

CNS II

Microbiology Lecture II

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Aseptic meningitis

- Aseptic meningitis is an illness characterized by serous inflammation of the meninges, usually with an accompanying mononuclear pleocytosis (increased lymphocyte count in the CSF) with negative bacterial and viral cultures.
- Clinical manifestations vary, with headache and fever predominating.
- The illness is usually mild and runs its course without treatment (self-limited); however, some cases can be severe and life threatening.
- Viral infection is the most common form of aseptic meningitis, however there are other non-infectious causes such as drugs.



- Aseptic meningitis:

- Viral
- Bacterial
- Drug-induced:
 - Chemotherapy
 - NSAIDs
 - Antimicrobials most commonly Trimethoprim-Sulfamethoxazole, etc.
- Autoimmune diseases (SLE, Behcet's disease)
- Malignancy



Viral aseptic meningitis

- Enteroviruses
- Herpes simplex virus 2 (HSV-2)
- Mumps virus
- Human immunodeficiency virus (HIV)
- Lymphocytic choriomeningitis virus (LCMV)
- Adenovirus serotype 7 (a rare cause of meningitis in immunocompetent individuals but a major cause in patients with acquired immunodeficiency syndrome (AIDS))



Enteroviruses

- RNA viruses that belong to the Picornaviridae family.
- They are transmitted feco-orally; they are shed in stool.
- Enteroviruses are the most common cause of viral aseptic meningitis (>90%). However, they cause many other different diseases.
- Aseptic meningitis caused by enteroviruses occurs mainly during the summer and fall.
- Infants and young children are most affected.



Enteroviruses

- Classification
 - Polioviruses
 - Coxsackie viruses
 - Echo viruses
 - Enteroviruses



Classification

Table 1. Classification of human enteroviruses (HEVs) within the *Picornaviridae* family.

Genus	Species (No. of serotypes)	Serotypes
Enterovirus	PV (3)	PV serotypes 1, 2, 3
	HEV-A (17)	CVA serotypes 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16; EV-71, 76, 89, 90, 91, 92
	HEV-B (56)	CVB serotypes 1,2, 3,4,5,6, CVA9 Echo serotypes 1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 24, 25, 26, 27, 29, 30, 31, 32, 33; EV-69, 73, 74, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 93, 97, 98, 100, 101
	HEV-C (13)	CVA serotypes 1, 11, 13, 17, 19, 20, 21, 22, 24, EV-95, 96, 99, 102
	HEV-D (3)	EV-68, EV-70, EV-94

Note: HEV-A: human enterovirus group A; HEV-B: human enterovirus group B; HEV-C: human enterovirus group C; HEV-D: human enterovirus group D; CVA, coxsackievirus A group; CVB, coxsackievirus B group; Echo, echovirus; EV, enterovirus; PV, poliovirus; SVDV, swine vesicular disease virus (a variant of CVB-5).

