

Managing CNS Infection Among Adults

Overview

■ Notable Diversity

- Range from common to rare
- Acute to chronic
- Trivial to fatal
- Some are self limited, easy to cure with modern treatment
- Some don't have specific treatment available

CNS Infection

■ Special characteristics

- Occur within a closed anatomic space
- Illness differs from that of infectious illness at other sites, even when the same organisms are the cause
- Associated with high mortality

CNS Infection

■ Four Cardinal Manifestations

- Fever
- Headache
- Alteration of mental status
- Focal neurologic signs

----- include age of the patient, locale, time of the year, and other epidemiologic factors.

CNS Infection

■ Important Characteristics

- Natural history
 - Temporal profile (predisposing factors, rate of progression, time to reach the peak of severity, time needed to respond to treatment, and the rate of resolution).
- Physical examination
 - Increased intracranial pressure
 - Meningeal irritation
 - Focal neurologic deficits

CNS Infection

■ Organisms

—Bacteria

—Fungi

—Viruses

—Parasites

—“Prions”

Mechanisms of disease

■ Direct invasion of neural tissue

■ Elaboration of toxic chemicals as TNF and cytokines

■ Induction of autoimmune response

■ Destruction of immune mechanisms

■ Elaboration of toxins

Approach to Patient with CNS Infection

■ Syndrome-Recognition Approach to Diagnosis

Acute Meningitis Syndrome

Sub-acute or Chronic Meningitis Syndrome

Acute Encephalitis Syndrome

Chronic Encephalitis Syndrome

Toxin-Mediated Syndrome

Encephalopathy with Systemic Infection

Postinfectious Syndrome

Slow Viral Disease

Space-Occupying Syndrome

CNS Infection

■ Manner of spread

—Direct invasion e.g. mastoid, penetrating skull wounds

—Phlebitis e.g. face to ophthalmic vein to cavernous sinus

—Hematogenous e.g. heart or lung to brain

—Lymphocyte as HTLV to brain

—Nerve as rabies, H. zoster

Approach to Patient with CNS Infection

■ Syndrome-Recognition Approach to Diagnosis

Acute Meningitis Syndrome

▪ Acute onset with fever, headache, photophobia, stiff neck, and altered mental state.

▪ Specific predisposing conditions

—Bacterial infection of the paranasal sinuses or mastoid, or a recent neurosurgical procedure

- Viruses (“aseptic meningitis”) and bacteria
- Acute Bacterial Meningitis
Acute Bacterial Meningitis

Bacterial Meningitis

- Acute purulent infection in the SAS that is assoc. with inflammatory reaction in the brain parenchyma and blood vessels
- Causes decreased consciousness, seizure activity, raised intracranial pressure, and stroke.

Bacterial Meningitis

- Most common etiologic organisms of community acquired bacterial meningitis.
 - Streptococcus pneumoniae
 - Neisseria meningitidis
 - Haemophilus influenzae type b
 - Gram negative bacilli (E. coli, klebsiella, pseudomonas aeruginosa, enterobacter)
 - Staphylococcus aureus

Acute Bacterial Meningitis

- Bacterial etiology of meningitis cases.

Organism	Adults (>15yrs), %)
S. pneumoniae	30-50
N. meningitidis	10-35
Gram (-) bacilli	1-10
Streptococci	5
Staphylococci	1-15
H. influenza type b	1-3

Antimicrobial Therapy

- Pneumococcal Meningitis

- Start with 3rd generation cephalosporin and vancomycin.
- If organism is sensitive to 3rd gen. cephalosporin, vancomycin can be discontinued.
- If intermediate or resistant to 3rd gen. cephalosporin, vancomycin is the drug of choice.
- Treated concomitantly with Dexamethasone and Rifampicin.
- 2 wks. course of IV treatment.

Antimicrobial Therapy

- Meningococcal Meningitis

- Start with Penicillin or ampicillin.
- If isolated organism is penicillin-resistant, cefotaxime or ceftriaxone should be used.
- 7 day course of IV therapy for uncomplicated cases
- For close contact, prophylaxis with a 2-day regimen of rifampicin (600mg. Q12 hrs.).
- Alternative – single 500mg oral dose of ciprofloxacin or single 500mg oral dose of azithromycin

Antimicrobial Therapy

■Adjunctive therapy with Dexamethasone.

- Inhibit the synthesis of inflammatory cytokines (interleukin and tumor necrosis factor) cause by bacterial multiplication and the lysis of bacteria by bactericidal antibiotics.
- Decrease CSF outflow resistance
- Stabilizing the blood brain barrier.
- Should be given before or together with antibiotic therapy.
- Given at 0.15mg IV q 6hrs. for 4 days.

