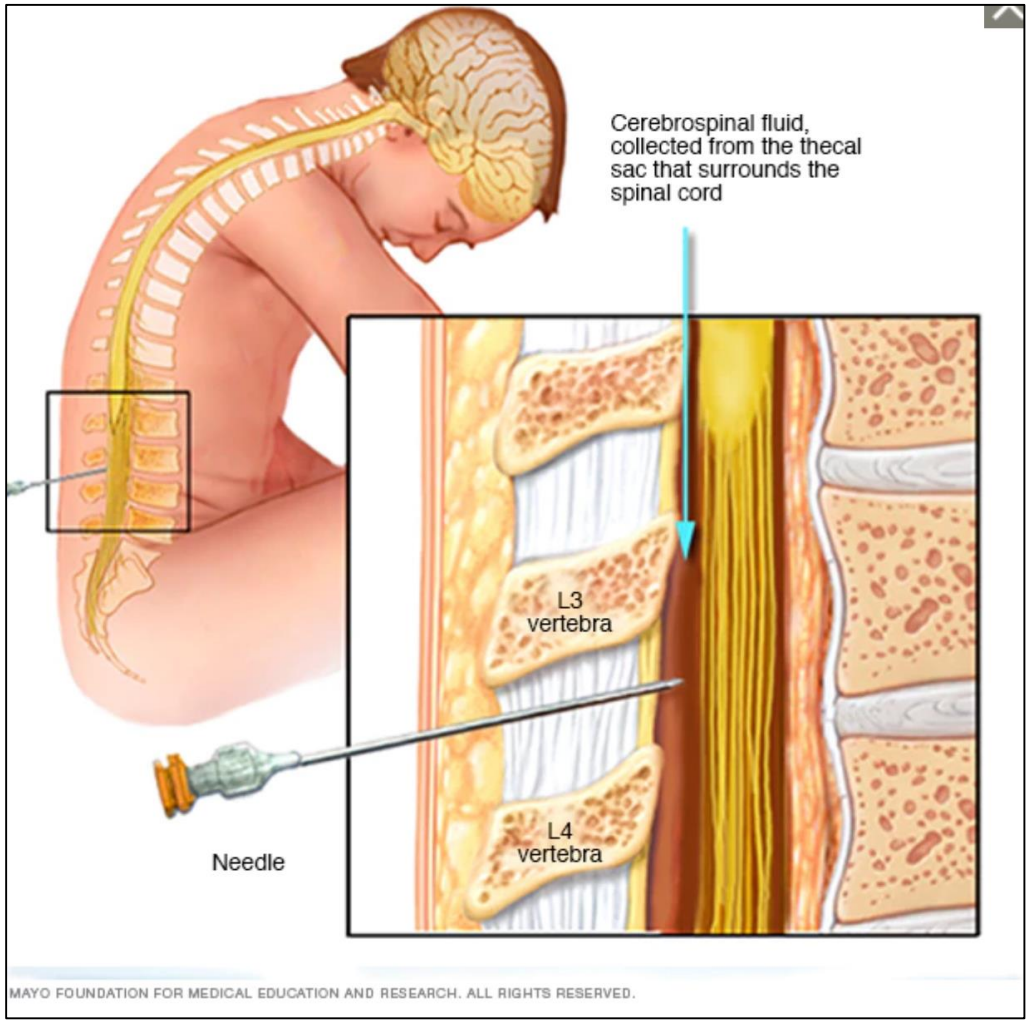
Abstract

During the summer-autumn of 1999, 390 specimens of cerebrospinal fluid were taken from infants and children younger than 15 years of age. They were suspected of having meningitis and were admitted to Princess Rahma Hospital, Northern Jordan. They were investigated for the presence of enteroviruses using shell vial culture and indirect immunofluorescence assays. Most cases (46.9%) occurred in children younger than 1 year of age in which males represented 71.9%. The common symptoms were fever, vomiting, and headache. Enteroviruses were isolated from 32 (8.2%) cases, coxsackievirus B types 2, 4, and 5 from 15 (46.9%) cases, and echovirus 9 (31.3%) was the most common identified serotype. The virus isolation rate was directly proportional to the number of leukocytes in the cerebrospinal fluid. However, enteroviral isolation was demonstrated in 4 (12.5%) of 32 cerebrospinal fluid specimens without pleocytosis. Leukocyte differential count revealed a predominance of polymorphonuclear cells in 71.4% of the cases. Hospitalization ranged from 1 day to 25 days with a mean of 7 days. The majority of enterovirus-infected patients (88.9%) were treated with at least one type of antibiotic. These results emphasize the importance of shell vial culture assay for diagnosing enteroviruses, especially in laboratories that do not have access to advanced techniques such as polymerase chain reaction.

https://pubmed.ncbi.nlm.nih.gov/11782931/

How to confirm a diagnosis of viral meningitis?

- **CSF examination** and **viral culture** are important.
- **Serology** for enteroviral infections is possible by detection of enteroviral IgM antibodies.
- Amplification o viral-specifc DNA or RNA rom CSF using **Polymerase chain reaction** (PCR) has become the **single most important method** for diagnosing CNS viral infections.



Test	*Bacterial*	*Viral*	*Fungal*	*Tubercular*
Opening pressure	Elevated	Usually normal	Variable	Variable
White blood cell count	≥1,000 per mm^3	<100 per mm^3	Variable	Variable
Cell differential	Predominance of PMNs*	Predominance of lymphocytes†	Predominance of lymphocytes	Predominance of lymphocytes
Protein	Mild to marked elevation	Normal to elevated	Elevated	Elevated
CSF-to-serum glucose ratio	Normal to marked decrease	Usually normal	Low	Low

CSF = cerebrospinal fluid; PMNs = polymorphonucleocytes.

**—Lymphocytosis present 10 percent of the time.*

†*—PMNs may predominate early in the course.*

How to manage viral meningitis?

- Based upon the history, physical examination, and cerebrospinal fluid (CSF) findings, patients can be classified as having **probable bacterial meningitis**, **probable viral meningitis**, or **indeterminant**.

- For patients with suspected bacterial meningitis (eg, WBC count >1000/microL, glucose concentration <40 mg/dL [2.2 mmol/L], protein concentration >100 mg/dL), antibiotics should be initiated promptly.

- Patients with probable viral meningitis include those with CSF findings of cell count <500/microL, >50 percent CSF lymphocytes, protein concentration less than 80 to 100 mg/dL, normal glucose concentration, and negative Gram stain. Patients who are elderly, immunocompromised, or have received antibiotics prior to presentation should be given antibiotics even if viral meningitis is the suspected diagnosis. Otherwise, the clinician can consider observing the patient without antibiotic therapy.

How to manage viral meningitis?

- When it is not clear whether the patient has a viral or bacterial process, the treating physician **can choose empiric antibiotics after obtaining blood and CSF cultures or observation with repeat lumbar puncture (LP) in 6 to 24 hours**. The majority of clinicians opt for empiric antibiotics until culture results are available in 24 to 48 hours.

- If the patient is symptomatically improved and culture results are negative, then antibiotics can generally be stopped without a repeat LP if the suspicion for bacterial meningitis is unlikely. However, repeat LP may be indicated in patients with persistent symptoms who do not have a clear diagnosis.

How to manage viral meningitis?

- Treatment of almost all cases of viral meningitis is primarily symptomatic and includes use of **analgesics**, **antipyretics**, an **antiemetics**. Fluid an electrolyte status should be monitored .

- In adults, the prognosis for **full recovery** from viral meningitis is **excellent**.

- The outcome in **infants and neonates** (<1 year) is less certain; **intellectual impairment**, **learning disabilities**, **hearing loss**, and other lasting sequelae have been reported in some studies.

How to manage viral meningitis?

Case Study and Questions

A 6-year-old girl was brought to the doctor's office at 4:30 PM because she had a sore throat, had been unusually tired, and was napping excessively. Her temperature was 39° C. She had a sore throat, enlarged tonsils, and a faint rash on her back. At 10:30 PM, the patient's mother reported that the child had vomited three times, continued to nap excessively, and complained of a headache when awake. The doctor examined the child at 11:30 PM and noted that she was lethargic and aroused only when her head was turned, complaining that her back hurt. Her CSF contained no red blood cells, but there were 28 white blood cells/mm^3—half polymorphonuclear neutrophils and half lymphocytes. The glucose and protein levels in the CSF were normal, and Gram stain of a specimen of CSF showed no bacteria.