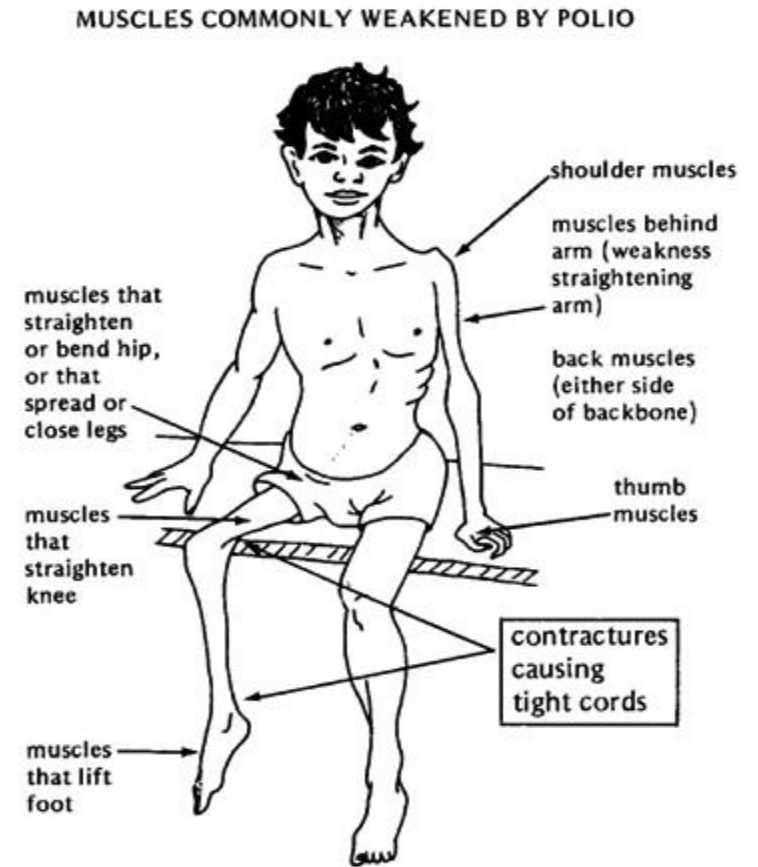


Spectrum of diseases

Enterovirus group	Mild disease	Severe disease
EV-A	HFMD Herpangina Onychomadesis Pharyngitis Diarrhea Respiratory symptoms –	NP-AFP Aseptic meningitis Encephalitis Death Pulmonary edema Neuromyelitis Optica Infant sepsis
EV-B	HFMD Herpangina Diarrhea Respiratory symptoms – – – – –	NP-AFP Aseptic meningitis Encephalitis Myocarditis Death Acute transverse myelitis Acute pancreatitis Papillitis Hepatitis
EV-C	HFMD Herpangina Acute hemorrhagic conjunctivitis Corneal endothelial dysfunction	NP-AFP Aseptic meningitis Hopkins syndrome –



- Enteroviruses that can cause meningitis:
 - Echovirus (especially Echovirus 30)
 - Coxsackie virus (A and B)
 - Enterovirus serotype 71
 - Poliovirus
- Enterovirus 71 can cause meningitis and/or encephalitis.



Poliovirus

- Poliovirus replicates in the intestinal tract and occasionally spreads to motor neurons of the spinal cord or brain stem.
- Most infections with poliovirus are **asymptomatic**. Poliovirus can also cause a minor illness characterized by fever, malaise, drowsiness, headache, and vomiting.
- About 4% of people infected with polio develop aseptic meningitis (**nonparalytic polio**).
- Less than 1% develop paralysis (**paralytic polio**). Paralysis occurs when poliovirus destroys anterior horn cells that innervate muscles of the arms and legs or cells of the brain stem that innervate muscles of respiration.
- Poliovirus incidence has decreased due to vaccination (OPV and IPV). It is part of our national vaccination program in Jordan.



Diagnosis (enteroviruses)

- Diagnosis of enterovirus infections is often clinical.
- Laboratory diagnosis can be achieved with:
 - CSF Polymerase chain reaction (PCR) (for detecting enteroviral RNA in CSF specimens, with a sensitivity of 100% and specificity of 97%.)
 - Viral isolation by cell culture (from CSF, blood, or feces samples)



Herpes simplex virus-2

- Large DNA enveloped virus belonging to the Herpesviridae family.
- Transmission is via contact with an infected area of the skin when the virus is active during sexual intercourse.
- HSV-2 causes genital herpes and aseptic meningitis.
- HSV-2 have been linked to **Recurrent Lymphocytic Meningitis (RLM)**. It is characterized by sudden attacks of meningitis symptoms that usually last for 2-7 days with unpredictable recurrences (symptom free intervals lasting for weeks, months or years). Symptomatic episodes of RLM usually subside within 5 years, but the total number of episodes may reach 30.
- The most important specific test on CSF is the polymerase chain reaction (**PCR for HSV-2 DNA**). Reported to be up to 98% sensitive and 100% specific.



Mumps



- RNA virus belonging to the paramyxovirus family.
- Transmitted via respiratory droplets and contact with infected saliva.
- Mumps usually causes parotitis, orchitis (inflammation of the testes), pancreatitis and aseptic meningitis.
- Aseptic meningitis occurs in up to 30% of patients with mumps, often without evidence of salivary gland disease.
- The incidence of mumps has decreased due to the live-attenuated vaccine (MMR).
- Diagnosis:
 - Mumps-specific IgM or IgG antibody titers from sera specimens.
 - PCR testing to detect viral RNA



Human immunodeficiency virus (HIV)

