MICROBIOLOGY

SHEET NO. 4

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Remember from the last lecture!

- Classical features of meningitis include fever, headache, meningism (neck stiffness, photophobia, positive Kernig's sign and Brudzinski's sign).
- They appears because of the inflammatory response in the brain
- Most common causes of bacterial meningitis varies among different groups of people, but generally they include N. meningitidis & S. pneumoniae, those spread through blood to the meninges

Viral menigitis

- We talked previously about the pyogenic meningitis, which is inflammation of the meninges associated with pus formation, caused by pyogenic bacteria that is called septic meningitis.

- Aseptic meningitis encompasses broad differential diagnoses related to inflammation of the meninges EXCLUDING pyogenic bacteria, they have similar symptoms to the septic meningitis.

- Aseptic meningitis can be caused by different causes both infective and non-infective, but viral meningitis is the most common etiology.

- The spectrum of non-infectious causes may include:

    1. Drug induced (e.g., amoxicillin, non-steroidal anti-inflammatory medications ortrimethoprim-sulfamethoxazole),
    2. Neoplastic,
    3. Neuro-sarcoidosis,
    4. rheumatoid arthritis,
    5. systemic lupus erythematosus,
    6. vasculitis (e.g., Kawasaki disease) (during the non-winter months)

- Viral meningitis (aseptic meningitis) has similar symptoms to bacterial meningitis (headache, fever, and signs of meningeal irritation), but is less severe than bacterial meningitis and rarely produces focal neurological defects and profound alterations in consciousness (meningoencephalitis) -because it's less likely to decrease the resorption of the CSF. Also, sequalae are less severe than those seen in cases of bacterial meningitis.

Common viral causes

- Enteroviruses are the leading cause of viral meningitis, e.g., echoviruses, Coxsackie viruses, enteroviruses 70 and 71.
- The mode of transmission of enteroviruses is feco-orally; after ingestion, they infect GI epithelial cells, followed by hematogenous spread to the CNS.

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

- Herpes simplex virus type 2 is considered as a common cause of viral meningitis, in contrast to type 1 which is a common cause of encephalitis
- Viral meningitis is more common than bacterial meningitis, but the bacterial meningitis is more severe and has higher morbidity and mortality rates than viral meningitis.
- Incidence is not clear but seasonal variations are found. (In temperate climates, there is a substantial increase in cases during the nonwinter months)

Specific viral presentations

- Enterovirus: In neonates, fever is seen 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 (pain and swelling in the parotid gland).
- VZV meningitis is also associated with a characteristic, diffuse vesicular rash, accompanied with meninges symptoms.
- HSV-2 meningitis presents with classical symptoms and existence of genital lesions.

Diagnosis

- Lumber puncture is used to examine the CSF.
- Viral culture can also be performed, through cultivating the virus with certain suitable types of cell lines, like the Rhesus Monkey cell line, then the cytopathic effects are observed.
  But it's time consuming and it is not very specific.
- Serology for enteroviral infections is possible by detection of enteroviral IgM antibodies, its specificity is also high.
- Hence, amplification of viral-specific DNA or RNA from CSF using Polymerase chain reaction (PCR) has become the single most important method for diagnosing CNS viral infections
- The table below summarizes the difference seen in CSF samples across the different causes of meningitis.

Test	*Bacterial*	*Viral*	*Fungal*	*Tubercular*
Opening pressure	Elevated	Usually normal	Variable	Variable
White blood cell count	≥1,000 per mm³	<100 per mm³	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.*

Notes regarding the table:

- In bacterial meningitis, there is overactivation of innate immunity (through the activation of PAMPs & DAMPs) leading to exaggerated rapid immune response, thus it's predominantly filled with PMNs.
- Meanwhile in viral meningitis, there is predominance of lymphocytes, because viruses need more time to replicate and cause disease (slower course) giving enough time for adaptive immunity to take over.
- Proteins and glucose are mostly normal (can be slightly elevated) unlike the bacteria.