Bacterial Meningitis

■Clinical Presentation:

- Fever, stiff neck, headache, lethargy, nausea, vomiting, and photophobia.
- Altered level of consciousness
- Seizure in approx. 40%
- Rash for meningococcal begins as a diffuse erythematous maculopapular that resembles a viral exanthem.
- Petechiae are found in the trunk and lower extremities in meningococcal occasionally on the palm and soles.

Bacterial Meningitis

Age group	Symptoms	Signs
Adult	fever, headache, lethargy, confusion or coma, nausea and vomiting, photophobia, respiratory symptoms	nuchal rigidity, altered level of sensorium, seizure, focal neurologic deficits, incl. CN palsy
Elderly	fever, confusion or coma, headache, respiratory symptoms	nuchal rigidity, altered level of consciousness, seizures – status epilepticus

Bacterial Meningitis

■Typical CSF findings in bacterial vs aseptic meningitis

CSF parameter	Bacterial meningitis	Aseptic meningitis
Opening pressure	>180 mm of water	normal to slightly elevated
Glucose	<40 mg/dl	>45 mg/dl
Protein	>50mg/dl	normal to elevated
WBC	>10 to <10,000 (neutrophils predominate)	50-2000/mm ³ (lymphocytes predominate)
Gram stain	(+) in 70-90% (untreated)	(-)
Latex agglutination	specific for antigens of s. pneumonia, n. meningitidis and h. influenza type b	(-)

Bacterial Meningitis

■ Recommended doses of antibiotics for bacterial meningitis in adults (15 yrs. and older)

Antibiotic	Total daily doses (dosing interval)
Penicillin G	20-24 miU/d (every 4 hrs.)
Ampicillin	12 g/d (every 4 hrs.)
Ceftriaxone	4 g/d (every 12-24 hrs.)
Cefatoxime	8-12 g/d (every 4-6 hrs.)
Ceftazidime	6 g/d (every 8 hrs.)
Vancomycin	2-3 g/d (every 8-12 hrs)
Nafcillin, oxacillin	9-12 g/d (every 4 hrs.)
Chloramphenicol	4 g/d (every 6 hrs.)
Gentamicin, tobramycin	5 mg/kg/d (every 8 hrs.)
Amikacin	15 mg/kg/d (every 8 hrs)

Bacterial Meningitis

■ Antimicrobial therapy in bacterial meningitis

Organism	Antimicrobial agent	Adverse Effects
Streptococcus pneumoniae	Ceftriaxone 4g/day (q12h)	Eosinophilia, biliary pseudolithiasis
	or	
	Cefotaxime 12g/day (q4h)	Nausea, vomiting + diarrhea
	Vancomycin 2g/day (q6-12h)	Leukopenia, eosin.
Neisseria meningitidis	Penicillin 20-24"mu"/d (q4h)	Rash
	Ampicillin 12g/day (q4h)	Maculopapular rash, nausea, vomiting

CNS Infection

■ Treatment of Increased Intracranial Pressure

- Head of the bed elevated to 30 degrees
- Hyperventilation to maintain PaCO₂ between 27 and 30 mm Hg
- Mannitol 20% 1g/kg bolus injection or 0.25 g/kg every 2-3 hours
- Pentobarbital
- Initial dose: 5-10mg/kg at a rate of 1 mg/kg/min.
- Maintenance dosage: 1-3mg/kg/h

Approach to Patient with CNS Infection

■ Syndrome-Recognition Approach to Diagnosis

Sub-acute or Chronic Meningitis Syndrome

- Course over weeks, months, or years
- Fever, headache, photophobia, stiff neck, and altered mental state.
- Focal neurologic findings are more common
- Tuberculosis, cryptococcosis, spirochetoses

Tuberculous Meningitis

- Meningoencephalitis cause by Mycobacterium Tuberculosis.
- Acid-fast bacteria seen in CSF sediment only in 5%-10%

- Culture are positive in less than 50%
- 1st few days of anti-TB therapy do not significantly affect the ability to culture M. tuberculosis from the CSF.
- Most promising diagnostic test is PCR

TB Meningitis

- Clinical presentation of patients with TB meningitis

Feature	among children	among adults
Headache	20-50%	50-60%
Nausea/vomiting	50-75%	8-40%
Apathy/behavioral	30-70%	30-70%
Seizures	10-20%	0-13%
Prior history of TB	55%	8-12%

TB Meningitis

Clinical staging of patients with tuberculous meningitis.

