ECHO Summary,28/MAR/2024
Session Title: Meningitis in Children & Adults

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Epidemiology

- Most common organisms in infectious meningitis
    - Bacterial: ***Streptococcus pneumoniae*****,** ***Haemophilus influenzae type b*** (mainly in young children), ***Neisseria meningitidis*****,** enteric bacilli (such as *Klebsiella pneumoniae* and *Eschericia coli*)
        - Organisms in bold are the most common bacterial etiologies
    - Viral: CMV, enteroviruses, mumps, HSV, VZV
    - *Cryptococcus neoformans* in immunosuppressed patients
    - *Mycobacterium tuberculosis* (MTB)[1]
- 60-80% of meningitis in sub-Saharan Africa is associated with HIV
    - Cryptococcal 60% of these cases
    - Tuberculosis 6-17% of these cases
- Autoimmune: lupus

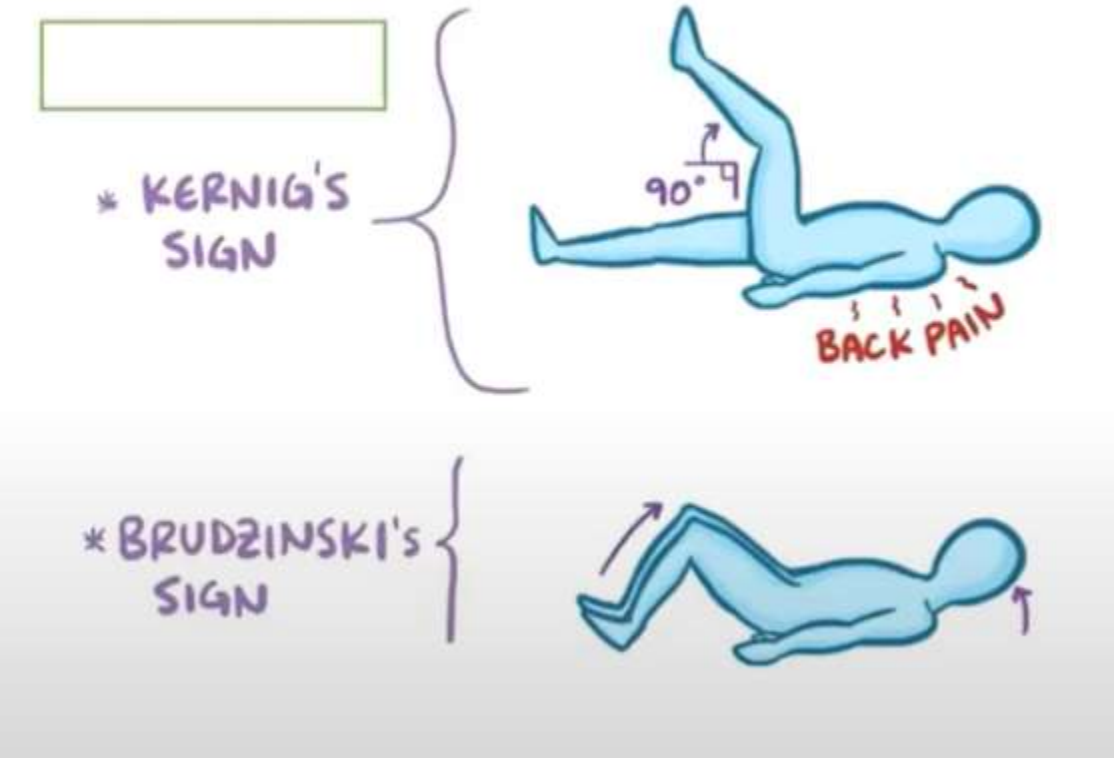
Risk Factors

- Meningitis belt - high prevalence
- Immunocompromised status, particularly HIV infection/AIDS
    - Patients with advanced HIV disease are at very high risk
        - CD4 < 200 + WHO stage 3 or 4 event
        - Age < 5 years with HIV disease regardless of CD4 count
    - CD4 < 100 is a risk factor for cryptococcal meningitis (CM)
- Children < 5 years of age, especially infants
- Malnutrition
- The elderly
- Cerebral malaria - nearly 30% of children with cerebral malaria have comorbid bacterial meningitis
- Overcrowding (for example, in refugee camps)

Clinical features

- **AIRWAY**:
    - Meningitis can lead to lethargy and seizures with subsequent failure to protect the airway
        - Secure the airway early if there is concern for inability to protect it!