Management

- 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.
- Viral meningitis don't need antibiotics, however, most doctors start antibiotic therapies before identifying the pathogen, because meningitis is an emergency, 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
- Treatment of almost all cases of viral meningitis is primarily symptomatic and includes use of analgesics, antipyretics and antiemetics. Fluid and electrolyte status should be monitored.
- NOTE: you must be sure that the patient is suffering from aseptic meningitis not bacterial, because the latter is deadly if not treated properly. For example, if you see meningitis along with petechial rash, increased protein and decreased glucose in the CSF sample but at the same time culture and gram stain yielded negative results. You might still want to give antibiotics, as it's a highly suspected case of meningococcemia.
- 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 somestudies

A CASE of aseptic 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?*

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.

Space-occupying brain lesions

- In this lecture we will talk about a group of diseases that form pus and occupy space within the brain. We call them suppurative space-occupying lesions.
- We expect to see general symptoms similar to those of meningitis such as headache and fever but because the meninges are not inflamed, we would not see meningeal signs (e.g. neck stiffness).
- Due to the mass effect within the brain, we would see increased intracranial pressure and focal neurological deficits depending on the specific location of the lesion.
- Taking a CSF sample would not be helpful in these diseases. Furthermore, if there is increased intracranial pressure lumbar puncture would be contraindicated anyway. Instead, for these diseases we mostly depend on brain imaging such as MRI and CT scans.

Brain abscesses

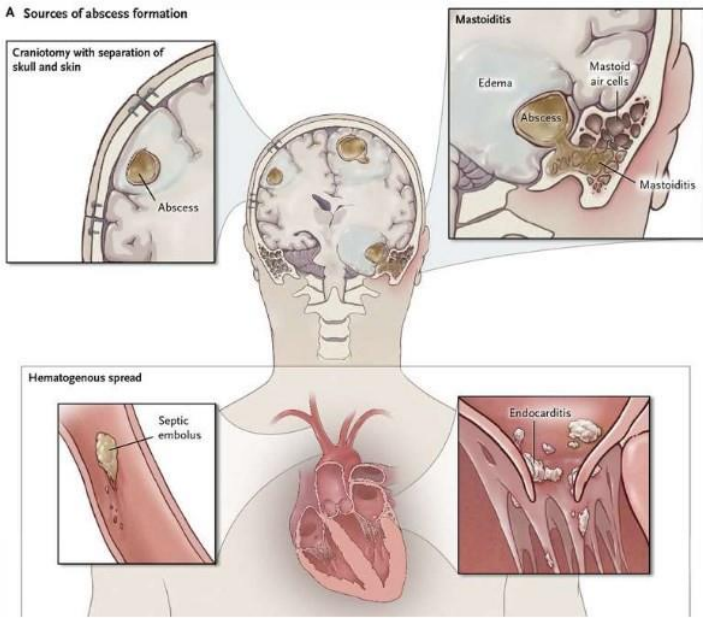
- A brain abscess is a focal, suppurative infection within the brain parenchyma, forming a cavity filled with dead and alive bacteria, white blood cells, and cell debris, typically surrounded by a vascularized capsule. The nearby brain parenchyma would also be edematous.
- Cerebritis is a similar lesion that has no capsule, and usually it precedes abscess formation
  ➔ The infection starts as cerebritis but with time it starts forming a capsule around itself, becoming a brain abscess.
- Brain abscess formation is rare in immunocompetent adults (less than 1 in 100,000 persons per year) unless there are some predisposing factors.

How do pathogens reach the brain?

- Similar to meningitis, pathogens can spread from nearby infections like in the ear, sinuses, and dental infections. If the infection persists for a long period in those sites it could infect the bone near them. For example, the mastoid bone is commonly infected in ear infections.
- They can also spread through blood vessels (hematogenous) or directly as in head trauma or cranial surgeries.

➲ The image below shows possible sources of infection.

