5. ACUTE AND SUB-ACUTE/CHRONIC MENINGITIS

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Background

Meningitis is a common presentation in patients with HIV. Clinical features are varied, and patients may be unable to provide a reliable history, which complicates diagnosis and management. This chapter covers both acute and chronic presentations with a suggested approach to investigation and management.

Determine whether the clinical features are compatible with meningitis

Meningitis is typically defined as any 2 of: fever, headache, neck stiffness, and confusion; but other features may occur such as a rash, photophobia, and seizures.

Meningitis is often life threatening, particularly in patients with HIV, and in general there should be a low threshold for investigating for meningitis. Patients with more chronic forms of meningitis have an increased likelihood of atypical presentations and there should be an even lower threshold for investigating such patients.

There is overlap between the presentation and causes of meningitis and encephalitis, so it is important to consider this approach in conjunction with the approach to a patient with altered mental state (see **Chapter 7**).

Determine the duration of symptoms

A rough guide in deciding whether this is acute or sub-acute/chronic meningitis is the duration of symptoms – if <7 days, acute meningitis is more likely; if ≥7 days sub-acute/chronic meningitis is more likely. But remember exceptions do occur. Deciding on acute vs chronic meningitis and impacts the differential diagnosis and aspects of investigation.

Approach to acute meningitis

Differential diagnosis

The differential diagnosis is broad and it is difficult to predict aetiology on clinical grounds alone. Table 5 shows possible infectious causes. *Mycobacterium tuberculosis* and *Cryptococcus neoformans* usually cause chronic meningitis but an acute presentation can sometimes occur. The median duration of TB meningitis symptoms is 12 days, and it is rarely less than 4 days.