Stage I (early)	nonspecific symptoms and signs no clouding of consciousness no neurologic deficits
Stage II (intermediate)	lethargy or alteration in behavior meningeal irritation minor neurologic deficits (CN palsies)
Stage III (advanced)	abnormal movement convulsions stupor or coma severe neurologic deficits (paresis)

TB Meningitis

- General principles for the treatment of tuberculous meningitis.

- Multiple antimicrobial drugs are required
- Drugs must adequately cross the blood-CSF barrier.
- Drugs should be taken on a regular basis
- Drugs should be taken for a sufficient period to eradicate the CNS infection.

TB Meningitis

- Antimicrobial therapy.

- A four, first-line drug regimen of INH, rifampicin, and pyrazinamide with addition of streptomycin or ethambutol given for 2 months, followed by 10 months of INH and rifampicin.
- INH is bactericidal impairing DNA synthesis.
- Rifampicin is bactericidal impairing RNA synthesis.
- Pyrazinamide kill slowly metabolizing mycobacteria.
- Ethambutol and streptomycin are bacteriostatic

TB Meningitis

■ Penetration of antimycobacterial agents into the CSF

Agents	usual daily dose	Range of mean peak conc.mcg/ml		
		serum	CSF, (normal meninges)	CSF (inflamed meninges)
Isoniazid	5-10mg/kg/d	3 -5	0.6-1.6	2-3.2
Rifampicin	10-20 mg/kg/d	0.4-12	0	4-1.0
Ethambutol	15-25 mg/kg/d	1.0-7.7	0	0.5-2.5
Pyrazinamide	25-30 mg/kg/d	35-50	30	30-50
Streptomycin	15mg/kg/d (max 1 g)	25-50	trace	2-9

TB Meningitis

■ Antimicrobial therapy.

–Dexamethasone 12 to 16 mg/day for the first 1 to 2 months of therapy is recommended for severely ill patients.

–Increased intracranial pressure may respond to acetazolamide (30 mg/kg/day in 3 divided doses PO) to reduce CSF formation and possibly repeated LP. Or VP shunting.

–Seizures occur in approx. 50% is treated with Phenytoin at 300 mg/day.

TB Meningitis

Chemotherapeutic options for TB meningitis in adults

Low probability of drug resistance

Drugs	Dose	Frequency	Duration
A. Isoniazid	300 mg	daily	6 months
Rifampicin	600 mg	daily	6 months
Pyrazinamide	1.5 grams	daily	2 months
B. INH	300 mg	daily	9-18mos.
Rifampicin	600 mg	daily	9-18mos.
PZA	1.5 grams	daily	9-18mos.
C. INH	300 mg	daily	1 month
	900 mg	twice weekly	8 months
Rifampicin	600 mg	daily	1 month
600 mg		twice weekly	8 months

TB Meningitis

Chemotherapeutic options for TB meningitis in adults

2. High probability of drug resistance.

Drug	Dose	Frequency	Duration
INH	300 mg	daily	9-18 mos. Rifampicin
	600 mg	daily	9-18 mos.
PZA	1.5 grams	daily	9-18 mos.
Streptomycin	1 gram	daily	2 months
Ethionamide	15 mg/kg	daily	2-18 mos.

TB Meningitis

■Corticosteroid use in TB meningitis

Indication

- Stage 2 or 3 disease
- Impending or established spinal block

Doses

- Prednisone 60 mg/day or 1 mg/kg/day or
- Dexamethasone 8-16 mg/day in divided doses

Approach to Patient with CNS Infection

■Syndrome-Recognition Approach to Diagnosis

Postinfectious Syndrome

- Usual sequence begins with a common, often rather trivial, viral infection
- Most patients recover uneventfully
- Immunologic response to the etiologic microbe or to antigens
- Guillain Barre Syndrome, Postinfectious encephalitis, Postinfectious encephalomyelitis, transverse myelitis

Guillain-Barre Syndrome

- Acute inflammatory demyelinating polyneuropathy
- Autoimmune disease
- Most frequent cause of acute flaccid paralysis
- Rapid progressive, usually ascending, and symmetric paralysis of the extremities
- Loss of deep tendon reflexes
- Approx. 50% preceded by bacterial or viral illness
- Pathologic hallmark – perivenular mononuclear cell infiltrate with segmental demyelination