        - Do not put anything in the mouth if the patient has altered level of consciousness
- **BREATHING**:
    - Several of the organisms that cause bacterial meningitis can also cause pneumonia
    - Assess breathing and SPO2
    - Listen to lung sounds and ensure that your antibiotic choices cover for concomitant pneumonia if that is present
- **CIRCULATION**:
    - Meningitis may present with vomiting and diarrhea, leading to dehydration and hypovolemic shock
    - Septic shock secondary to infectious meningitis may occur
    - Patients may need intravenous (IV) fluid resuscitation
- **DISABILITY**
    - AVPU - in children, determine whether they are **A**lert, responsive to **V**oice, responsive to **P**ain, or **U**nresponsive
    - Evaluate pupil size and reactivity
    - Look for neck stiffness, Kernig's and Brudzinski's signs



    - If patients have concomitant encephalitis or intracranial abscess, they may have focal neurologic deficits. Do a full neurologic exam, including cranial nerves, strength, sensation, reflexes, and evaluate for ataxia

    - Meningitis can cause hypoglycemia, especially in children. Check the glucose early, particularly if the patient is lethargic
- **EXPOSURE**:
    - Look for signs of trauma or exposure to toxins such as organophosphates that could suggest an alternate cause for symptoms
        - If there is toxin exposure, ensure appropriate decontamination to protect yourself and your staff
    - Fever is the most common presenting symptom children
        - Make sure to check a rectal temperature
        - Treat fever with antipyretics such as paracetamol (rectally if the patient is too altered to swallow oral medication)
    - Check for petechiae and purpura on skin exam - these may be signs of fulminant bacterial meningitis such as with *N. meningiditis*. CM may also present with skin lesions
- **GENERAL SIGNS AND SYMPTOMS**
    - Fever
    - Headache
    - Neck stiffness
    - Sensitivity to light and noise
    - Nausea and vomiting

Diagnostics

- Lumbar puncture (LP) is required for diagnosis but should NOT performed if any of the following contraindications are present
    - Increased intracranial pressure (ICP) - if patients have any of these history items/signs, they need a CT or MRI BEFORE LP. Performing an LP on a patient with increased ICP could lead to brain herniation and death
        - History of central nervous system (CNS) lesion, trauma, or shunt
        - Focal neurologic deficits
        - Papilledema
    - Coagulopathy
    - Hemodynamic instability (as they would be unlikely to tolerate LP)
- An opening pressure should be checked
- The following studies should be sent on CSF after LP
    - Gram stain and culture - this is the most important!
    - Cell count
    - Protein
    - Glucose
    - +/- India ink stain, cryptococcal antigen if suspicion for *Cryptococcus neoformans*
        - Culture is the gold standard since the antigen test can’t distinguish current from prior infection
    - +/- MTB Xpert/Ultra, MTB culture, Ziehl–Neelsen stain
- Test for coinfection with malaria, HIV

- If suspicion for MTB, consider chest x-ray, brain imaging, or abdominal ultrasound, as indicated

	Normal	Bacterial	Viral	Fungal/TB
Pressure (cmH20)	5-20	> 30	Normal or mildly increased	
Appearance	Normal	Turbid	Clear	Fibrin web
Protein (g/L)	0.18-0.45	> 1	< 1	0.1-0.5
Glucose (mmol/L)	2.5-3.5	<2.2	Normal	1.6-2.5
Gram stain	Normal	60-90% Positive	Normal	
Glucose - CSF:Serum Ratio	0.6	< 0.4	> 0.6	< 0.4
WCC	< 3	> 500	< 1000	100-500
Other		90% PMN	Monocytes 10% have >90% PMN 30% have >50% PMN	Monocytes