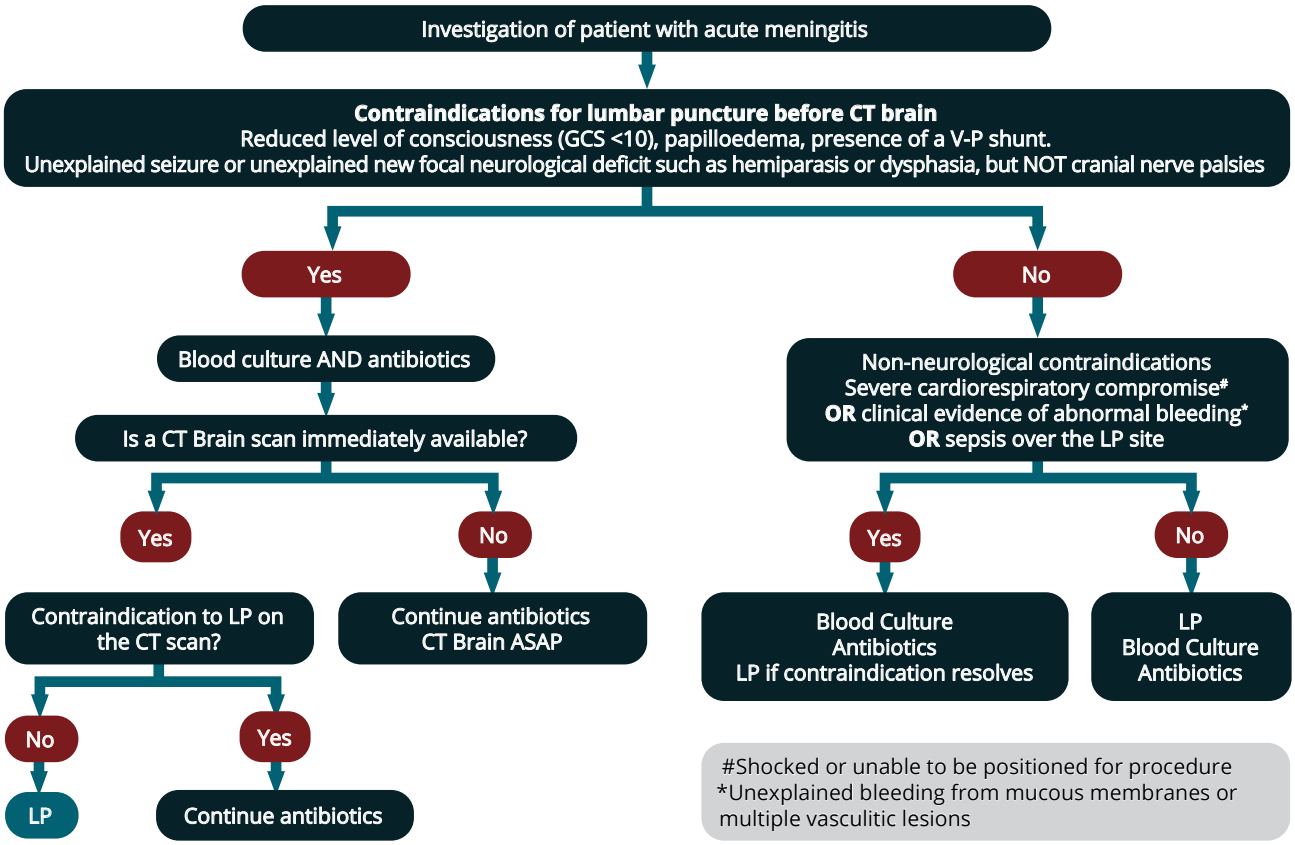
Initial hospital management

Acute meningitis is a medical emergency. The algorithm below shows an initial approach to suggested investigations and providing the first dose of antibiotics. Antibiotics should not be delayed while waiting for a CT scan.

TABLE 5: Infectious causes of acute meningitis in a patient with HIV

Bacteria	Viruses	Fungi
Streptococcus pneumoniae	Enteroviruses, including polio	*Cryptococcus neoformans*
Neisseria meningitidis	Human immunodeficiency virus	
Haemophilus influenzae	Herpes viruses	
Escherichia coli	Mumps	
Rickettsia species		
Leptospira species		
Staphylococcus aureus		
Salmonella non-typhi		
Listeria monocytogenes		
Streptococcus agalactiae (Group B)		
Treponema pallidum		
Mycobacterium tuberculosis		

FIGURE 3: Investigation of a patient with acute meningitis



Initial management:

- Administer ceftriaxone 2 g intravenously.
  - Use intramuscular or intraosseous routes if there is no vascular access.
  - Penicillin allergy is not a contraindication to ceftriaxone. Avoid ceftriaxone only if there has been documented cephalosporin anaphylaxis. Give instead vancomycin plus moxifloxacin *or* meropenem.
- If Listeria is suspected, *add* ampicillin 3 g intravenously six hourly.
  - *Listeria monocytogenes* is a relatively uncommon cause of bacterial meningitis but is intrinsically resistant to cephalosporins.
  - Suspect Listeria if patient > 50 years old or immunocompromised because of immunosuppressive drugs, alcoholism, liver cirrhosis, asplenia, end-stage renal failure or diabetes mellitus. HIV infection is not an indication.
  - In a patient with penicillin allergy give instead high dose co-trimoxazole.
- Provide adequate analgesia.

The yield of CSF and blood cultures post antibiotics will be lower but there will be no significant difference in CSF white blood cell count in the first 24 hours. However, CSF glucose and protein begin to normalise within a few hours of antibiotic therapy. Blood cultures are particularly important to increase the chances of isolating the causative organism and enabling targeted antibiotic therapy, especially in the case of a delayed LP.

Previously adjunctive corticosteroids were recommended for a patient with bacterial meningitis. Recently, an individual patient meta-analysis showed that adjunctive dexamethasone (the most widely studied corticosteroid) does not significantly reduce death or neurological disability. Therefore, corticosteroids are not recommended in a patient with bacterial meningitis.

Contraindications to lumbar puncture

An LP is considered an essential part of the assessment of a patient with suspected meningitis. However, there is a risk of transtentorial or cerebellar herniation if there is markedly increased pressure in the brain, or in one compartment compared to another. Evidence regarding clinical contraindications to LP in this setting is inadequate and guidance is based on the limited evidence available and expert opinion.

Neurological contraindications to lumbar puncture include:

- Coma or markedly decreased level of consciousness (Glasgow Coma Scale < 10).
- Papilloedema on fundoscopy.
- Unexplained new focal neurological deficit, such as a hemiparesis or dysphasia.