1. *What were the key signs and symptoms in this case?*
2. *What was the differential diagnosis?*
3. *What signs and symptoms suggested an enterovirus infection?*
4. *How would the diagnosis be confirmed?*
5. *What were the most likely sources and means of infection?*
6. *What were the target tissue and mechanism of pathogenesis?*

How to manage viral meningitis?

Answers

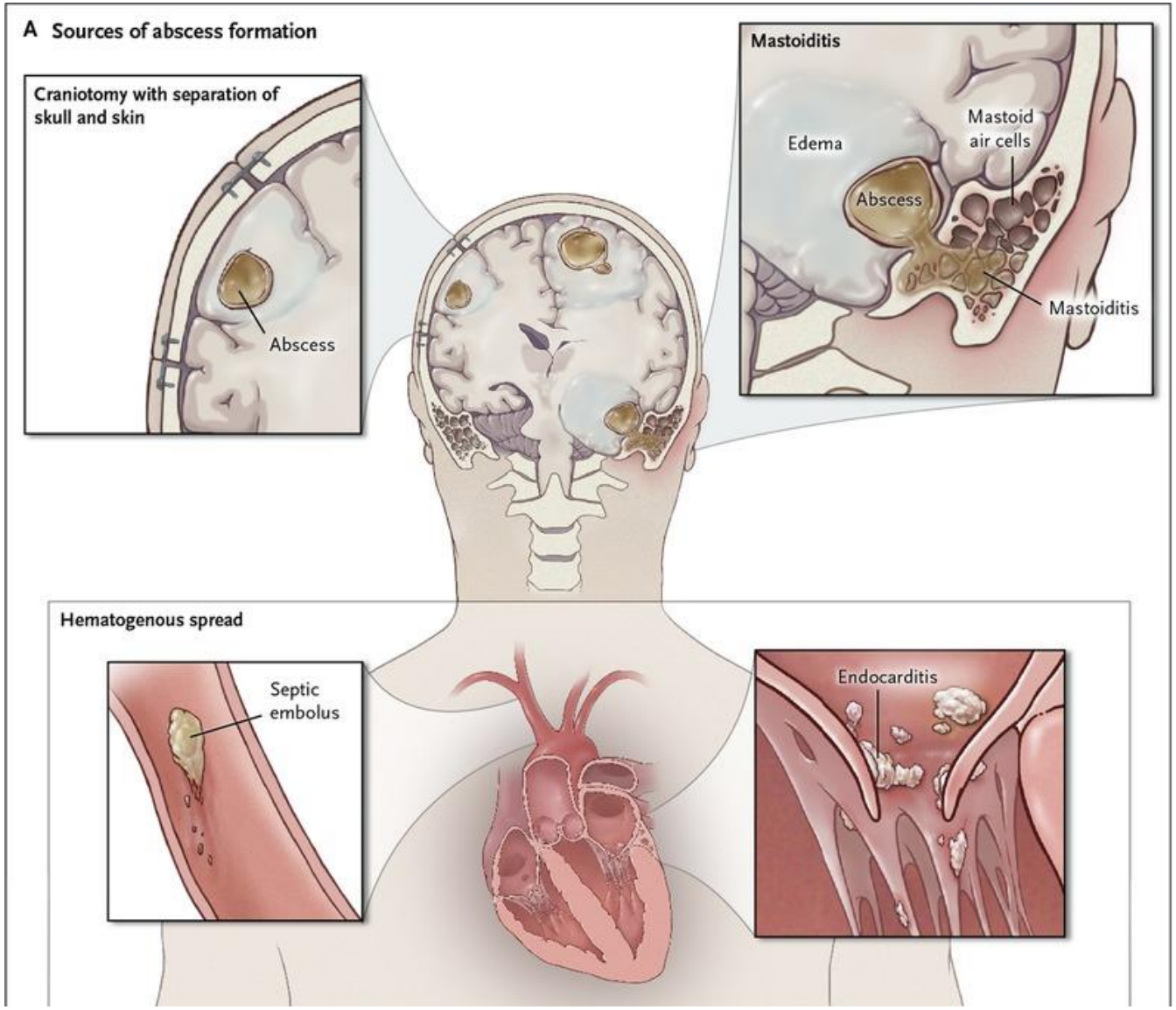
1. The key signs and symptoms were sore throat, fever, faint rash, excessive napping, lethargy, headache, and pain upon turning head (stiff neck). The presence of lymphocytes in the CSF and normal glucose and protein levels minimizes the diagnosis of a bacterial infection.
2. The differential diagnosis is aseptic meningitis that is likely caused by a virus such as an enterovirus, HSV, or lymphocytochoriomeningitis virus, or by an arboencephalitis virus from the Togaviridae, Flaviviridae, or Bunyaviridae families. *Cryptococcus neoformans* (fungus), *Mycobacterium tuberculosis,* and *Borrelia burgdorferi* are also possible. However, the presence of a rash and sore throat before signs of meningitis strengthen the likelihood of an enterovirus infection, such as coxsackievirus A or echovirus. At an earlier time (30 years ago), polio would also be in the differential diagnosis.
3. The rash and sore throat in the prodrome period and the presence of lymphocytes in the CSF distinguish an enterovirus meningitis from other microbial causes.
4. An RT-PCR analysis would identify the enterovirus in the CSF and confirm the diagnosis.
5. Enteroviruses are spread by the fecal-oral and aerosol routes.
6. The initial target tissues for enteroviruses are the mucoepithelium, lymphoid tissue of the tonsils and pharynx, and Peyer patches of the intestinal mucosa. The virus is cytolytic.

What is a brain abscess?

- A **brain abscess** is a **focal**, **suppurative** infection within the brain parenchyma, typically surrounded by **a vascularized capsule**. **Cerebritis** is a similar lesion with **no capsule**, and sometimes **precedes** abscess formation.

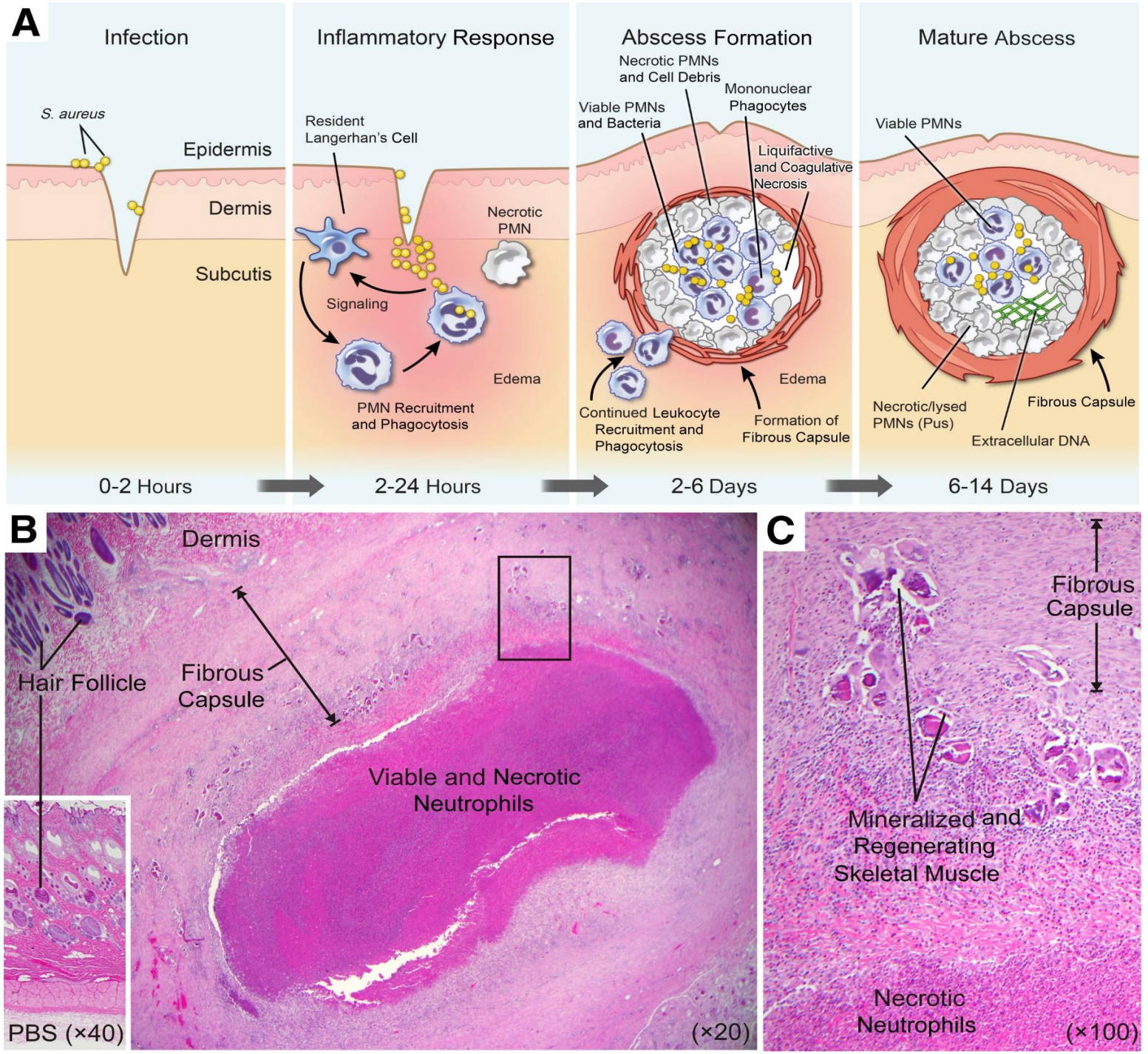
- Brain abscess formation is **rare** in immunocompetent adults less than 1 in 100000 person per year.