- Enveloped RNA virus that belongs to Retroviridae family.
- Transmitted by **sexual contact** or **parenteral route** (blood transfusion or intravenous drug use). HIV should always be suspected as a cause of aseptic meningitis in a patient with risk factors such as IV drug use or high-risk sexual behaviors.
- HIV meningitis:
 - Patients with **acute** HIV infection may present with aseptic meningitis mostly at the time of **seroconversion**; HIV spreads to the meninges hematogenously. These patients will have negative results on HIV serologic tests; the diagnosis is made by the detection of serum HIV RNA on PCR testing.
 - HIV infection also increases susceptibility to meningitis due to loss of immunity, including cryptococci, *M. tuberculosis*, syphilis, cytomegalovirus, varicella zoster virus, and *Listeria* species.



Lymphocytic choriomeningitis virus

- LCM virus is a member of the RNA arenavirus family.
- The modes of transmission include aerosols and direct contact with rodents. Outbreaks have also been traced to infected laboratory mice and hamsters.
- Cases tend to be more common in the winter.
- LCM virus causes asymptomatic to influenza-like to aseptic meningitis-type disease.



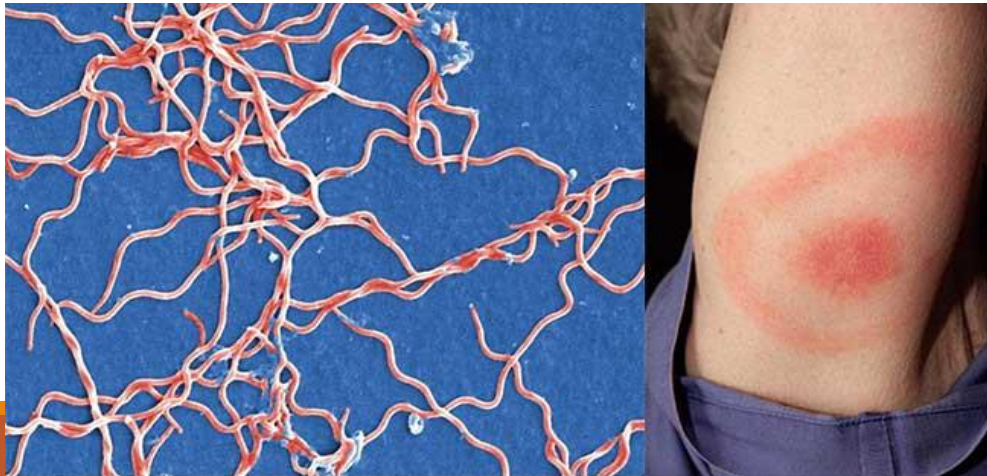
Bacterial causes of aseptic meningitis

- Partially treated purulent meningitis; it accounts for many meningitis cases with a negative microbiologic workup.
- *Borrelia burgdorferi* (lyme disease)
- *Treponema pallidum* (syphilis)
- *Leptospira* species (leptospirosis)
- *Rickettsia*, etc.



Lyme disease

- *Borrelia burgdorferi*, a tick-borne spirochete, is the agent of **Lyme disease**, the most common vector-borne disease in the United States.
- Transmitted by the *Ixodes* deer tick
- Aseptic meningitis is a prominent feature of the neurologic manifestations of Lyme disease. The main symptoms of neuroborreliosis are peripheral and cranial neuropathies.
- Lyme disease meningitis is typically associated with a facial palsy that can sometimes be bilateral.



Neurosyphilis

- *Treponema pallidum* is a slender, tightly coiled spirochete that is usually acquired by sexual contact.
- *T. pallidum* is the causative agent of **syphilis**.
- Aseptic meningitis occurs in syphilis, especially secondary syphilis.
- **Diagnosis of neurosyphilis** depends on a combination of:
 - Cerebrospinal fluid (CSF) tests (CSF cell count or protein)
 - A reactive CSF-VDRL
 - Reactive serum serologic test results (RPR or FTA-ABS)
 - Neurologic signs and symptoms.



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- **Chronic meningitis:**
 - Bacterial:
 - Tuberculous meningitis
 - Neurobrucellosis
 - Fungal Meningitis
 - Parasitic causes of meningitis
 - Neurocystocercosis



Chronic meningitis

- Chronic meningitis has a more insidious onset, with progression of signs and symptoms over a period of 4 weeks. The cellular response in the CSF reflects the **chronic inflammatory nature** of the disease.
- Chronic meningitis affects about 10% of patients diagnosed with meningitis.
- If a diagnosis is not made the illness progresses; the course is characterized by remissions and exacerbations and is most often fatal if untreated.