Guillain-Barre Syndrome

■Features that strongly supportive of GBS

- Rapid progression of motor weakness
- Symmetry of motor weakness
- Mild sensory symptoms
- Cranial nerve involvement
- Recovery ensues
- Autonomic dysfunction
- Albumino-cytologic dissociation
- Abnormal EMG-NCV

Guillain-Barre Syndrome

■Treatment

- Most patient require in-hospital observation
- Careful respiratory monitoring
- Vital capacity measured every 4 to 6 hrs.
- Elective intubation when VC falls 15 ml/kg of BW
- Weaning should not begin until VC is greater than 7 ml/kg BW
- Extubation when VC is 15 ml/kgBW
- Watch out for autonomic dysfunction
- Intensive care for UTI, GI hemorrhage
- Physical and occupational therapy

Guillain-Barre Syndrome

■Treatment

IVIg empirically set at 2 g/kg. dividing the total dose for infusion into 5 daily doses of 400mg/kg each. The rate of infusion should not exceed 200ml/hr or 0.08 ml/kg/min.

Plasma exchange (Plasmapheresis) given as second-line therapy in patient with relative contraindication to IVIg

Guillain-Barre Syndrome

■Prognosis

- Mortality rate remains at 5% to 10%
- Dysautonomia and respiratory failure
- Approx. 60% fully recover
- Older age, rapid progression to quadraparesis, and need for ventilatory support predict severe disease and prolonged or incomplete recovery.
- The most powerful predictor of severe disease and prolonged or incomplete recovery appears to be a low CMAP amplitude (0 to 20% of normal).

Fungal Meningitis

■Cryptococcus Neoformans

- Most common cause of FM
- Occurs through inhalation of small yeast form from the environment
- Usually affects immunocompromised patient
- Currently, 30% to 50% assoc. with AIDS
- Conclusive diagnosis by identification of the fungus in brain tissue or in the CSF

Cryptococcus Neoformans

■Clinical presentation.

- 90% cases have headache.
- 50% to 60% complain of fever, nausea and vomiting, altered mental status, and meningeal signs.
- 1/3 of patients have visual disturbances and cranial nerve palsies.

Cryptococcus Neoformans

■CSF findings:

- Increased opening pressure.
- Mononuclear pleocytosis, increased protein and low sugar.
- India ink stain positive in approx. 50%
- Culture positive in 75%
- Antigen in 90% to 95%

Fungal Meningitis

■Treatment for Cryptococcal Meningitis

-Antifungal drugs

▪Amphotericin B 0.7 to 10 mg/kg/day IV with

5-flucytosine 25 to 37.2 mg/kg/day until the patient is afebrile and CSF culture are negative usually after about 6 weeks of therapy and fluconazole initiated at 200 to 400 mg/day for 8 to 10 weeks.

Cerebral Malaria

■Mosquitoborne disease caused by four species of protozoa belonging to the genus of Plasmodium.

■Plasmodium falciparum

■Signs of cerebral dysfunction (impaired consciousness, seizures), hyperparasitemia, hyperthermia, severe anemia, renal failure, adult respiratory distress syndrome, and metabolic abnormalities.

Cerebral Malaria

■Pathogenesis of diffuse encephalopathy in cerebral malaria.

- Microvascular cytoadherence
- Severe anemia
- Hypoxia
- Metabolic derangements
- Hyperthermia
- "toxins"

Cerebral Malaria

■Diagnosis:

-History

- Travel to an endemic area.
- 95% of falciparum infections in nonimmune travelers become clinically apparent within 1 month of return from endemic area.
- Continuous fever with spikes at irregular interval
- Physical examination

- Splenomegaly and orthostatic hypotension
- Positive plasmodia parasite by thick and thin blood film microscopy.

Cerebral Malaria

■ Therapy

- IV quinidine gluconate at 10 mg (of base)/kg in normal saline (max. of 600 mg) given over 1-2 hrs. loading dose and then maintenance infusion of 0.02 mg/kg/min. continuous infusion until the parasitemia is less than 1% and the patient can tolerate oral medication.
- Oral quinine sulfate 650 mg q8hrs for 7 days
- Plus Doxycycline 100 mg bid for 7 days
- Or tetracycline 250 mg qid for 7 days
- Or clindamycin 900 mg tid for 5 days

Cerebral Malaria

■ Precautions:

- Continuous cardiac monitoring due to arrhythmogenic toxicity of the quinidine.
- If QT is prolonged at greater than 25%, stop infusion and restart when QTc return to less than 25%.
- IV fluid should contain glucose

Approach to Patient with CNS Infection

■ Syndrome-Recognition Approach to Diagnosis

Acute Encephalitis Syndrome

- Diffuse or focal
- Early abnormalities of mental status
- Seizures is common
- Herpes Simplex Encephalitis

Herpes Simplex Encephalitis

- Most severe in all viral infections of the human brain.
- Treatable viral disease
- High mortality of >70%
- Age, disease duration, and level of consciousness at the onset of therapy were proved to be the major determinants of clinical outcome.
- Institute treatment prior to onset of hemorrhagic necrosis of a dominant temporal lobe.