- A first generalised seizure in the preceding week, or changing pattern of seizures in a known epileptic.
- Presence of a ventriculoperitoneal shunt.
- Isolated cranial nerve palsies are not a contraindication to LP, but caution is advised if there is co-existing reduced level of consciousness.

CT of the brain should be performed as soon as possible in cases in which LP is delayed for neurological reasons. Taking blood cultures and provision of antibiotics should not be delayed if there is a delay in obtaining a CT scan. CT features of gross generalised brain swelling or significant hemispheral shift related to a mass lesion are contraindications to a LP. However, it is important to note, that a normal CT brain does not exclude the presence of raised intracranial pressure.

Non-neurological contraindications to lumbar puncture include:
- Severe cardiorespiratory compromise
- Severe coagulopathy
- Local sepsis at the LP site

In general, a patient who is shocked or unable to be positioned for an LP should have the procedure delayed until this has been corrected. In an emergency, it is unlikely that relevant laboratory values will be available, so unexplained bleeding from mucous membranes or multiple vasculitic lesions suggestive of disseminated intravascular coagulation should delay the LP. Once laboratory findings are known consensus opinion suggests that an LP is safe when the platelet count > 40 000/mm^3 and international normalised ratio is <1.5.

Diagnostic tests

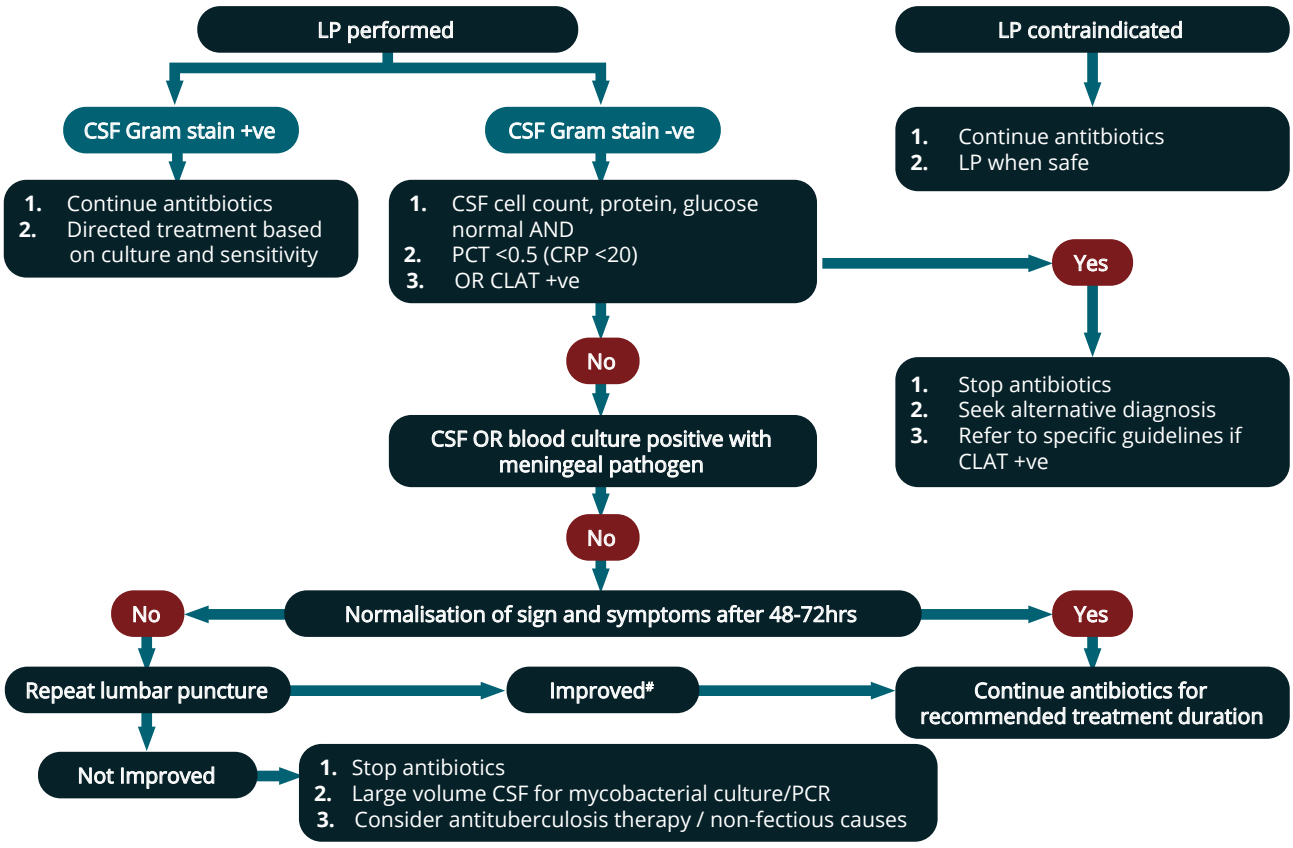
The following CSF and blood tests are required in all cases:
- Opening CSF pressure
- CSF differential cell count, glucose, total protein, gram stain, bacterial culture and sensitivity
- Cryptococcal antigen (CrAg)
- Serum glucose
- Peripheral white cell count and differential
- C-reactive protein (CRP)
- Store up to 10mls of CSF for future tests