- Pathogen can spread from nearby **ear**, **sinus**, and **dental infections**, through **blood vessels**, or **directly** as in head trauma.



How are abscesses formed?

- Abscesses may occur in any kind of tissue, and are the result of the immune response to invading pathogens.
- Destruction of nearby tissue leads to a cavity filled with live and dead bacteria, white blood cells, and cell debris.
- With time the abscess matures and becomes walled off, extra septation within the abscess can take place.



What are the common causative agents?

- The organism usually depends on the **primary focus of infection**. (e.g. *Streptococcus pneumoniae, Haemophilus influenzae Enterobacteriaceae, and bacteroids* are commonly associated with sinusitis and otitis media).

- *S. Aureus* is commonly encountered after **head trauma**.

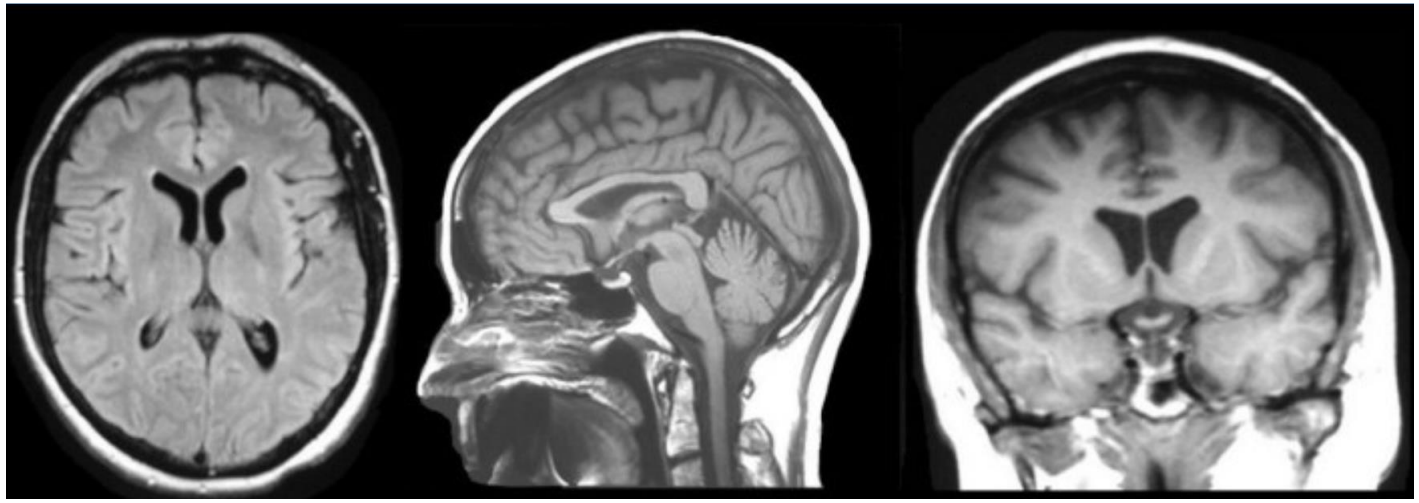
- In **immunocompromised** patients *Nocardia spp., Toxoplasma gondii, Aspergillus spp., Candida spp.* Should be considered.

Table 19.10 Factors predisposing to cerebral abscess

Predisposing condition	Microorganisms
Otitis media/mastoiditis	Streptococci, *Enterobacteriaceae, Bacteroides* spp., *P. aeruginosa*
Sinusitis	Streptococci, *Haemophilus* spp., *Bacteroides* spp., *Fusobacterium* spp.
Dental sepsis	Streptococci, *Haemophilus* spp., *Bacteroides* spp., *Fusobacterium, Prevotella*
Pulmonary/pleural sepsis	Streptococci, *Fusobacterium, Actinomyces, Bacteroides, Prevotella* spp., *Nocardia* spp.
Endocarditis	*S. aureus*, streptococci
Congenital heart disease	Streptococci, *Haemophilus* spp.
Urinary tract	*Enterobacteriaceae, P. aeruginosa*
Head trauma	*S. aureus, Enterobacter* spp., *Clostridium* spp.
Neurosurgery	*Staphylococcus* spp., *Streptococcus* spp., *P. aeruginosa, Enterobacter* spp.
Immunocompromised hosts	*T. gondii, L. monocytogenes, N. asteroides, Aspergillus, C. neoformans, C. immitis, Candida* spp., mucormycosis, zygomycosis
HIV infection	*T. gondii, Nocardia* spp., *Mycobacterium* spp., *L. monocytogenes, C. neoformans*

How do patients present?

- Headache, fever, seizures, and **focal neurological signs** are common. (**location** is important).
- **Brain imaging** (**MRI**, CT scan with contrast) should be performed urgently to confirm the diagnosis.
- Remember! An LP is **contraindicated** if there are focal symptoms or signs.
- Blood cultures can be positive in some patients (around 10%) and can help in the diagnosis.