- Specific parameters that raise concern for CM

— CSF opening pressure not useful to distinguish meningitis cause but often elevated in CM patients (can be normal)

— Total CSF white cell count is of limited use for immunocompromised (HIV+) patients: it may be below 10 cells/ul or 10-500 cells/ul

— CSF glucose levels may be normal or low

— CSF protein levels may be normal or slightly elevated

— Low CSF WBC may be a poor prognostic sign

Treatment

- Prioritize ABCDE
    - Airway - secure the airway if necessary and do not put anything in the mouth if the patient is altered

- Breathing - treat hypoxia or labored breathing with oxygen as necessary
- Circulation - obtain IV access and address shock
- Disability -
  - Treat seizures with benzodiazepines (use rectal diazepam 0.5 mg/kg/dose if IV access is not present)
  - If signs of increased ICP
    - Elevate the head of the bed 30 degrees
    - Give hypertonic saline or mannitol (+/- hyperventilation - this is not a long-term solution)
- Exposure - remove tight clothes. Control body temperature

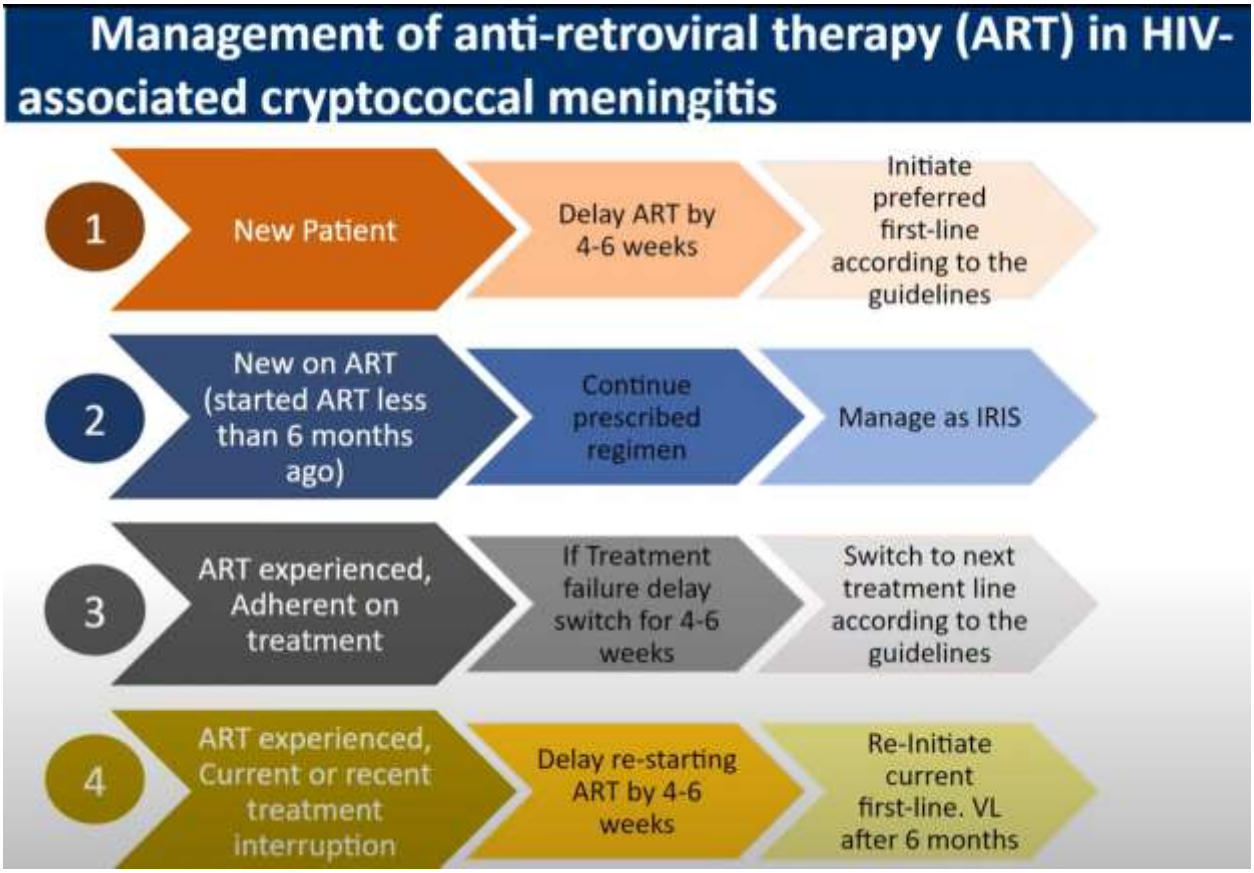
- Antibiotics
  - Proceed with treatment if there is high suspicion for meningitis, even if LP cannot be performed due to one of the contraindications above
  - Proceed with treatment before LP if there is going to be a significant delay in performing the LP (i.e. need to transfer to a higher level of care)
  - Per national guidelines:
    - First-line
      - Adult - ceftriaxone 2 g IV or IM every 12 hours for 10-14 days
      - Child - ceftriaxone 100 mg/kg IV or IM every 12 hours for 10-14 days
      - Neonate -
        - Ampicillin IV
          - < 7 days: 50-100 mg/kg every 12 hours
          - > 7 days: 50-100 mg/kg every 8 hours
        - PLUS gentamicin 2.5 mg/kg IV every 12 hours
    - Alternative therapy if ceftriaxone is unavailable OR the patient is not improving
      - Adult - chloramphenicol 1 g IV every 6 hours for up to 14 days (IV is preferred over IM)
        - Once clinically improving, can change to 500-750 mg orally every 6 hours to complete the course
      - Child - chloramphenicol 25 mg/kg IV every 6 hours for up to 14 days (IV is preferred over IM)
    - **Ongoing antibiotic therapy should be tailored to the specific organism identified**
      - *Streptococcus pneumoniae* - 10-14 day course; up to 21 days in severe case)
        - First-line
          - Adult - benzylpenicillin 3-4 MU IV or IM every 4 hours
          - Child - benzylpenicillin 100,000 IU/kg per dose
        - Alternative therapy
          - Adult - ceftriaxone 2 g IV or IM every 12 hours
          - Child - 100 mg/kg daily dose