1. Direct Inoculation of bacteria (possibly staph aureus) while the patient is undergoing craniotomy.
2. A septic embolus coming from another place such as pulmonary infections and
   -in cases of endocarditis- vegetations on cardiac valves. This septic embolus could go into the brain parenchyma, bypassing the blood brain barrier and forming an abscess.
   ➲ This can happen even in immunocompetent patients.
3. Hematogenous.
4. Mastoiditis.



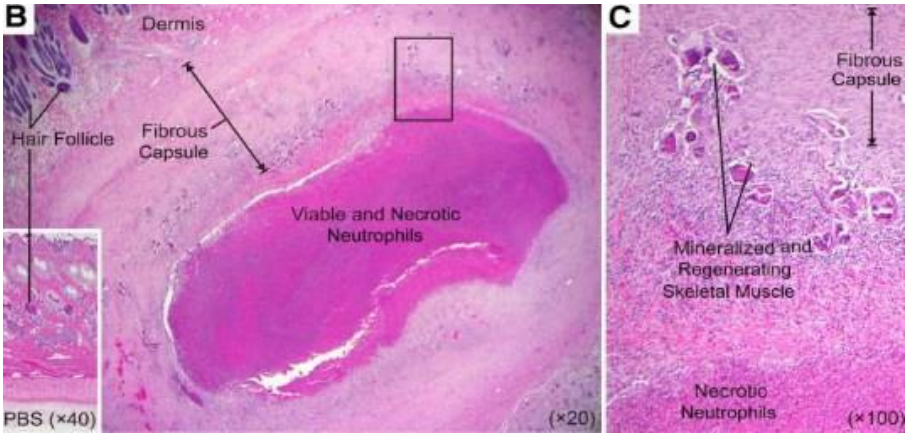
How does an abscess form?

❖ Basically, an invading organism gains access into an organ's parenchyma; for example, bacteria can get into the dermis of the skin or brain parenchyma.

❖ An immune response is mounted against this invading organism. Immune cells such as neutrophils try to eliminate the pathogen, and in that process, unintentional damage to nearby structures occur. This leads to the formation of a cavity filled with mostly dead neutrophils (because they have a short lifespan), alive and dead bacteria and white blood cells, cell debris and extracellular DNA from neutrophils (NETs).

❖ Eventually a capsule is formed around this cavity. With time the abscess matures and becomes walled off and extra septation within the abscess can take place.

❖ Due to the capsule formation, antibiotics would have poor penetrance into the abscess thus you first need to surgically drain the abscess then give antibiotics. Or, the abscess and capsule can be both removed.



Pathogens involved in brain abscesses

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

- In endocarditis the pathogen is usually S. aureus and streptococci.

- S. Aureus is commonly encountered after head trauma. As are other staphylococcus species, such as S. epidermidis.

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*

- With urinary tract conditions, we expect Enterobacteriaceae like E.coli.

- In immunocompromised patients, the spectrum is widened to include fungi such as C. neoformans and bacteria that aren't normally found in infections for immunocompetent patients such as L. monocytogenes, Nocardia.
  Nocardia spp., Toxoplasma gondii, Aspergillus spp., Candida spp. should be considered for these patients.

- Toxoplasma gondii should be considered in HIV patients

How do patients present?

- Headache, fever, seizures, and focal neurological signs are common.
  A focal neurologic deficit is a problem with nerve, spinal cord, or brain function that affects a specific location, such as the left side of the face, right arm, or even a small area such as the tongue. Speech, vision and hearing problems are also considered focal neurological deficits. It depends on location of the lesion.