Normal brain MRI

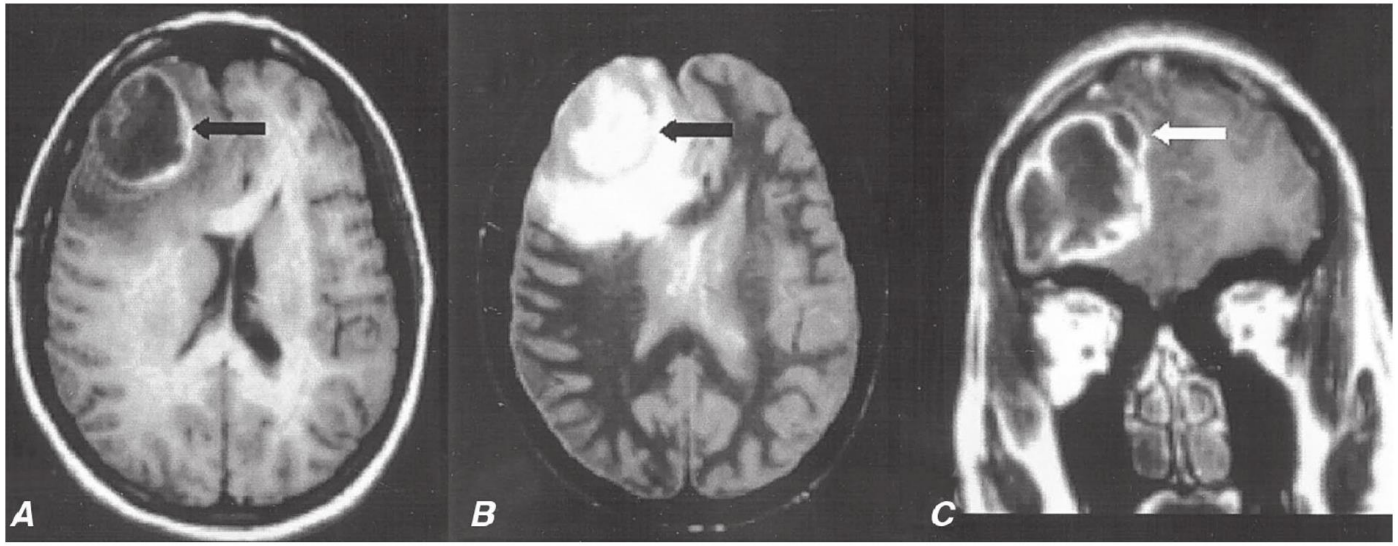


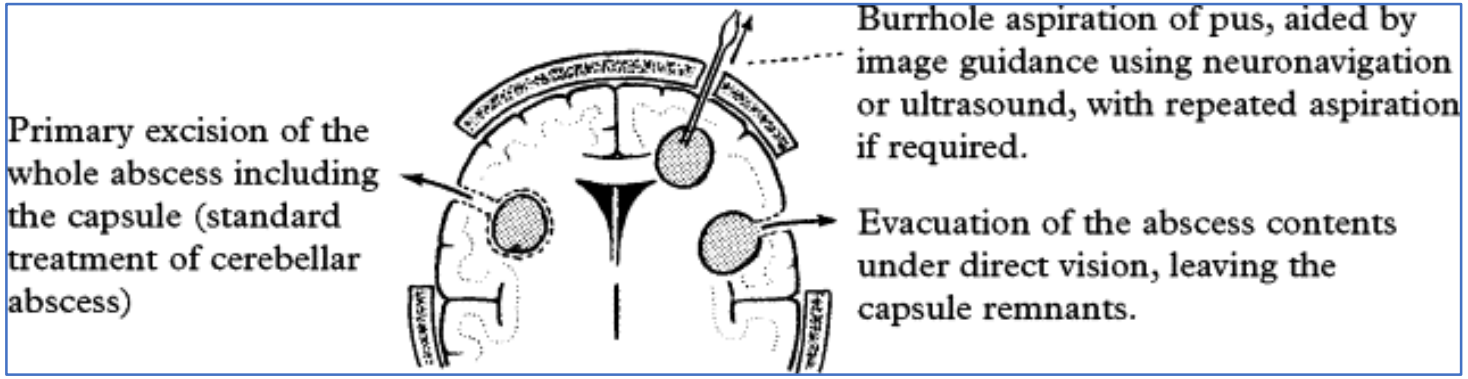
FIGURE 36-4
Pneumococcal brain abscess. Note that the abscess wall has hyperintense signal on the axial T1-weighted magnetic resonance imaging (MRI) (A, black arrow), has hypointense signal on the axial proton density images (B, black arrow), and enhances prominently after gadolinium administration on the coronal T1-weighted image (C). The abscess is surrounded by a large amount of vasogenic edema and has a small "daughter" abscess (C, white arrow). (Courtesy of Joseph Lurito, MD; with permission.)

How to manage brain abscess ?

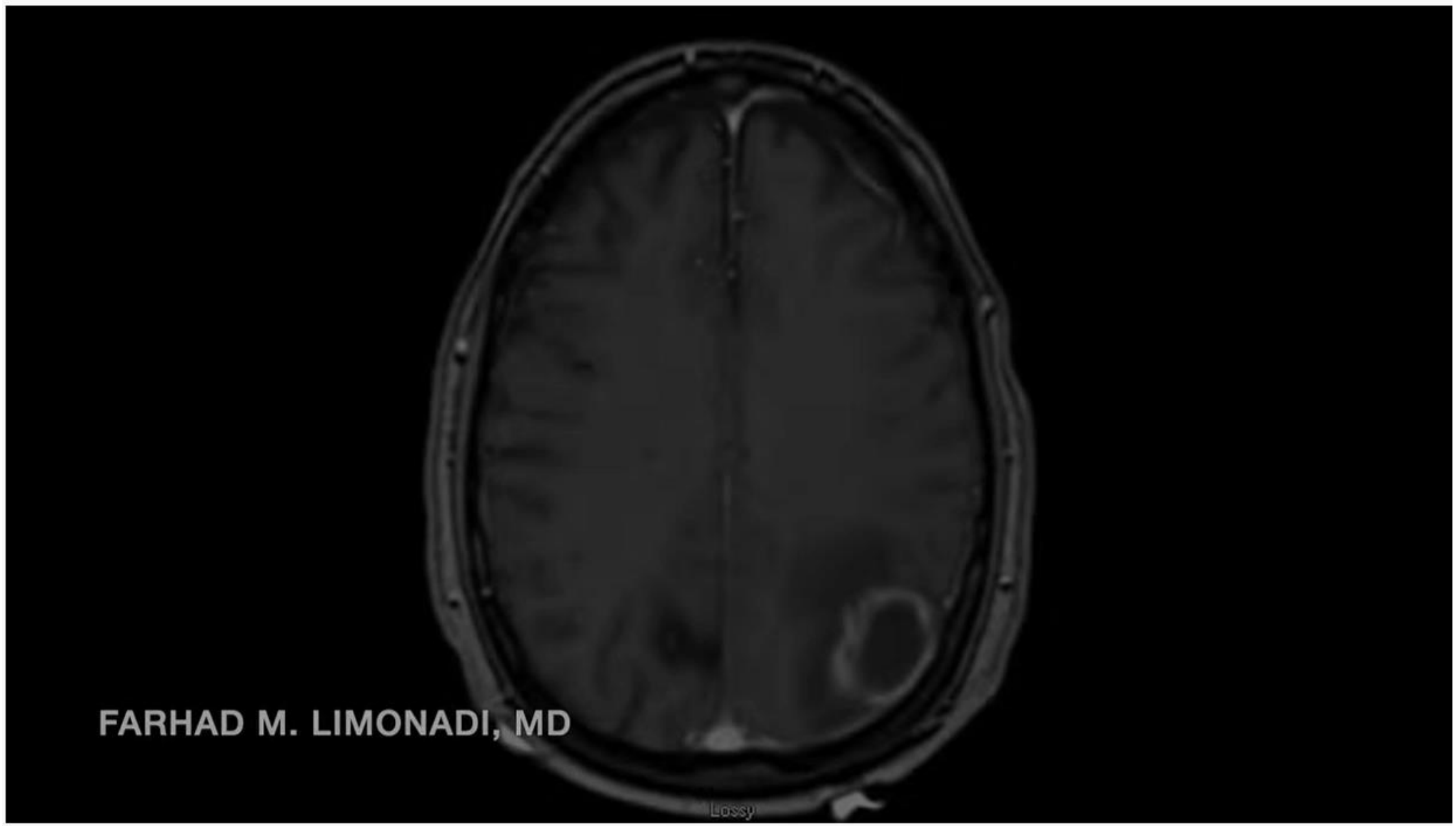
- Treatment involves a combination of high dose parenteral **antibiotics** an neurosurgical **drainage.**

- Empiric therapy with **3rd generation cephalosporin** can be started, in addition to antibiotics depending on suspicion. (e.g. History of recent head trauma increases chances of S. aureus, and Vancomycin can be added).

- Drainage of the abscess is usually necessary along with culture and cytology of the suppuration to identify the pathogen and do sensitivity testing.



How to manage brain abscess ?



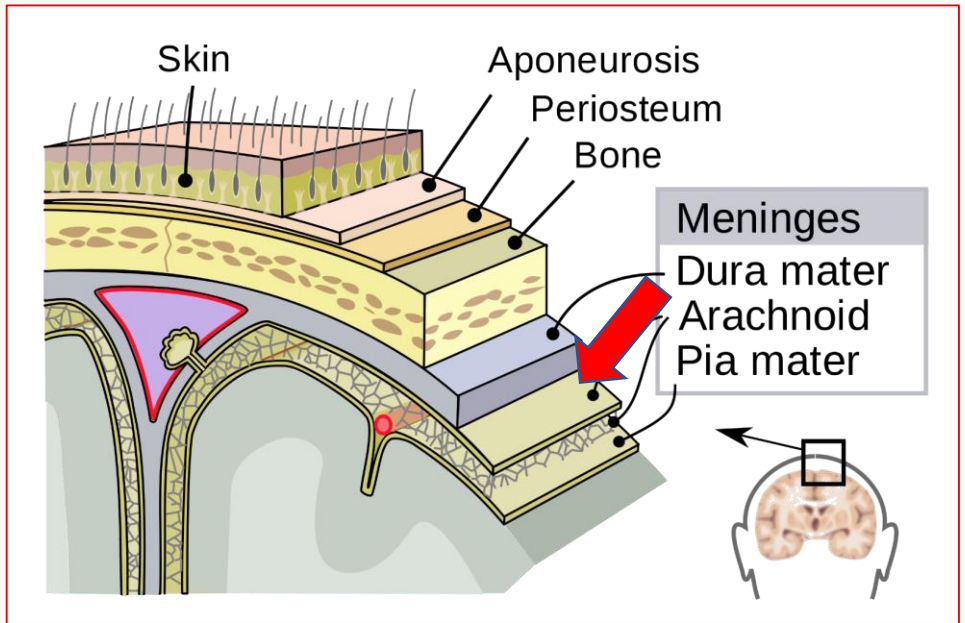
https://www.youtube.com/watch?v=__HelmnvyBs

Follow up and prognosis of brain abscess

- Serial MRI or CT scans should be obtained on a monthly or twice-monthly basis to document resolution of the abscess.
- Enhanced neuroimaging techniques, improved neurosurgical procedures, and improved antibiotics helped decrease mortality.
- In modern series, the mortality rate is typically <15%. Significant sequelae, including seizures, persisting weakness, aphasia, or mental impairment, occur in ≥20% o survivors.