Tuberculous meningitis

- Tuberculous meningitis (TBM) is caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) and is the most common form of central nervous system (CNS) tuberculosis (TB). It is caused by *M. tuberculosis* is an acid-fast bacillus.
- It is spread through airborne droplets, and it infects one third of the world's population.
- Individuals with increased risk for TBM include young children with primary TB and patients with immunodeficiency caused by aging, malnutrition, or disorders such as HIV and cancer.



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- TBM is typically a subacute disease. In one seminal review, symptoms were present for a median of 10 days (range, one day to nine months) prior to diagnosis.
 - A prodromal phase of low-grade fever, malaise, headache, dizziness, vomiting, and/or personality changes may persist for a few weeks, after which patients can then develop more severe headache, altered mental status, stroke, hydrocephalus, and cranial neuropathies.
 - Seizures are uncommon manifestations of TBM in adults but are commonly seen in children with TBM, occurring in up to 50% of pediatric cases.
 - Classic features of bacterial meningitis, such as stiff neck and fever, may be absent.
 - TBM is associated with a high frequency of neurologic sequelae and mortality if not treated promptly.



Diagnosis (TBM)

- The diagnosis of TBM can be difficult and may be based only on clinical and preliminary cerebrospinal fluid (CSF) findings without definitive microbiologic confirmation. Common CSF findings include, CSF pleocytosis, elevated protein levels and low glucose.
- CSF sample should be sent for an acid-fast smear and culture. While culture can take several weeks and also has low sensitivity (~40–80%), it should be performed to determine drug susceptibility.
- A meta-analysis determined that commercial nucleic acid amplification assays utilizing polymerase chain reaction (PCR) for the diagnosis of TBM had an overall sensitivity of 56% and a specificity of 98%. Newer PCR tests amplify several target genes simultaneously and have been shown to result in much higher sensitivities in the range of 85%–95%.



Neurobrucellosis

- *Brucella species* are small gram-negative coccobacilli that cause brucellosis (الحمى المالطية).
- Transmission to humans occurs after direct exposure to infected animals (sheep, goats, or cattle) or their products (through intake of unpasteurized milk products).
- Infection of the CNS occurs in fewer than 5% of cases, with most patients presenting with aseptic or chronic meningitis.
- **Diagnosis of neurobrucellosis:**
 - Symptoms and signs consistent with neurobrucellosis; chronic meningitis.
 - Isolation of *Brucella* species from cerebrospinal fluid (CSF) culture
 - Presence of anti-*Brucella* antibodies in CSF and serum.
 - CSF analysis: lymphocytosis, increased protein, and decreased glucose levels.



Fungal meningitis

- *Cryptococcus neoformans*
- *Histoplasma capsulatum*: is one of the dimorphic fungi that exist in mycelial and yeast forms. It is usually found in soil and can occasionally cause chronic meningitis in **immunocompromised individuals**. It is an AIDS defining illness (CD4 count < 200).
- *Candida species, Coccidioides species, Blastomyces species, etc....*
- NOTE: fungi “fun-gee or fun-gai”



