Guidelines for the management of acute meningitis in children and adults in South Africa

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This guideline provides a rational and cost-effective approach to patients with acute meningitis, which causes considerable morbidity and mortality, predominantly in children.There are many aetiologies, but a small number of bacteria and viruses account for the majority of cases. There should be a low threshold for suspecting acute meningitis, which is a medical emergency and antibiotics should not be delayed. Blood culture and cerebrospinal fluid (CSF) analysis are the most important diagnostic tests and should be performed whenever it is safe and practical. Contraindications to lumbar puncture are discussed and an algorithm is given regarding administering empiric antibiotics and antivirals, performing blood cultures, computer tomography brain scanning and cerebrospinal fluid analysis, depending on the clinical features and availability of resources. Administration of steroids is not recommended. Guidelines are provided for definitive therapy whenever a causative organism is identified. When no organism is identified, treatment and further investigation should be guided by laboratory results and clinical response. An approach to this process is outlined in a second algorithm. The epidemiology of resistance to common pathogens is described and advice given regarding special groups, including those with recurrent meningitis or base-of-skull fractures. Advice regarding infection control, post-exposure prophylaxis and vaccination is provided.

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Introduction

Meningitis has a wide variety of infectious and noninfectious causes. Acute bacterial or viral meningitis is a medical emergency which causes considerable morbidity and mortality in southern Africa.[1] Early initiation of appropriate therapy, particularly antibiotics for bacterial meningitis, improves outcome.[2] Because of the high prevalence of human immunodeficiency virus (HIV) and tuberculosis in South Africa, the incidence of meningitis caused by *Cryptococcus neoformans* and *Mycobacterium tuberculosis* has increased in recent years. Although either can present acutely, they more commonly present with chronic symptoms. Guidelines for their management have been published elsewhere.[3-4] Estimated annual incidence of bacterial meningitis in the South African general population is 4/100 000, highest in < 1 year-olds (40/100 000), followed by 1-4 year-olds (7/100 000).[5] This is likely to be an underestimate of true incidence as it excludes those with culture-negative cerebrospinal fluid (CSF) and those with nonbacterial aetiologies.

Aim of the guideline

The aim of the guideline was to improve the outcomes of children and adults with acute meningitis by providing rational and cost-effective recommendations for the diagnosis and treatment of acute meningitis in South Africa.

Level of evidence should be:

A. At least two randomised controlled trials supporting the recommendation.
B. Single randomised controlled trials and/or a meta-analysis of nonrandomised studies supporting the recommendation.
C. Consensus opinion of experts based on cohort/observational studies and clinical experience.

Strength of recommendations should be:

I. Evidence or general agreement that a given treatment or a diagnostic approach is beneficial, useful and effective.
II. Conflicting evidence and/or a divergence of opinion that a given treatment or a diagnostic approach is beneficial,

useful and effective.

III. Evidence or general agreement that the treatment or a diagnostic approach is not useful or effective, and in some cases may be harmful.

Case definition of suspected acute meningitis

Duration of symptoms

There is no absolute cut-off that differentiates acute from chronic meningitis. For the purposes of this guideline, we have defined the duration of symptoms of acute meningitis as < 7 days. Longer duration of symptoms suggests meningitis with different aetiologies.

Signs and symptoms

Acute meningitis should be suspected in an adult with any two of the following: headaches, fever > 37.5°C, neck stiffness or altered mental status of < 7 days duration[6] (B-I). Kernig and Brudzinski signs are unreliable indicators of meningitis and should not be used[7] (B-III). Clinical presentation of meningitis in children is age-dependent (Table I) which limits the diagnostic accuracy of clinical features, compared to adults.[8-9] Therefore, a lower threshold for suspecting meningitis should be applied to infants and young children, than to older age groups. Fever, vomiting and altered level of consciousness are common to everybody. Seizures are not a reliable predictor of meningitis in children, particularly in those between six months and six years of age, when febrile convulsions are common.[10] The signs and symptoms of acute meningitis merge with those of adults beyond 3-5 years of age.[10]

Determining aetiology

The major infectious causes of acute meningitis are listed in Table II. Uncommon aetiologies include measles, rubella, West Nile virus and Rift Valley fever virus. Rabies usually presents with encephalitis, which may be confused with meningitis, particularly in children. Cytomegalovirus (CMV) encephalomyelitis occurs in patients with HIV and cluster differentiation 4 (CD4) < 100 cells/mm^3, and in those with associated radiculomyelitis it is characterised by CSF neutrophils > 500/mm^3. Clinical grounds alone do not define meningitis aetiology, although a detailed travel and exposure history (Table III) may predict some aetiologies.