CSF tests that are not usually useful are lactate, chloride and adenosine deaminase.

Interpretation of laboratory tests

A positive CSF gram stain is diagnostic of bacterial meningitis and treatment should be continued as outlined below. If the gram stain is negative, the diagnosis must be made using other CSF and blood results and clinical response to empiric therapy. There is considerable overlap in CSF results between aetiologies. An approach for making treatment decisions after the first dose of antibiotics, based on the availability of test results over time, is presented in figure 4 below.

FIGURE 4: Approach to meningitis following the first dose of antibiotics



#Opening pressure, protein, total WCC and % neutrophils reduced % Lymphocytes and CSF/serum glucose increased

Second line tests

If meningitis is confirmed, consider requesting enterovirus PCR on the stored CSF. A positive result will allow you to stop antibiotics and discharge the patient. Other tests to consider are herpes simplex virus (HSV) PCR, varicella zoster virus (VZV) PCR and Xpert Ultra (ask lab to centrifuge sample).

Stopping antibiotics

Serum CRP < 20 mg/l has a negative predictive value for bacterial meningitis of 99%. If initial cell counts, protein, serum/CSF glucose ratio, and CRP are all normal, bacterial meningitis can be excluded, and antibiotics stopped.

Stopping ampicillin

If the CSF gram stain, culture or CLAT confirms an alternative pathogen, empiric ampicillin for Listeria can be stopped.

What to do if the diagnosis is unclear after 48-72 hours

It is common for patients to have negative CSF and blood cultures but abnormal CSF findings, particularly if antibiotics were given prior to taking CSF and blood cultures. In this case the diagnosis should be reviewed after 48-72 hours of antibiotics. Clinical improvement suggests a bacterial aetiology and therefore ceftriaxone should be continued for 10-14 days and, if initiated, ampicillin for 21 days. Clinical improvement cannot be quantified as signs and symptoms vary and they are age-dependent, but normalisation of fever and an improvement in most symptoms is suggestive.

If there is no clinical improvement or there is doubt about the significance of clinical improvement after 48-72 hours, the LP should be repeated. In bacterial meningitis, effective antibiotic therapy will lead to a reduction in CSF opening pressure, protein, total white cell count and percentage neutrophils, and an increase in percentage lymphocytes and CSF/serum glucose. If this does not occur bacterial meningitis is very unlikely, and antibiotics can be stopped. Alternative diagnoses, particularly tuberculous meningitis, should be considered. In this case, the stored CSF should be tested for TB with Xpert Ultra (ask lab to centrifuged sample first), and mycobacterial culture and sensitivity.

The section on chronic meningitis provides information for decision making if TB meningitis is likely.

Directed therapy

Table 6 details the recommended treatment based on a confirmed pathogen.