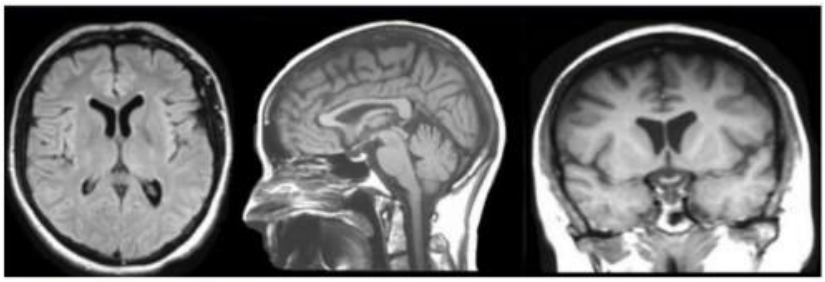
What to do as a doctor

- Non-invasive techniques such as brain imaging (MRI, CT scan with contrast) should be performed urgently to confirm the diagnosis and rule out meningitis.

- Remember! A lumbar puncture is contraindicated if there are focal symptoms or signs. And CSF samples wouldn't be beneficial for diagnosis anyway.

- Blood cultures can be positive in some patients (around 10%) and can help in the diagnosis (especially in cases of hematogenous spread).

- You can clearly see a lesion surrounded by a capsule. Depending on how the MRI is done, it can show different results, for example hypointense pus with hyperintense capsule or vice versa.



Normal brain MRI

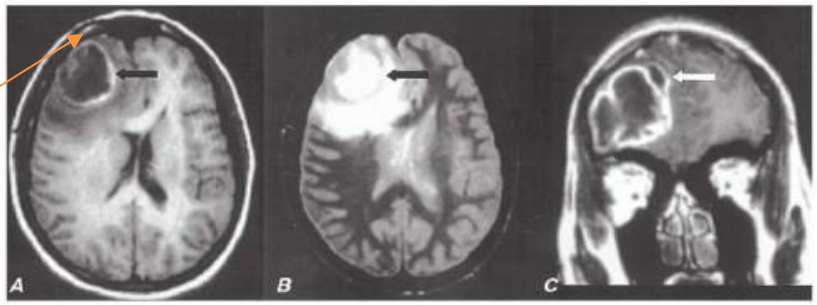


FIGURE 36-4
Pneumococcal brain abscess. Note that the abscess wall has hyperintense signal on the axial T1-weighted magnetic resonance imaging (MRI) (A, black arrow), has hypointense signal on the axial proton density images (B, black arrow), and enhances prominently after gadolinium administration on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

Treatment

- Treatment involves a combination of high dose parenteral antibiotics and neurosurgical drainage.
- Empiric therapy with 3rd generation cephalosporins (due to its good microbial coverage) can be started, in addition to antibiotics depending on suspicion. (e.g., History of recent head trauma or surgery increases chances of S. aureus, so 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.

For drainage we either do craniotomy or craniectomy. We first drain the abscess and then remove the capsule (to prevent recurrence of abscess). In some cases, we might leave the capsule in, especially if it's near important structures and there is risk of damaging them.

Here is a video from the slides showing how brain abscesses are drained: https://youtu.be/pZe8L4bScCE

Follow up and prognosis

- After abscess drainage and treatment, serial MRI or CT scans should be obtained on a monthly or twice-monthly basis to document total resolution of the abscess and make surethere is no recurrence.
- Enhanced neuroimaging techniques, improved neurosurgical procedures, and improvedantibiotics helped decrease mortality.
- In modern countries, the mortality rate is typically <15%.
- In ≥ 20% of the survivors, significant sequelae (due to loss of neurons) take place, including seizures, persisting weakness (hemiparesis & hemiplegia in the contralateral side in case of frontal lobe damage), aphasia, or mental impairment.

Subdural empyema (SDE)

- A subdural empyema is a collection of pus between the dura and arachnoid membranes.
- Has the same routes of spread as in brain abscesses. but most notable in cases of chronicsinusitis.
- SDE is a rare disorder that accounts for 15–25% offocal suppurative CNS infections. It has a striking predilection for young males. (more in males due anatomical differences in the sinuses between the two sexes)
- Pathogens, pathophysiology, and clinical presentation in SDE is similar to brain abscessesand other infectious space-occupying lesions.