Pre-hospital care

Acute meningitis is a medical emergency. All suspects should receive their first dose of antibiotics immediately and be transferred to hospital as soon as possible[2] (B-I). If facilities for blood culture and/or lumbar puncture (LP) are immediately available, they should be performed before administration of the first dose of antibiotics (see contraindications to LP below). Neither procedure should lead to a significant delay in antibiotic administration.

Administer ceftriaxone 80-100 mg/kg (maximum 2 g, 12 hourly) intravenously. The intramuscular or intraosseous route can be used if there is no vascular access. Penicillin allergy is not a contraindication to ceftriaxone in acute meningitis (C-1). Omit ceftriaxone only if there has been documented ceftriaxone anaphylaxis. Give chloramphenicol 25 mg/kg (maximum 500 mg) intravenously instead, if available. Administer adequate analgesia and transfer the patient immediately to hospital, detailing all administered medication in the referral letter.

Table II: Major infectious aetiologies of acute meningitis

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

Table I: Signs and symptoms of acute meningitis specific to age groups

	Neonates and infants: < 3 months	Infants and young children: 3 months to 3 years	Older children and adults: > 3 years
Symptoms	Irritability	Headaches	Headaches
	Poor feeding	Neck stiffness	Neck stiffness
			Photophobia
Signs	Bulging fontanelle		Rash: maculopapular or petechial*
	Hypothermia		Neck stiffness**

*: Most common in *Neisseria meningitidis* infections, although may be noted in any cause of bacterial septicaemia associated with meningitis, especially *Streptococcus pneumoniae.*
**: The sensitivity in adults is only approximately 30%.

Table III: Risk exposures and clinical features associated with particular meningeal pathogens

Pathogen	*Risk exposure*	*Suggestive clinical features*
Neisseria meningitidis	Childcare facilities, learning institutions and military barracks	Nonblanching petechial rash (some have a maculopapular rash). Conjunctival lesions
Varicella-zoster virus	Persons with chickenpox	Chickenpox vesicular rash
Mumps virus	Persons with mumps	Parotid swelling (unilateral or bilateral)
Herpes simplex virus	Mother with active herpes simplex virus (can occur when mother is asymptomatic)	Cutaneous or mucosal herpes simplex lesions (within the neonatal period)
Rickettsia species	Tick exposure during outdoor activity *(Rickettsia africae).* Close contact with dogs *(Rickettsia conorii)*	Eschar, ± regional lymphadenopathy, maculopapular rash (40% may be vesicular in *Rickettsia africae*) involving palms and soles in some patients
HIV (seroconversion)	Recent unprotected sex and occupational exposure	Generalised lymphadenopathy, a sore throat and a maculopapular rash
Treponema pallidum (syphilis)	Unprotected sex	Maculopapular rash involving palms and soles, any HIV-positive patient or recent genital ulcer disease
Leptospira species	Exposure to rats or contaminated water	Jaundice and conjunctival suffusion
Rabies virus	Animal bite, scratch or mucous membrane lick	Hallucinations, hypersalivation hydrophobia and spasms

HIV: human immunodeficiency virus

Initial hospital management

Patients presenting directly to hospital should be treated in the same way as those presenting to a clinic or primary care facility: blood cultures ± LP if immediately available, followed by intravenous ceftriaxone. Those having already received antibiotics should still have a blood culture and LP performed, unless contraindicated (see below). Antibiotic pre-treatment significantly decreases the yield of blood and CSF cultures with sterilisation of CSF occurring within two hours of intravenous therapy in meningococcal meningitis, and within four hours of therapy in pneumococcal meningitis.[11] A retrospective study of children with bacterial meningitis found no significant differences in CSF white blood cell count between those given antibiotics up to 24 hours prior to LP, and those who received no prior antibiotics.[12] The same study suggested that CSF glucose and protein begin to normalise within a few hours of antibiotic therapy.[12] Blood cultures are particularly important to increase the chances of isolating the causative organism and enabling antibiotic de-escalation, especially if LP is delayed for any reason.