Herpes Simplex Encephalitis

- History, physical and neurological examination, MRI scan, and initial CSF profile form the basis to suspect possible viral encephalitis.
- Alteration of consciousness with focal neurologic findings, personality change, fever and seizure.
- CSF pleocytosis and proteinosis, elevated IgG
- Absence of bacterial and fungal pathogens in the CSF

- Focal EEG (periodic epileptiform discharges over the temporal region).
- MRI may show abnormality in the inferior frontal and temporal lobe
- Positive PCR for HSV

Herpes Simplex Encephalitis

■ Acute management:

- IV Acyclovir 10 mg/kg q 8hrs for a total of at least 14 days,
- Treat increased intracranial pressure
- Dexamethasone 0.15 mg/kg IV at first, followed by 0.25 mg/kg/day, given in divided doses every 6 hrs.
- Phenytoin for seizure control.

Approach to Patient with CNS Infection

■ Syndrome-Recognition Approach to Diagnosis

Chronic Encephalitis Syndrome

- Evolves over weeks to months or years
- Progress gradual to severe disability
- Relapses and recrudescences may occur over a long period
- Complications may develop during the course

Approach to Patient with CNS Infection

■ Syndrome-Recognition Approach to Diagnosis

Toxin-Mediated Syndrome

- Less likely to show the four cardinal manifestations of CNS infection
- Findings result from over stimulation of neural cells or interruption of neural transmission
- Tetanus and botulism

Approach to Patient with CNS Infection

■ Syndrome-Recognition Approach to Diagnosis

Encephalopathy with Systemic Infection

- Usually the manifestation of the primary disease dominate the clinical picture
- Consider whenever an undiagnosed CNS syndrome is under evaluation
- Rickettsial infections, infective endocarditis, typhoid fever, malaria, Whipple's disease

Approach to Patient with CNS Infection

■ Syndrome-Recognition Approach to Diagnosis

Slow Viral Diseases

- Insidiously over months or longer
- Slow progressive signs of neuronal destruction
- Often affecting motor function severely
- Do not become febrile and do not have signs of increased intracranial pressure or seizure
- Mortality is high

Approach to Patient with CNS Infection

■ Syndrome-Recognition Approach to Diagnosis

Space-Occupying Syndrome

- Results from a focal lesion and raised intracranial pressure
- Onset may be acute, subacute, or chronic
- Crisis may consist of
 - Focal to generalized seizure
 - Obtundation progressing to coma
- Cerebral abscess

Common manifestations of acute meningitis

- Fever, malaise, headache, photophobia, vomiting
- Leucocytosis
- Nuchal rigidity
- Stupor and coma
- CSF findings

Partially treated acute meningitis

- Antibiotics given without definite diagnosis
- Suboptimal dose
- Often in interrupted intervals
- CSF similar to TB
- Difficult to culture
- Diligent examination of Gram smear

Brain abscess

- Common foci – lungs, ear
- Polycythemia in children with congenital heart disease
- Marked edema
- Behave as a mass lesion
- Focal signs, high cranial pressure, convulsions, coma

Cerebral malaria

- Caused by *falciparum*
- Actual entry of parasite in brain capillaries
- Produce hemozoin that fluoresces with polarized light

Pathology of cerebral malaria

- Petechiae mostly in the *white matter*
- Multifocal perivenous demyelination
- Sludging of capillaries

Clinical features of cerebral malaria

- Acute onset
- Dominantly mental with mutism and reticence
- Seizures

■ Abrupt recovery with good response to therapy

Bacterial Meningitis

■ nasopharyngeal colonization local invasion bacteremia

meningeal invasion bacterial replication

increase SAS inflammation
permeability

inc. CSF outflow resistance

vasogenic cytotoxic hydrocephalus
edema edema

cerebral vasculitis

interstitial edema and or infarction

Increase intracranial pressure

Words of wisdom

■ “There are what it takes to be. Then we shall so be it because it was. To do or not to do is in the what now or what also, without which there never to you.”