TABLE 6: Directed treatment based on a confirmed pathogen

Pathogen	Suggested antimicrobial	Alternative antimicrobial	Duration (in days)
Streptococcus pneumoniae **(penicillin MIC ≤ 0.06 µg/ml)**	Benzyl penicillin	Ceftriaxone	10-14
Streptococcus pneumoniae **(penicillin MIC > 0.06 µg/ml)**	Ceftriaxone	Vancomycin plus ceftriaxone	10-14
Streptococcus pneumoniae **(ceftriaxone MIC ≥ 1 µg/ml)**	Vancomycin plus ceftriaxone	Moxifloxacin plus rifampicin	10-14
Neisseria meningitidis	Benzyl penicillin	Ceftriaxone	5-7
Haemophilus influenzae	Ampicillin (if sensitivity confirmed)	Ceftriaxone	7-14
Listeria monocytogenes	Ampicillin plus gentamicin	Co-trimoxazole	21
Streptococcus agalacticae **(Group B)**	Penicillin	Ampicillin	14-21
Escherichia coli	Cefotaxime	Ceftriaxone	21
Salmonella non-typhi	Ceftriaxone	Ciprofloxacin	28

An approach to sub-acute/chronic meningitis

The differential diagnosis is broad. Table 7 below indicates possible infectious causes. Table 8 indicate possible non-infectious causes, which are also important to consider. The viruses HSV, VZV, and CMV more commonly cause encephalitis or ventriculitis (CMV) than meningitis. This is covered further in **chapter 8** Altered mental State.

TABLE 7: Possible pathogens causing sub-acute/chronic meningitis. Note: most common treatable causes in a patient with HIV in South Africa are indicated in **bold.**			
(Myco) bacterial	**Fungal**	**Viral**	**Parasitic**
Tuberculosis	**Cryptococcosis**	**Herpes Simplex (HSV)**	Toxoplasmosis
Syphilis	Candida	**Varicella Zoster (VZV)**	Cysticercosis
Listeria	Aspergillus	**Cytomegalovirus (CMV)**	Angiostrongylus cantonensis
	Mucormycosis	HIV	Gnathostomiasis
	Histoplasmosis		

TABLE 8: Possible non-infectious causes sub-acute/chronic meningitis. Note: this table excludes medication-related causes.	
Non-infectious (except drugs)	**Drugs**
Haematological malignancy	NSAIDS
Solid organ malignancy	Trimethoprim-sulfamethoxazole
Primary brain tumours	Isoniazid
Sarcoidosis	Azathioprine
SLE	
Vasculitis, Sjogrens, Behcet	

Does the patient require a CT brain before lumbar puncture?

It is important to determine if it is safe to perform an LP without first having a CT brain. There is limited evidence but in general the contra-indications to LP in sub-acute/chronic meningitis are similar to those for acute meningitis. It is particularly important to assess if the patient has papilloedema.

If there is a neurological contra-indication to LP, perform a CT brain. If there is a contra-indication to LP on the CT brain it is most likely a space occupying lesion (refer to space occupying lesion algorithm). If both CT brain and LP are not possible (this is rare), discuss with an Infectious Diseases specialist.

Initial tests on CSF

- CSF opening pressure
- Gram stain and bacterial culture
- Protein, cell count, glucose
- CrAg
- Syphilis
- Serum glucose
- Store up to 10mls of CSF for future tests

Initial treatment

There is no need to start empiric ceftriaxone and specific treatment can wait until the CSF results are received.

How useful are the initial CSF results?

The following are listed in order of usefulness:

- Gram stain - rarely positive but if it is, confirms diagnosis
- CrAg - if positive, confirms cryptococcal meningitis (unless previously treated)
- VDRL- if positive, confirms neurosyphilis
- FTA-Abs – a negative result excludes neurosyphilis
- CSF glucose - if <2.5, suggestive of TBM but bacterial cause cannot be excluded
- CSF protein - if around 1.5 suggestive of TBM, if > 5 suggestive of bacterial meningitis (but not definitive)
- Cell counts - not very useful- normal results are suggestive of no meningitis but up to 5% of cases with TB and bacterial meningitis may have normal results
- Very high polymorphs suggest bacterial or CMV meningitis

BOX 4: Typically normal result in a patient with HIV

- Glucose >3.5
- Protein <0.75
- 1 polymorph
- 5 lymphocytes

If the diagnosis remains unclear, consider the following tests on the stored CSF:

- Xpert Ultra (ask lab to centrifuge sample first)
- Mycobacterial culture (for future reference)
- Viral PCR – some laboratories offer a panel. If not, do HSV, VZV (rash may not be present), CMV, and enterovirus
- Bacterial PCRs, including Listeria

Next, think about other ways of making a diagnosis:

- Search for extra-neural TB, including urine LAM
- Examine for rashes suggestive of VZV or HSV
- Consider malignancy and autoimmune diseases
- Review medication history carefully and, if possible, stop any medications that may be implicated.