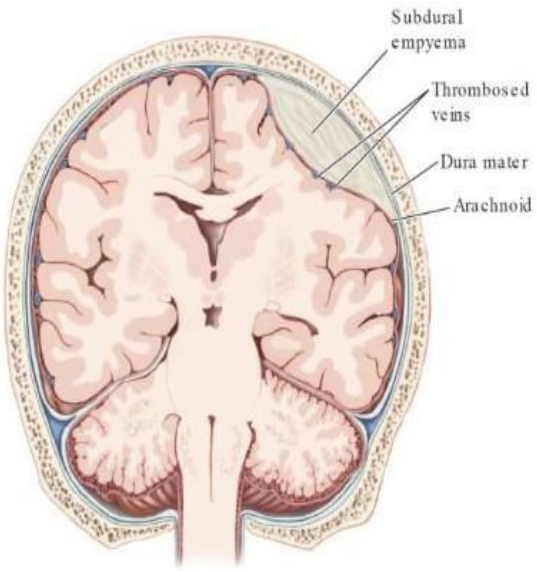


FIGURE 36-5
Subdural empyema.

- 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 (unlike epiduralabscesses which we will see next).

- 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 of venous infarction.

- 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.

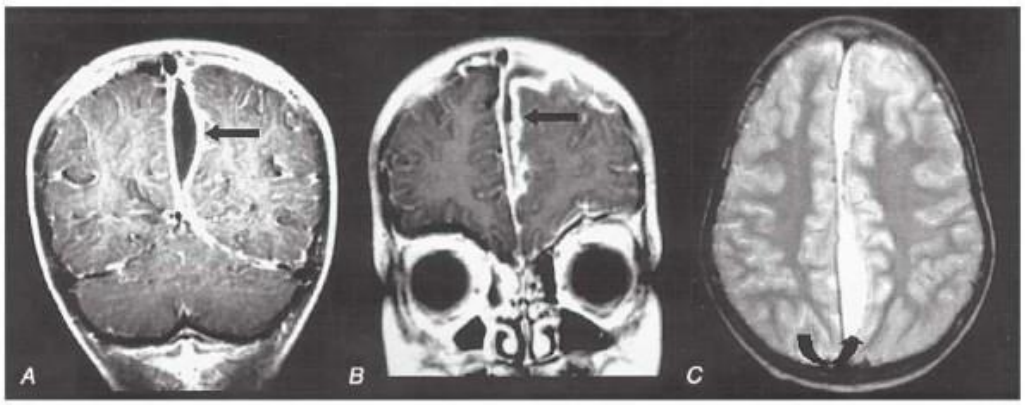


FIGURE 36-6
Subdural empyema. There is marked enhancement of the dura and leptomeninges (A, B, straight arrows) along the left medial hemisphere. The pus is hypointense on T1-weighted images (A, B) but markedly hyperintense on the proton density–weighted (C, curved arrow) image. (Courtesy of Joseph Iurito,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

SDE Treatment

- SDE is a medical emergency. Emergent neurosurgical evacuation of the empyema, either through craniotomy, craniectomy, or burr hole drainage, is the definitive step in the management of this infection.
- Empiric antibiotic therapy should include a 3rd generation cephalosporin, vancomycin (for staph) and metronidazole (for anaerobes such as Bacteroides). (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 NOT CSF.

Epidural abscess

- Cranial epidural abscess is a suppurative infection occurring in the potential space between the inner skull table and dura.
- Has similar routes of infection to other suppurative space occupying infections. It's more commonly encountered after craniotomy procedures, cranial fractures and nearby infected bones (but rarely due to hematogenous spread)
- Presentation, diagnosis, causative agents (and hence empiric treatment) are similar to SDE.