Cryptococcus neoformans

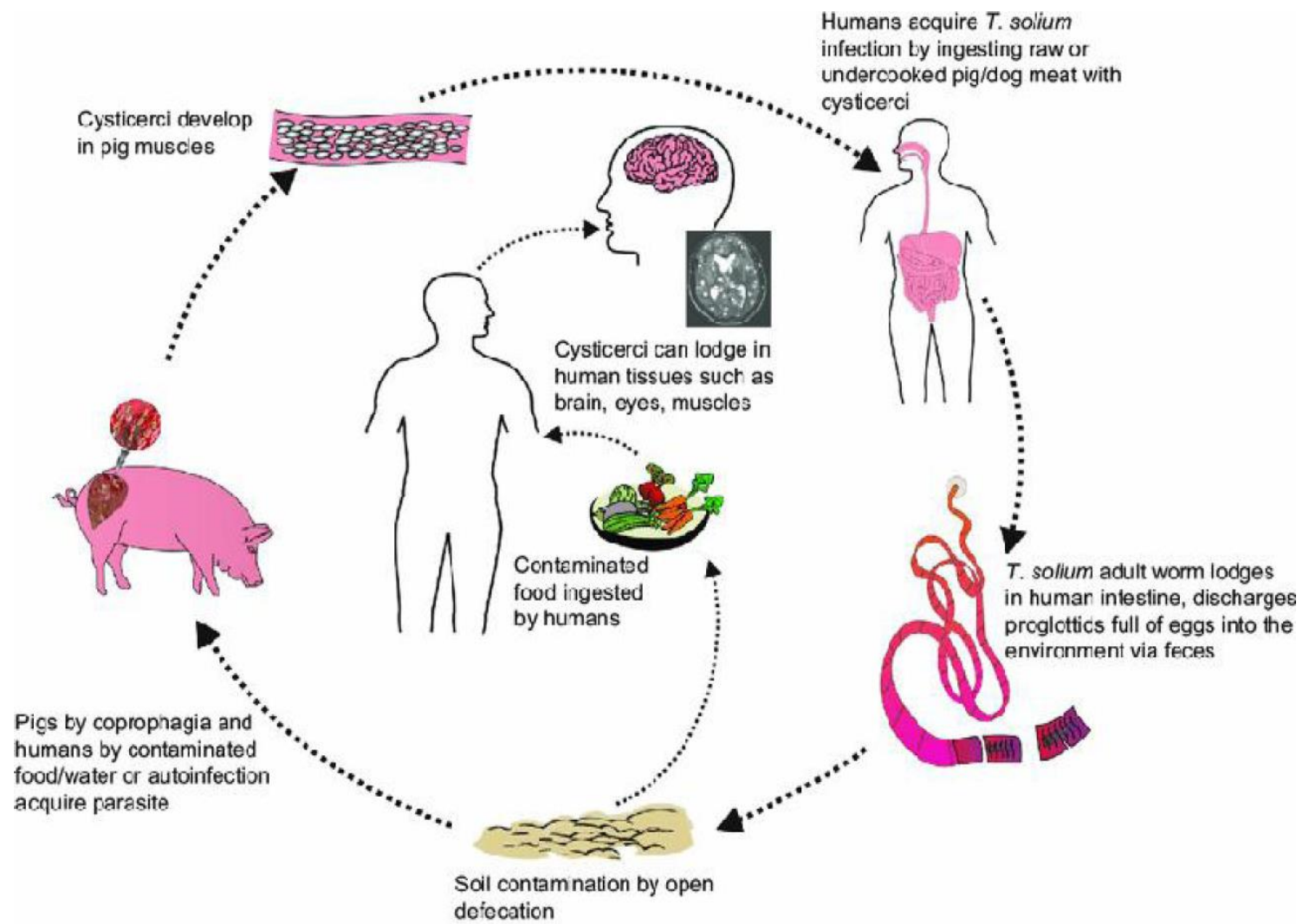
- *Cryptococcus neoformans* is an encapsulated, yeast-like fungus. *C. neoformans* polysaccharide capsule is the most potent virulence factor, which allows it to evade the immune system.
- It has been found in high concentrations in aged **pigeon** droppings and pigeon nesting places.
- *C. neoformans* continues to be an important cause of morbidity and mortality and is the **most common** central nervous system (CNS) mycosis in immunocompromised patients, particularly those with AIDS. Numerous cases occur in healthy hosts; however, approximately 50-80% of cases occur in immunocompromised hosts. It is considered as an AIDS defining illness (CD4 count < 200).
- Laboratory diagnosis is accomplished either by:
 - CSF cryptococcal antigen agglutination test has a high sensitivity of 92% in CSF
 - Visualization of the capsule upon direct examination of fresh cerebrospinal fluid (CSF) with **India ink stain**
 - Observing yeast-like cells on direct wet mount preparation.



Parasitic causes of chronic meningitis

- *Tenia solium*, a pork tapeworm, is responsible for cysticercosis, a disease that can affect subcutaneous, muscle, or central nervous system (CNS) tissue.
- Humans become infected after consuming undercooked food, particularly pork, or water contaminated with tapeworm eggs, or through poor hygiene practices.
- The parasitic infection is caused **by larval cysts** (enclosed sacs containing the immature stage of a parasite) of the pork tapeworm (*T. solium*). The larval cysts can infect various parts of the body causing a condition known as cysticercosis. Larval cysts in the brain cause a form of cysticercosis called neurocysticercosis which can lead to seizures.