- *Haemophilus influenzae* - 10 day course
    - First-line
        - Adult - ceftriaxone 2 g IV or IM every 12 hours
        - Child - 100 mg/kg per dose
    - Alternative therapy if the organism is not susceptible to ceftriaxone
        - Adult - chloramphenicol 1 g IV every 6 hours OR ampicillin 2-3 g IV every 4-6 hours
        - Child - chloramphenicol 25 mg/kg per dose OR ampicillin 50 mg/kg per dose
- *Neisseria meningitidis* - up to 14 day course
    - First-line
        - Adult - Benzylpenicillin IV 5-6 MU every 6 hours OR ceftriaxone 2 g IV or IM every 12 hours OR Chloramphenicol 1 g IV every 6 hours (IM if IV not possible)
        - Child - 100,000-150,000 IU/kg every 6 hours OR ceftriaxone 100 mg/kg daily dose OR chloramphenicol 25 mg/kg IV per dose
    - Once clinical improvement occurs
        - Adult - change to chloramphenicol 500-750 mg orally every 6 hours to complete the course
        - Child - change to chloramphenicol 25 mg/kg per dose
    - Consider prophylaxis of close contacts (especially children < 5 years). See guidelines for details, page 110 - chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.health.go.ug/wp-content/uploads/2023/11/UCG-2023-Publication-Final-PDF-Version-1.pdf
- *Listeria monocytogenes* - at least 3-6 week course
    - Adult - benzylpenicillin 3 MU IV or IM every 4 hours OR ampicillin 3 g IV every 6 hours
- Group B streptococci (in the neonate) - 3 week course
    - Benzylpenicillin 100,000-150,000 IU/kg IV every 4-6 hours
    - Neonates <7 days: 50,000-100,000 IU/kg IV every 8 hours PLUS gentamicin 2.5 mg/kg IV every 12 hours[1]
- *Cryptococcus neoformans*
    - Induction - 2 weeks
        - Note that flucytosine needs renal dose adjustment and is a pregnancy category C. Patients need close monitoring of complete blood count, creatinine, and electrolytes
    - Consolidation - 8 weeks
    - Maintenance - at least 1 year PLUS CD4 ≥ 200