What is a subdural empyema (SDE)?

- A subdural empyema is a collection of pus between the dura and arachnoid membranes.
- SDE is a rare disorder that accounts for 15–25% of focal suppurative CNS infections. With a striking predilection for **young males**.



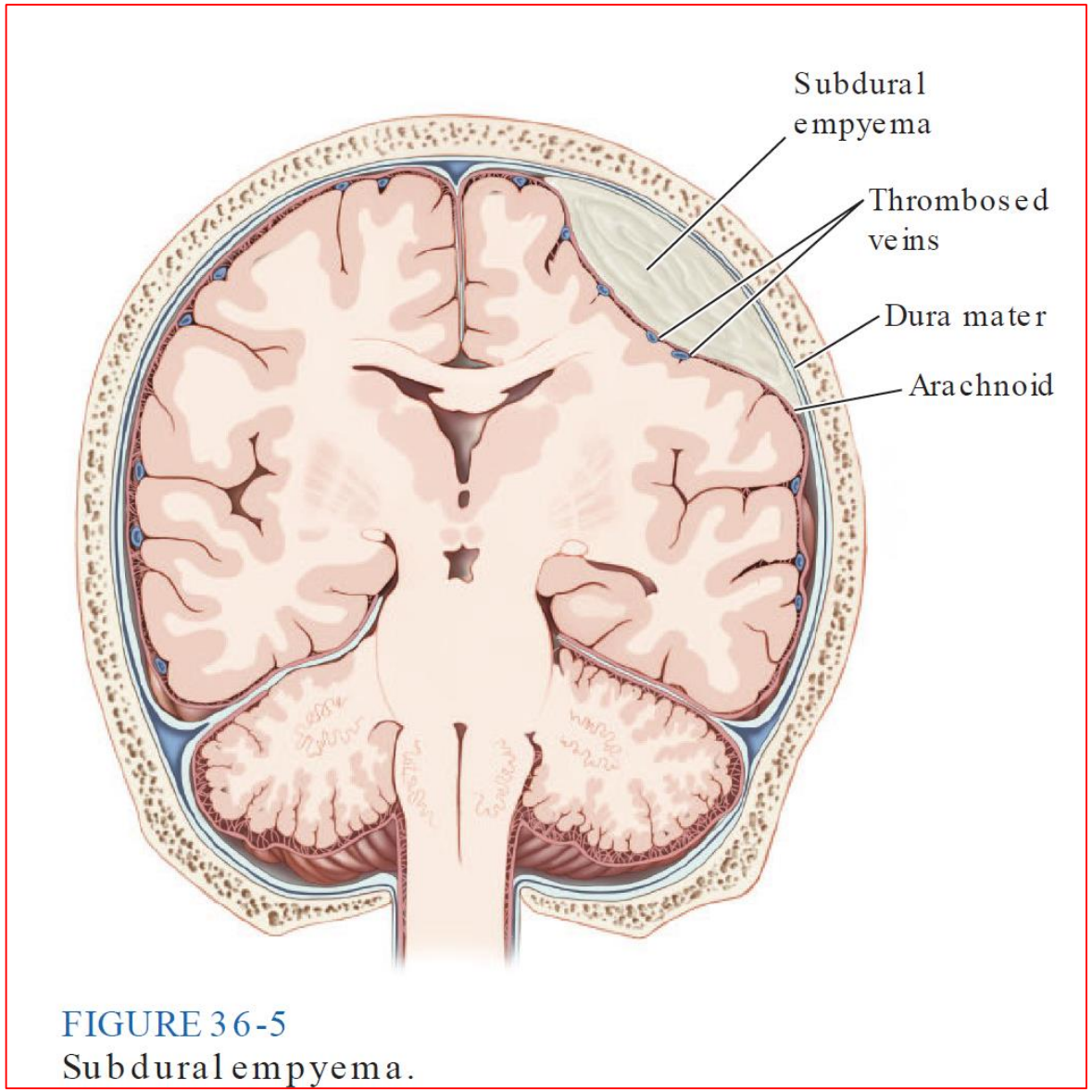


FIGURE 36-5
Subdural empyema.

What is a subdural empyema (SDE)?

- Pathogens, pathophysiology, and clinical presentation in SDE is similar to a brain abcsess, and other infectious space occuping lesions.

- Aerobic and anaerobic streptococci, staphylococci, Enterobacteriaceae, and anaerobic bacteria are the most common causative organisms of sinusitis-associated SDE.

- The evolution of SDE can be **extremely rapid** because the subdural space is a large compartment that offers **few mechanical barriers to the spread of infection**.

- A patient with SDE typically presents with fever and a progressively worsening headache, Presence of underlying sinusitis should raise suspicion of SDE.

- Contralateral **hemiparesis** or **hemiplegia** is the most common focal neurologic deficit and can occur from the direct effects of the SDE on the cortex or as a consequence o venous infarction.

How to diagnose subdural empyema (SDE)?

- MRI is superior to CT in identifying SDE and any associated intracranial infections.
- **CSF examination** should be **avoided** in patients with known or suspected SDE because it adds no useful information and is associated with the risk of cerebral herniation.