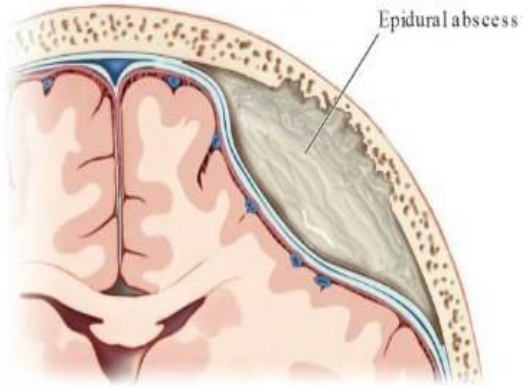


FIGURE 36-7
Cranial epidural abscess is a collection of pus between the dura and the inner table of the skull.

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

Suppurative Intracranial Thrombophlebitis

- Sometimes veins draining infected meninges or sinuses can be damaged by suppuration, followed by clotting of those veins. This forms what is known as suppurative intracranial thrombophlebitis.
  - ➲ Definition: Suppurative intracranial thrombophlebitis is septic venous thrombosis of cortical veins and sinuses. Note: (Thrombophlebitis is a phlebitis (inflammation of a vein) associated with a thrombus (blood clot)).
  - ➲ The thrombosis may extend from one sinus to another, and usually at autopsy, thrombosis of different histologic ages can be detected in several sinuses.
- It is commonly a complication of other CNS infections like bacterial meningitis, SDE, and epidural abscess. Or it may be related to skin infections on the face.

Diagnosis and treatment

- MRI of SITP can show decreased blood flow in the affected veins.
- For treatment: The primary infection must be treated and regarding the thrombus, it is treated with removal of infected tissue and thrombus, and then antibiotics and hydration.
- Anticoagulation with dose-adjusted intravenous heparin is sometimes recommended.

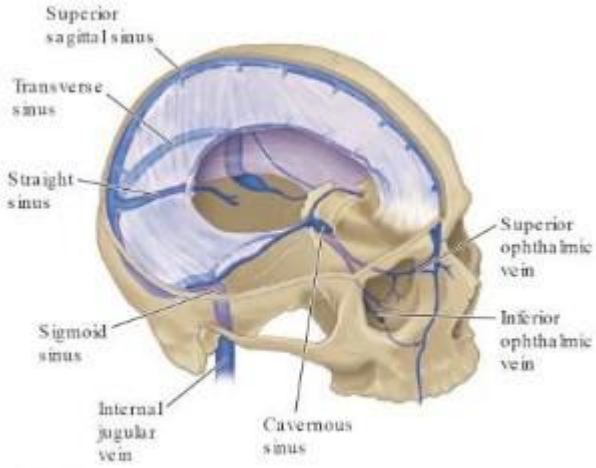
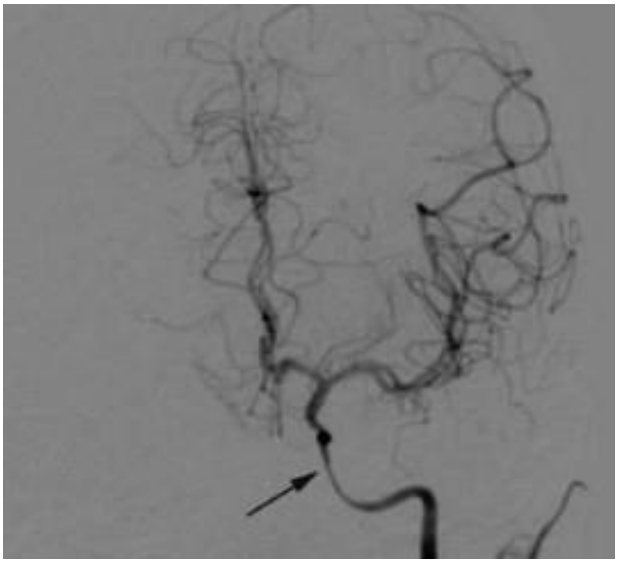


FIGURE 36-8
Anatomy of the cerebral venous sinuses.



GOOD LUCK