Uganda Treatment Protocols for CM (1/2)

Phase	Drug	Comments
	Newly Diagnosed Patient	
Induction Phase (2 weeks)	**Recommended:** SINGLE high dose Amphotericin B liposomal (10mg/kg) AND Flucytosine (100mg/kg/day in four divided doses) + Fluconazole 1200mg/day for 14 days Or Amphotericin B deoxycholate (1mg/kg/day) + Flucytosine (100mg/kg/day in four divided doses) for 1 week, followed by 1 week of fluconazole (1200 mg/day for adults, 12 mg/kg/day for children and adolescents). Or Fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents) + Flucytosine (100 mg/kg/day, divided into four doses per day for 14 days. Or Amphotericin B deoxycholate (1mg/kg/day) + high-dose Fluconazole 1200mg/day for 14 days Alternative: Fluconazole 1200mg/day (or 6-12mg/kg/day in children)	**Preventing Amphotericin toxicity:** To prevent nephrotoxicity and hypokalaemia, do the following: · Pre-hydration with 1L normal saline before starting the daily Amphotericin dose. · Monitor serum potassium and creatinine levels at initiation and at least twice weekly to detect changes in renal function. · Routine administration of 40 mEq/day of potassium chloride can decrease the incidence of Amphotericin-related hypokalemia. · Consider alternate day Amphotericin if creatinine is >3mg/dl.
Consolidation phase (8 weeks)	Fluconazole 800mg/day (or 6-12mg/kg/day in children and adolescents)	Initiate ART 4–6 weeks after starting CM treatment and there is clinical response to antifungal therapy.
Maintenance Phase (18 months)	Fluconazole 200mg/day (or 6 mg/kg/day up to 200mg in children and adolescents)	Criteria to stop after a minimum of 18 months of maintenance phase: Adults: VL<1,000 copies/mm^3 & CD4 ≥ 200 or CD4 ≥200 (if viral load not available) after 12

- Raised ICP in CM
  - If opening pressure ≥ 25 mmHg, need therapeutic LP daily until pressure is normalized/symptoms have improved for 2 days
  - Do not remove ＞30 mL at a time, and check pressure every 10 mL



- MTB
    - Anti-MTB therapy PLUS corticosteroids (dexamethasone 0.4 mg/kg in the first week, 0.3 mg/kg the second week, then transition to oral steroids)
- See guidelines regarding the management of MTB (page 252) and for more details regarding *Cryptococcus neoformans* (page 255) - chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.health.go.ug/wp-content/uploads/2023/11/UCG-2023-Publication-Final-PDF-Version-1.pdf

Complications

- Seizures and hypoglycemia, as above
- Encephalitis
- Brain abscess
- Especially with CM - cranial nerve deficits (particularly CN VI), hearing loss

Disposition

- All patients with meningitis should be admitted to a capable hospital

Collaborating Partners

1. Ministry of Health of the Republic of Uganda
2. Seed Global Health
3. Techies Without Borders

Reference

The Republic of Uganda Ministry of Health. *Uganda Clinical Guidelines 2023: National Guidelines for Management of Common Health Conditions*. Accessed May 11, 2024. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.health.go.ug/wp-content/uploads/2023/11/UCG-2023-Publication-Final-PDF-Version-1.pdf