Most tests take time, except for Xpert Ultra. If the Xpert Ultra is negative, there is confirmed meningitis and test results are outstanding, consider the following empiric therapies in this order:

- Consider TBM therapy – refer to box 5
- Treat for HSV - meningitis does not have as high mortality as encephalitis but treatment has limited side-effects
- Treat for neurosyphilis (unless the FTA-Abs are negative) - if VDRL is negative, then syphilis is less likely. It is important to consider suggestive neurological signs
- Give ampicillin - Listeria is uncommon outside of an outbreak but consider empiric treatment if the patient is > 50 years old, on chronic immunosuppressive medication or has brainstem signs and symptoms

BOX 5: Decision making in TB meningitis

- TB meningitis has a very high mortality, even with appropriate treatment.
- The consequences of withholding treatment from a patient with possible TBM are extremely serious (almost certain death).
- Therefore, the threshold for initiating treatment is low, particularly if the patient is clinically unstable.
- The incidence of TBM in patients with HIV in South Africa is high.
- Therefore, in a patient with confirmed sub-acute/chronic meningitis, with no evident alternative diagnosis, consider empiric TBM therapy.
- If an alternative diagnosis becomes evident later on (e.g., VZV PCR is positive) stopping TB treatment may be considered.

How to follow-up a patient who improves on treatment

In general, once empiric therapy has been started and the patient is improving clinically, completion of the full course is necessary, unless an alternative cause is found. This includes a patient who improves on TB treatment but has a negative CSF culture as this is not sufficient to exclude the diagnosis. However, if the patient develops signs of treatment related toxicity, the diagnosis should be reviewed including re-consideration of the CSF culture result.

How to follow-up a patient who does not improve on treatment

Full investigations should be guided by the likely reason for deterioration. In general, if the patient deteriorates despite TB treatment and the CSF culture is negative, it is unlikely that the diagnosis was TBM. Possibilities for not improving include IRIS, non-adherence, poor drug absorption, drug-drug interactions or incorrect diagnosis.

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7. ALTERED MENTAL STATE

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Background

Altered mental states are common in patients with AHD. The list of possible causes is vast and so it is vital to have an approach to such patients. This chapter begins with a description of the 3 cardinal syndromes (delirium, dementia, and psychosis) and then provides a practical approach to diagnosis and treatment.

Presentations of altered mental state

A definition of each of the 3 cardinal symptoms is given below:

Delirium

A serious disturbance in mental abilities that results in confused thinking and reduced awareness of the environment. Poor thinking skills (cognitive impairment), behaviour changes and emotional disturbance may be present.

Dementia

A group of symptoms that together affect the memory, normal thinking, communicating, reasoning ability and social abilities severely enough to interfere with daily life.

Psychosis

Gross impairment in reality testing, presence of hallucinations and/or delusions, marked disturbance in personality, with impairment in social, interpersonal, and occupational functioning. There is marked impairment in judgment and absence of understanding of presenting/current symptoms and behaviour (lack of insight).

Table 10 gives features that can help differentiate between the 3 syndromes. It is important to realise that the causes are overlapping, and more than one syndrome may be present. For example, delirium is common in patients with dementia, and delirium can present with features of psychosis. As a result, it may not be possible to immediately fit the patient into a single category.

A suggested approach to a patient with HIV who presents with an altered mental state is provided below:

Emergency assessment (within the first hour)

Measure and correct any of the following if present:

- Hypoglycaemia
- Hypotension
- Hypoxia

Take a rapid focused history and examination to determine if the patient fits the case definition of **meningitis** and if so, refer to meningitis sections.