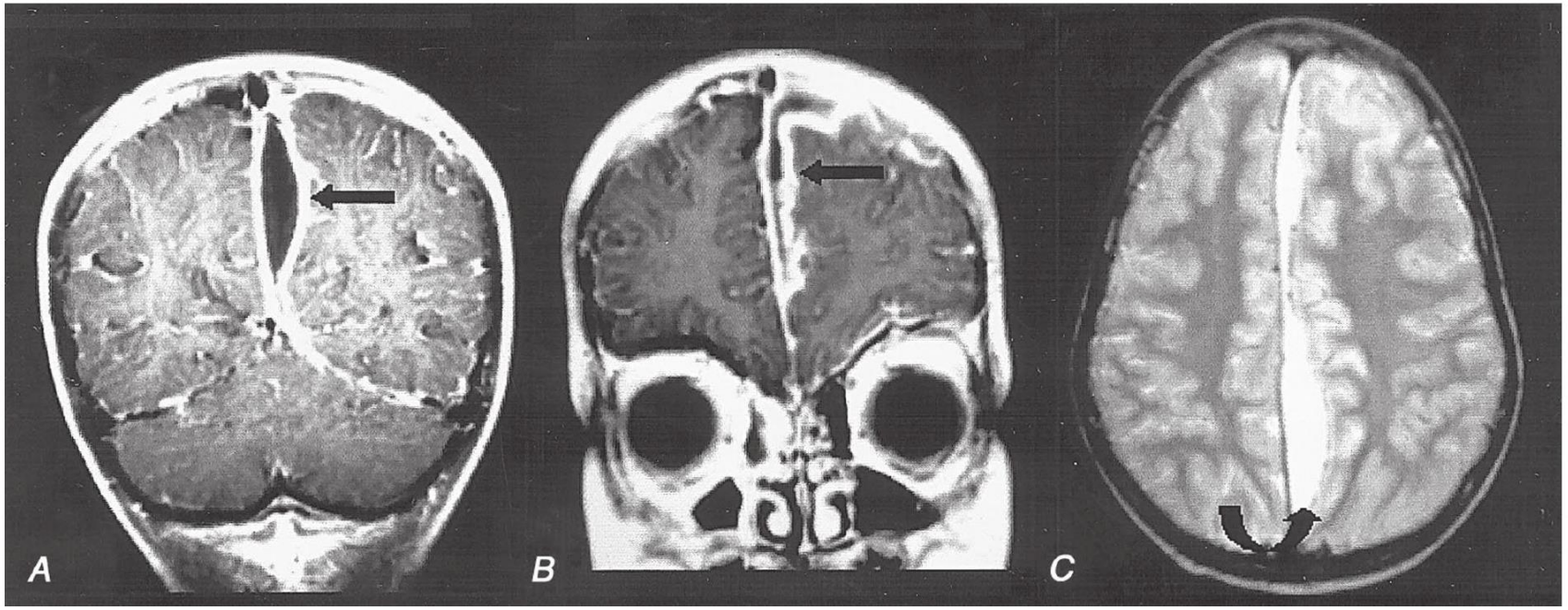


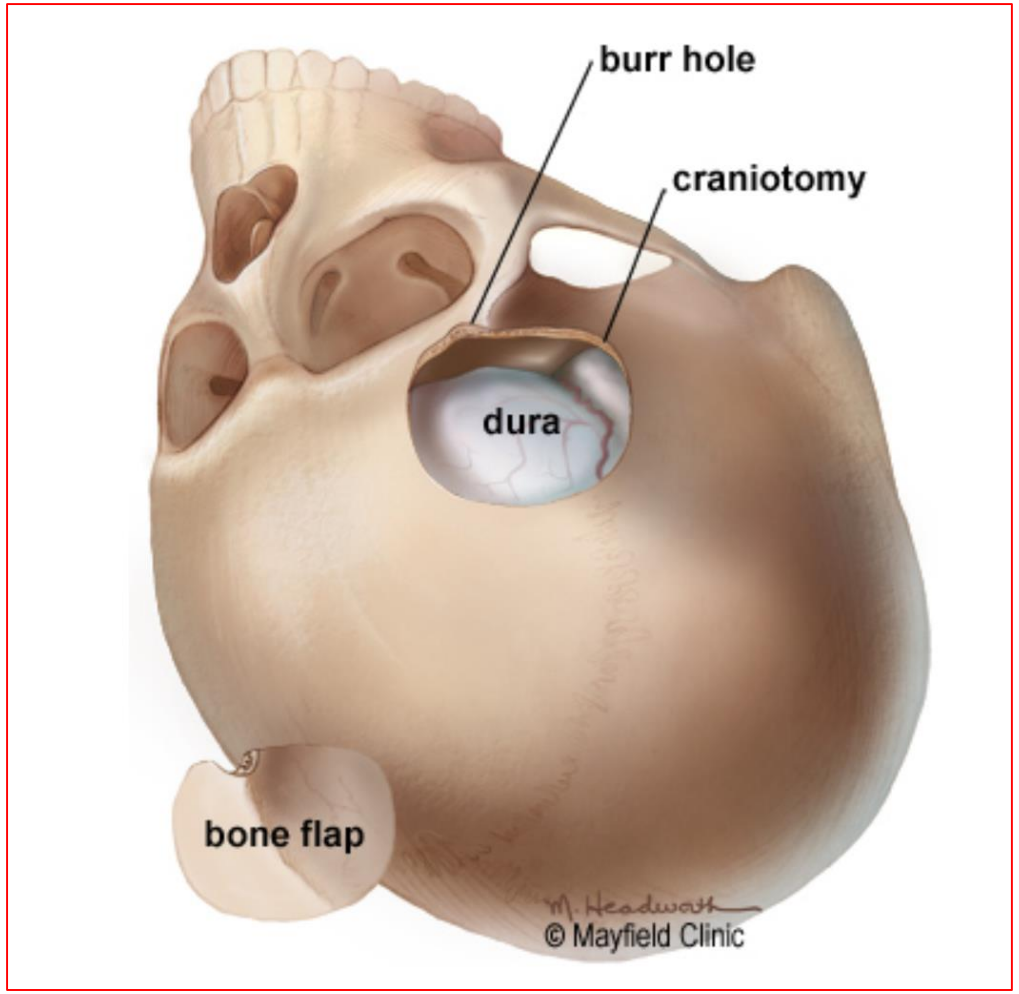
FIGURE 36-6
Subdural empyema. There is marked enhancement of the dura and leptomeninges (A, B, straight arrows) along the left medial hemisphere. The pus is hypointense on T1-weighted images (A, B) but markedly hyperintense on the proton density–weighted (C, curved arrow) image. (Courtesy of Joseph Lurito, MD; with permission.)

How to treat subdural empyema (SDE)?

- SDE is a medical emergency. Emergent neurosurgical **evacuation** of the empyema, either through craniotomy, craniectomy, or burrhole drainage, is the definitive step in the management of this infection.

- **Empiric antibiotic therapy** should include a 3rd generation cephalosporin, vancomycin and metronidazole. (again depending on suspicion from patient's history).

- Specific diagnosis of the etiologic organisms is made based on **Gram's stain** and **culture** of fluid obtained via either burr holes or craniotomy.



What is an epidural abscess ?

- Cranial epidural abscess is a suppurative infection occurring in the potential space **between the inner skull table and dura**.

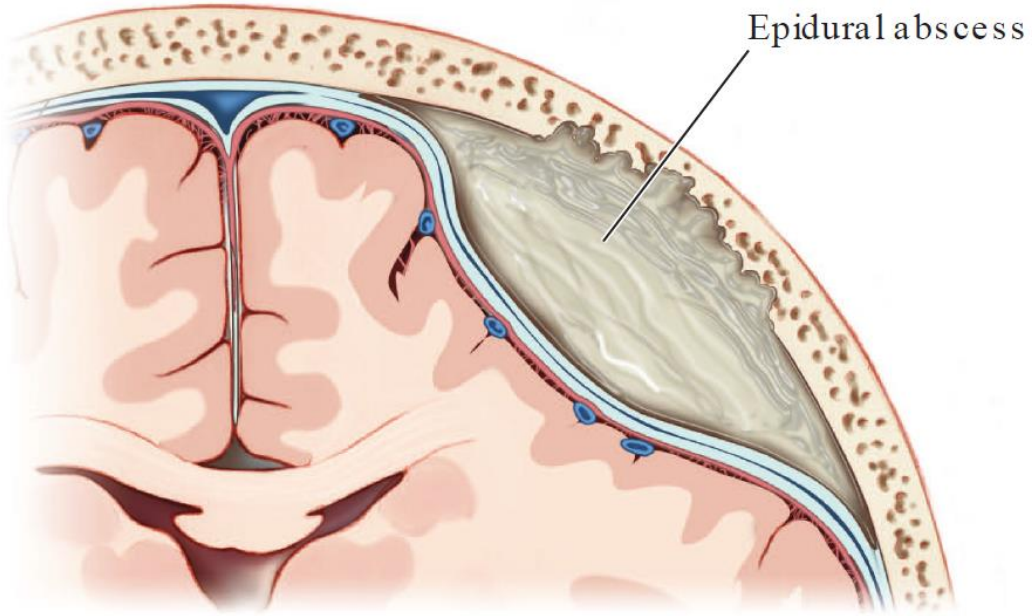


FIGURE 36-7
Cranial epidural abscess is a collection of pus between the dura and the inner table of the skull.