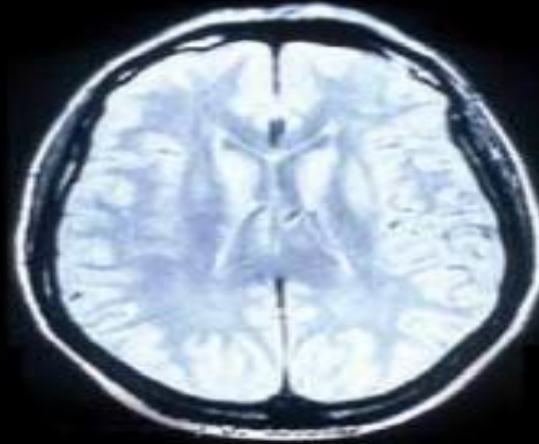




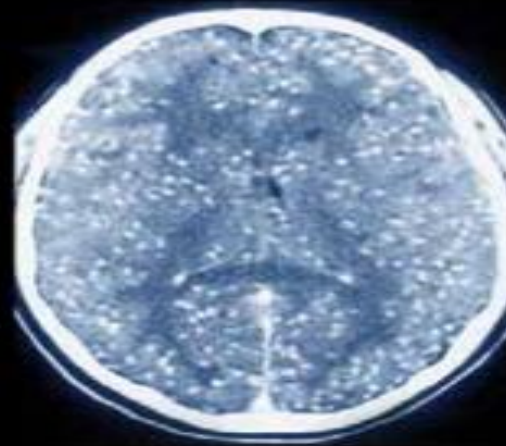
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- Neurocysticercosis is the most common parasitic infection of the CNS. It can be asymptomatic, but sometimes symptoms such as severe headache, seizures and vision changes. About half of patients who develop cysticercosis present with meningitis.
 - CSF findings usually include elevated protein levels, normal glucose levels, and eosinophilia.
 - Neurocysticercosis is commonly diagnosed with the routine use of diagnostic methods such as computed tomography (CT) and magnetic resonance imaging (MRI) of the brain.



Healthy brain



Brain of a patient with neurocysticercosis



MRI credit: Courtesy of Medscape Reference
<http://reference.medscape.com/features/slideshow/neurocysticercosis/>



Treatment of viral meningitis

- No specific treatment exists for most of the viruses that cause meningitis; therefore, management, for the most part, is supportive and includes analgesics (for fever and headaches), anti-nausea medications, intravenous fluids, and prevention and treatment of complications.



Treatment of chronic meningitis

Causative agent	Treatment
<i>Borrelia burgdorferi</i> (neuroborreliosis)	Ceftriaxone or penicillin
<i>T. pallidum</i> (neurosyphilis)	Penicillin G
Tuberculous meningitis	Antituberculosis therapy ± steroids
Fungal meningitis	Amphotericin B + flucytosine
<i>Tenia solium</i> (neurocysticercosis)	Albendazole ± surgical intervention



Prevention of meningitis

- Hand washing and other general good health measures may reduce the risk of developing an infection that can progress to meningitis.
- Prophylaxis is suggested for contacts of patients with meningitis (rifampin, ceftriaxone or ciprofloxacin).
- Vaccination.



Complications of meningitis

- Meningitis is a serious disease if left untreated. **Without treatment**, the case-**fatality rate** can be as high as 70 percent, and one in five survivors of bacterial **meningitis** may be left with permanent sequelae including hearing loss, neurologic disability, or loss of a limb.
- Immediate complications of meningitis include:
 - Septic shock
 - Disseminated intravascular coagulation (DIC)
 - Coma with loss of protective airway reflexes
 - Seizures, which occur in 30-40% of children and 20-30% of adults
 - Cerebral edema
 - Death



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- Delayed complications include the following:
 - Decreased hearing or deafness
 - Cranial nerve dysfunctions
 - Multiple seizures
 - Focal paralysis
 - Subdural effusions
 - Hydrocephalus
 - Intellectual deficits
 - Ataxia
 - Blindness



Thank you 😊