TABLE 10: Differentiation in symptoms between delirium, psychosis and dementia

Symptom	Delirium	Psychosis	Dementia
General presentation	**Sick (abnormal vital signs, sweaty, look sick)**	**Not sick**	**Not sick**
Onset	Sudden onset (was OK yesterday)	No sudden onset	No sudden onset but may have stepwise deterioration
Course	Fluctuating course	Non-fluctuating	Non-fluctuating
	Forgetfulness	Preserved memory	Forgetfulness
Attention	Inattention or distraction	Attention often preserved	Attention often preserved (unless delirium co-existing) or advanced disease
Level of consciousness	Altered level of consciousness	Normal level of consciousness	Normal level of consciousness
Orientation	Disoriented (time, place, person)	Oriented	Disoriented
Hallucinations	Visual hallucinations	Hallucinations more likely to be auditory	Hallucinations less common

Begin a full assessment (within the first day)

It is likely that the problem is acute or sub-acute in a patient presenting to hospital. Think first about delirium but it is important to remember that delirium is common in patients with dementia and can present with psychotic features, so unless the diagnosis is already clear at this point it will be necessary to consider all causes of delirium. There are a vast number of causes of delirium. Table 11 provides a non-exhaustive list.

Assess the following:

- History
  This is often difficult to obtain from the patient but any collateral history from relatives or previous clinical notes can be helpful, particularly the duration of symptoms. A medication history is important, including all prescribed, over the counter, traditional medications, and consumption of alcohol and/or illicit drugs.Past psychiatric history is very important.

- Physical examination
  Thorough examination of all systems is vital. In particular, neurological signs that may suggest a space occupying lesion.

- Mental state examination
  Focus specifically on behaviour and appearance of the patient. Speech and speed of thoughts should be assessed, and mood, affect, suicidality and neuro-vegetative symptoms evaluated. Perceptual disturbances, thought form, thought content, and insight and judgement also needs to be assessed.

- Chest X-ray

- Blood tests
  Request FBC, U and E, LFTs, TSH, Calcium, CRP, CD4 count with reflex CrAg (if not done recently), and HIV viral load (if on ART for ≥4 months)

TABLE 11: Possible causes to consider in a patient presenting with delirium

Infectious	Non-infectious
Primary brain disease • HSV • VZV • CMV • TB • HIV • JCvirus (PML) • Cryptococcosis **Secondary brain disease** • Disseminated TB • Sepsis syndrome due to bacterial infection	**Drugs and toxins** • Efavirenz • Isoniazid • Steroids • Alcohol • Illicit drugs • Traditional meds • Withdrawal • Unknown toxin **Metabolic** • Hypoglycaemia • Hyponatraemia • Hypernatraemia • Hypercalcaemia • Uraemia • Liver failure • Wernicke's **CVS/respiratory** • Hypotension • Hypoxia

Urgent actions (before full assessment is complete if suspicion high)

Consider serious bacterial infection as a cause, take a blood culture, urine culture and give a broad-spectrum antibiotic, typically ceftriaxone 2g IV stat.

Consider a CNS infection if the cause is unclear, particularly if there is a fever. If suspicious, do the following:

- Lumber puncture (unless contra-indicated): (see **Chapter 5: meningitis**).
  - Measure opening pressure
  - Gram stain and bacterial culture
  - CSF protein, cell count, glucose (send
  - Serum glucose
  - CrAg
  - Syphilis
  - Store 10mls of CSF for possible future tests
- CT brain

Normal CSF findings (see box 7) suggests that CNS infection is unlikely and further tests on the stored CSF are unlikely to be helpful. However, herpes simplex virus (HSV) encephalitis can occur with normal CSF findings and PCR can be negative in early disease (< 3 days), so acyclovir may be necessary even when CSF is normal, if the symptom duration is short. In this case, the LP should be repeated when at least 3 days have elapsed since the onset of symptoms. Acyclovir can safely be stopped if an alternative cause is found, or if the clinical or radiological picture is no longer suggestive of HSV and the herpes simplex virus PCR on ≥ 0.5ml of CSF remains negative.