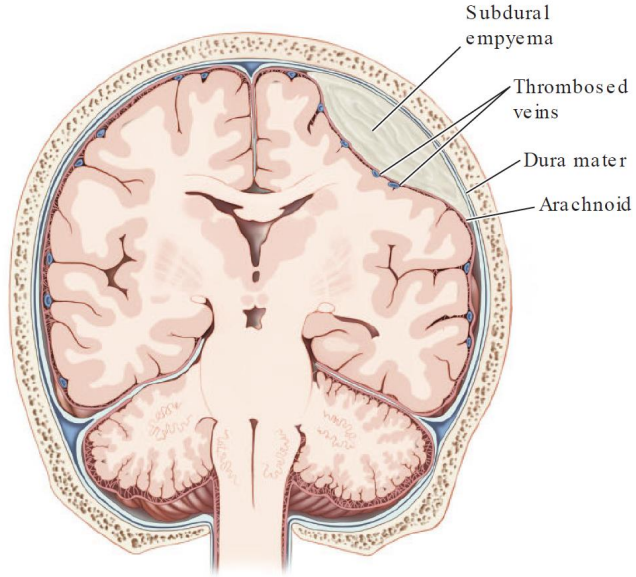
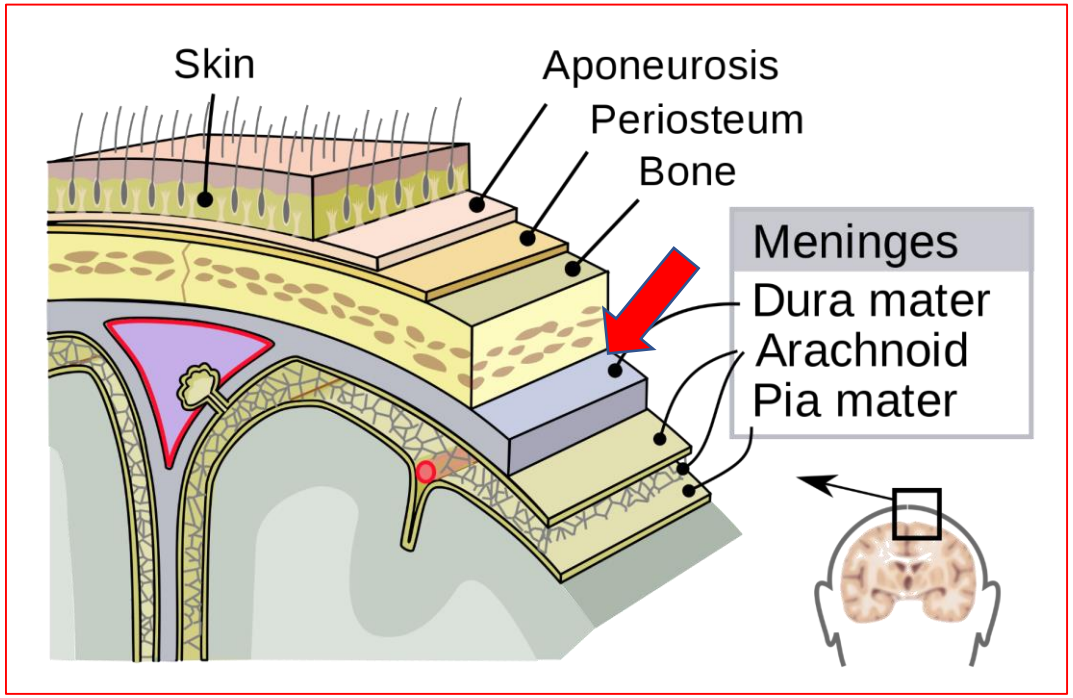


FIGURE 36-5
Subdural empyema.



What is an epidural abscess ?

- Similar routes of infection to other suppurative space occupying infections (but more commonly encountered after craniotomy procedures and cranial fractures. And **rarely hematogenous**)

- Presentation, diagnosis, Causative agents (and hence empiric treatment) are **similar to SDE**.

- Note that dura are tightly adherent to the skull, so an epidural abscess spreads **slower** than SDE, and is usually **smaller** in size. Moreover, focal neurological deficits are **uncommon** (5% of patients).

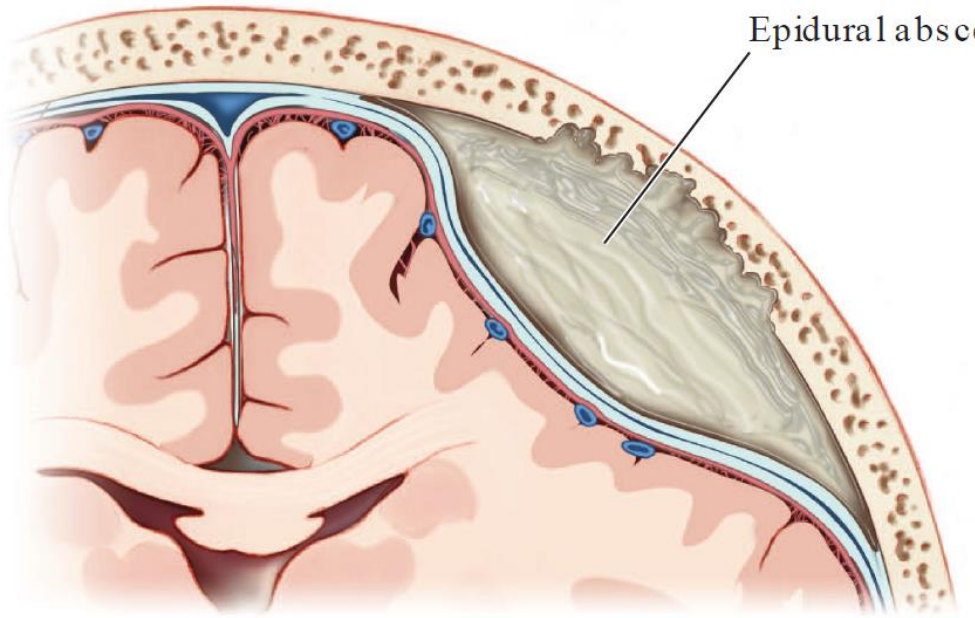


FIGURE 36-7
Cranial epidural abscess is a collection of pus between the dura and the inner table of the skull.

What is Suppurative intracranial thrombophlebitis?

- Suppurative intracranial thrombophlebitis is septic venous thrombosis of cortical veins and sinuses.
  Note: (**Thrombophlebitis** is a phlebitis (inflammation of a vein) related to a thrombus (blood clot))

- Commonly a **complication** of other CNS infections like bacterial meningitis; SDE; and epidural abscess. Or related to skin infections on the face.

- Veins draining infected meninges or sinuses can be damaged by the suppuration followed by clotting of those veins.

- Thrombosis may extend from one sinus to another, and at autopsy, thrombosis of different histologic ages can be detected in several sinuses

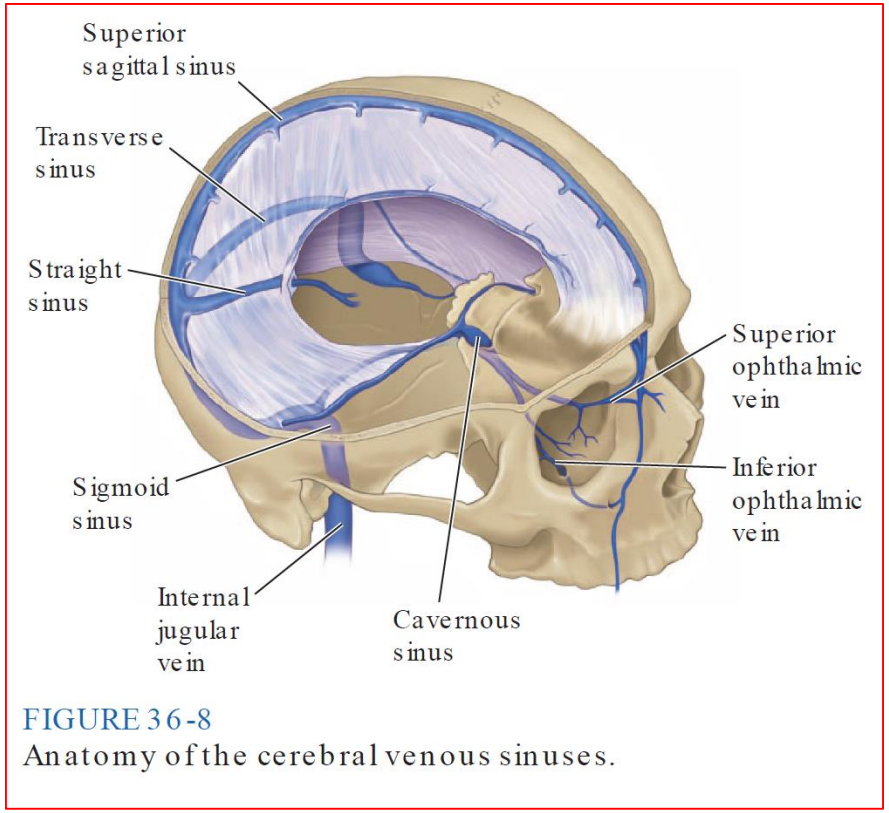
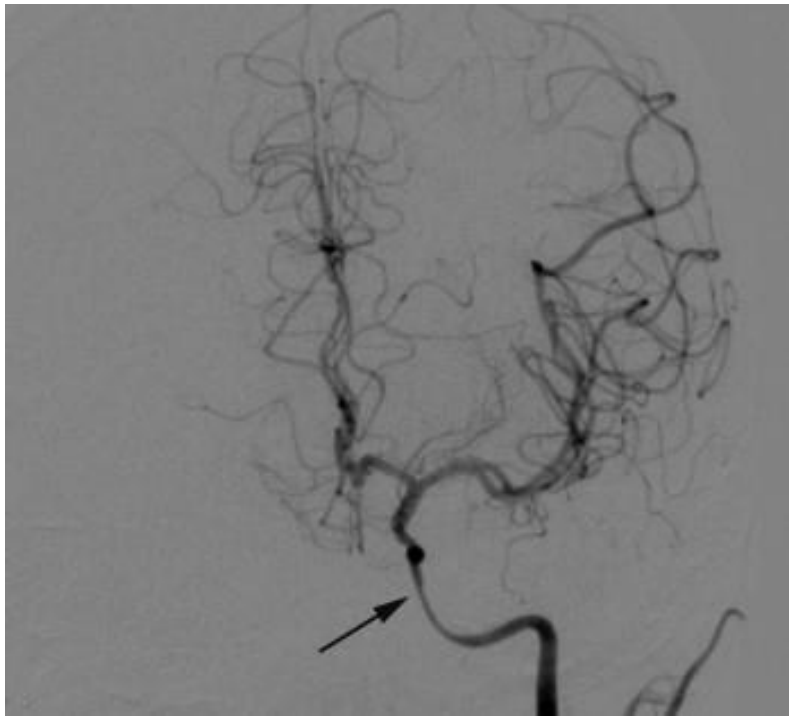


FIGURE 36-8
Anatomy of the cerebral venous sinuses.

How is Suppurative intracranial thrombophlebitis diagnosed and treated ?

- MRI can show decreased blood flow in the affected veins.
- Septic venous sinus thrombosis is treated with **antibiotics**, **hydration**, and **removal of infected tissue and thrombus**.
- **Anticoagulation** with dose-adjusted intravenous heparin is sometimes recommended.



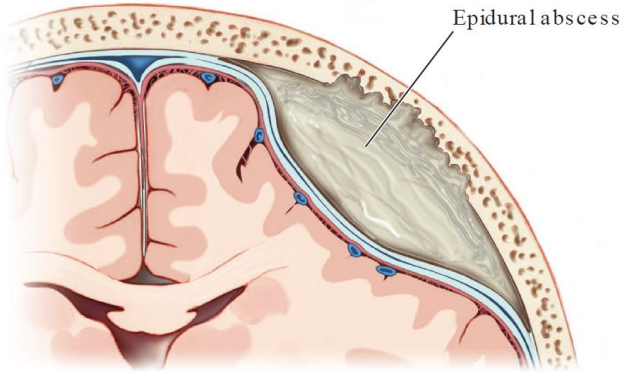


FIGURE 36-7
Cranial epidural abscess is a collection of pus between the dura and the inner table of the skull.

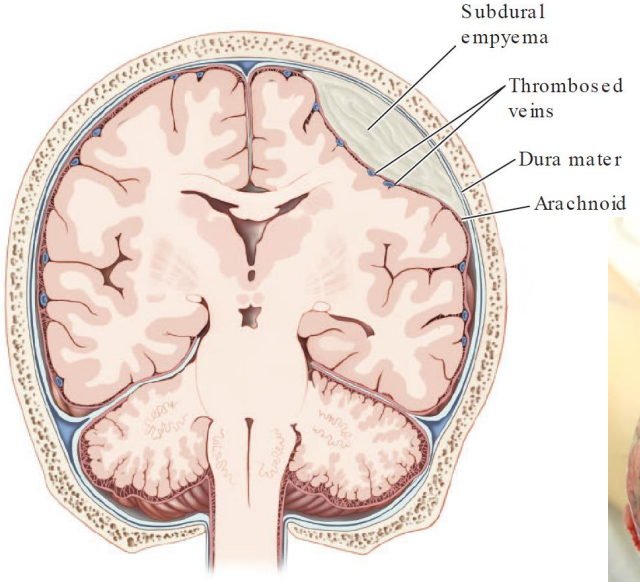
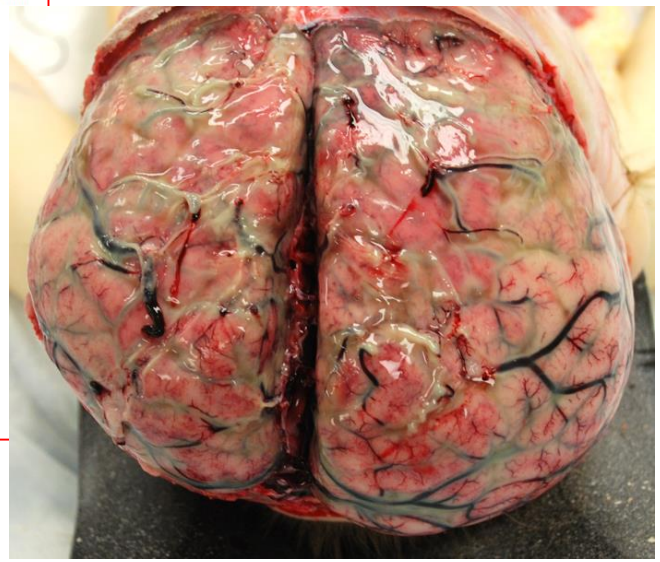
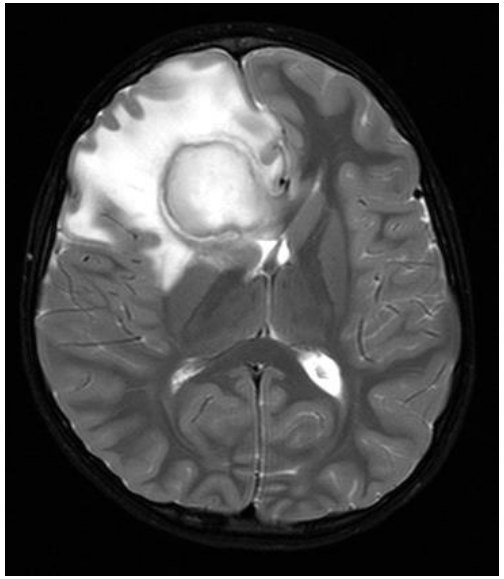
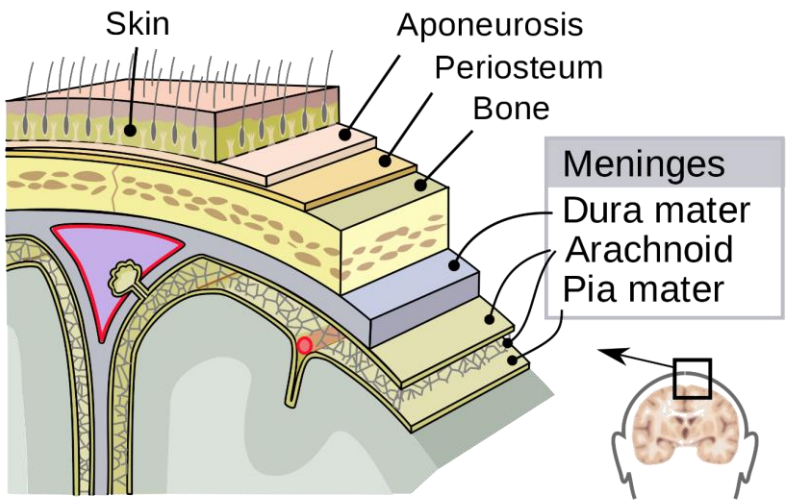


FIGURE 36-5
Subdural empyema.







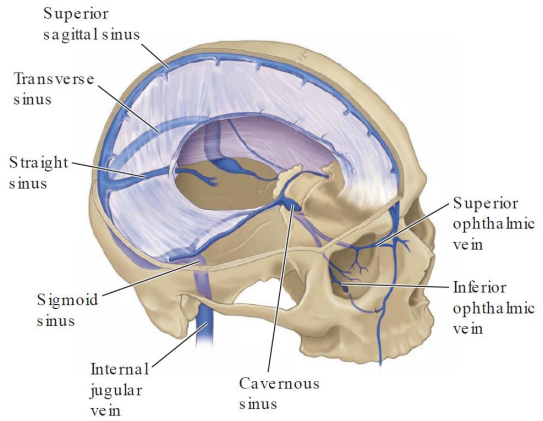


FIGURE 36-8
Anatomy of the cerebral venous sinuses.

Further reading:

- Oxford handbook of infectious diseases and microbiology-

Part4: Clinical syndroms

Chapter 19: Neurological infections

- Harrison's Infectious Diseases 3rd Edition

SECTION III Infections in organ systems

Chapter 36