BOX 7: CSF results that are typically considered normal in HIV patients, although exceptions occur

- Glucose >3.5
- Protein <0.75
- 1 polymorph
- 5 lymphocytes

Abnormal CSF findings strongly suggest brain infection (encephalitis). The common and treatable causes include HSV, VZV and TB in which case empiric therapy (acyclovir and RHZE) can be considered. Confirmatory testing with Ultra, mycobacterial culture and viral PCR should be done. CMV is less common but a potential cause. However, there is no need to request a serum CMV viral load. If the CrAg is positive, treat as for cryptococcal meningitis. If the VDRL or FTA-Abs are positive with abnormal cells present and no other clear cause, treat for neurosyphilis.

Reassess the situation based on results received (from day 1 post admission)

If the cause is clear, it can be treated and, if possible, withdraw potentially responsible drugs (see box 8 if on efavirenz). Consider other drugs (not just INH related if they are on it), substance abuse and withdrawal.

BOX 8: Efavirenz toxicity

Efavirenz toxicity is more likely if the any of the following are present: short history of efavirenz exposure, psychomotor retardation, cerebellar signs, female sex, low BMI or recently initiated isoniazid therapy.

If efavirenz toxicity is a consideration, send a random serum efavirenz level (if available), change to an alternative agent (e.g., dolutegravir) and monitor for symptom improvement. Improvement in symptoms may take many weeks if the level was high, as efavirenz has a half-life of around 2 weeks.

If may be necessary to continue the work up for other causes at the same time.

If the cause is unclear but there are significant abnormalities, ensure they are monitored (e.g., liver or renal impairment) Always consider looking for TB in the usual way.

If the cause is not clear at this point - are the symptoms primarily psychotic?

The pathophysiology of psychosis and other forms of severe mental illness in HIV infection is complex, and multifactorial causation is likely in most instances. Severe mental illness has been identified as a risk factor for the acquisition of HIV infection and occurs as both a manifestation of an opportunistic infection and a result of the neurotropic effects of the virus. In this case, seek specialist psychiatric advice as drugs, infections and delirium are unlikely.

While primary psychiatric disease is a possibility, HIV associated neurocognitive disorders (HAND) can also present with features of psychosis and this remains high on the differential diagnosis. If the viral load is high, start suppressive ART.

If psychiatry referral is not possible, start antipsychotic medication according to national guidelines. Typical agents include haloperidol 0.5 mg - 2.5 mg p.o. nocte and/or lorazepam 1 - 2 mg p.o. q 8 h. If extrapyramidal side-effects occur, change to an atypical agent such as risperidone 1 - 2 mg p.o. nocte or in divided doses (1 mg p.o. b.d.)

If manic symptoms are a prominent feature, consider using valproate 300 mg twice daily, increasing to 600 mg twice daily. If liver function is impaired, use lower doses and monitor liver function tests.

If causes of delirium have been excluded or treated some patients may continue to have features of dementia

HIV associated neurocognitive disorders (HAND) are a group of disorders with high prevalence in South Africa. HIV-dementia (HIV-D) is the most severe form of HAND. A validated screening tool is the CAT-rapid which can be accessed here: **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5771655/#APP1**

A score above 10 on CAT-rapid screening suggests that HIV-D is not present. A score below 10 suggests that it may be a cause for the patient's symptoms.

It is important to rule out other causes as best you can before settling on a diagnosis of HIV-D.

If the HIV viral load is high, start suppressive ART.

If available, refer for neuropsychiatric assessment. Consider a social grant and supportive management such as a treatment buddy.

Treatment of a behaviourally disturbed patient with HIV

While searching for and treating the underlying cause, it may be necessary to treat behavioural symptoms.

Haloperidol (0.5 mg - 2.5 mg p.o daily) is safe to use in this case, however; there is a high potential for

extrapyramidal side-effects. If available, atypical antipsychotics, such as risperidone 0.5 - 2 mg twice daily or quetiapine 50 - 200 mg twice daily, may be better.

If needed, lorazepam 2 - 4 mg 8-hourly (or oxazepam if liver function is impaired) may be used for sedation in the short term.

If manic symptoms are a prominent feature, consider using valproate 300 mg twice daily, increasing to 600 mg twice daily. If liver function is impaired, use lower doses and monitor liver function tests.

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