Indication for ampicillin

Listeria monocytogenes, a relatively uncommon cause of bacterial meningitis in South Africa, is intrinsically resistant to cephalosporins. Empiric treatment for *Listeria* (ampicillin 3 g intravenously six hourly) in addition to ceftriaxone, is indicated in patients > 50 years old, or those who are immunocompromised because of immunosuppressive drugs, alcoholism, liver cirrhosis, asplenia, end-stage renal failure or diabetes mellitus[13-14] (B-I). HIV infection is not an indication. Ampicillin, in combination with cefotaxime, is often recommended in neonatal meningitis. However, *Listeria*. is rarely isolated from neonates in South Africa. Ampicillin should be administered to children < 1 month of age (50 mg/kg/dose intravenously six hourly) for at least 48 hours until *Listeria*. infection is excluded (C-2).

Indication for acyclovir

Clinical features of encephalitis can overlap with those of meningitis. Patients with acute encephalitis syndrome, i.e. acute onset of fever and a change in mental status (confusion, disorientation, coma, an inability to talk, somnolence or abnormal behaviour greater than that seen with usual febrile illnesses), or new onset of seizures excluding simple febrile seizures, should receive aciclovir (children and adults 10 mg/kg eight hourly, neonates 20 mg/kg eight hourly intravenously by infusion over one hour), in addition to antibiotic therapy.

Steroids

Previously adjunctive corticosteroids were recommended in patients with bacterial meningitis. Recently, an individual patient meta-analysis[15] showed that adjunctive dexamethasone, the most widely studied corticosteroid, does not significantly reduce death or neurological disability. This meta-analysis included two large, well-designed studies conducted in Thailand and Malawi.[16-17] The results from the Malawian study, which showed no benefit of adjunctive steroids, are of particular relevance to South Africa as the majority of the participants were HIV-infected. Most other studies were conducted in high-income countries. Therefore, we do not recommend the routine use of adjunctive corticosteroids (A-1).

Cephalosporin and penicillin allergy

Patients with documented cephalosporin anaphylaxis should be treated with vancomycin and ciprofloxacin or moxifloxacin. Alternatives are chloramphenicol or meropenem, although the

Table IV: Doses of antibiotics by age group

Antibiotic	Dose (all administered IVI)	
	Infants and children	Adults
Ampicillin	50 mg/kg/dose given 6 hourly	3 g/dose given 6 hourly
Benzyl penicillin	100 000 u/kg/dose given 6 hourly	5 MU/dose given 6 hourly
Cefotaxime	50 mg/kg/dose given 6 hourly	2 g/dose given 6 hourly
Ceftriaxone	50 mg/kg/dose given twice daily	2 g/dose given 12 hourly
Meropenem	40 mg/kg/dose given 8 hourly	2 g/dose given 8 hourly
Moxifloxacin	Not recommended	400 mg given daily
Vancomycin	15 mg/kg/dose given 8 hourly (aim for trough levels of 15-20)	15 mg/kg/dose given 8 hourly
Gentamicin	5 mg/kg/dose given daily	1-2 mg/kg given 8 hourly (or 5 mg/kg/day)
Co-trimoxazole	8-12 mg TMP/kg/day given as divided doses 6-12 hourly	20 mg TMP/kg/day given as divided doses 6-12 hourly
Chloramphenicol	100 mg/kg/day given 6 hourly*	1 g/dose given 6 hourly

*: Neonates 0-7 days: 40 mg/kg given initially, then 25 mg/kg/dose given daily. Neonates 8-28 days: 40 mg/kg given initially, then 25 mg/kg/dose given 12 hourly

IVI: intravenously by injection, TMP: trimethoprim

latter should only be used if absolutely necessary. Patients with penicillin allergy requiring empiric treatment for *Listeria* spp. should receive co-trimoxazole. See Table IV for doses.

Neurological contraindications to lumbar puncture without prior computed tomography head scan

The evidence base regarding clinical contraindications to LP in the setting of suspected acute meningitis is inadequate and guidance is given based on available evidence and expert opinion. Figure 1 is a suggested algorithm for lumbar puncture, blood culture and antibiotic therapy, based on clinical characteristics and availability of computed tomography (CT) scanning. An LP is considered an essential part of the examination of the patient with suspected meningitis. The risk of herniation is highest where there is markedly increased pressure in the brain, or in one compartment compared to another. Therefore, clinical signs suggesting these scenarios should be sought.

Neurological contraindications to lumbar puncture in the setting of suspected acute meningitis include:

- Coma or markedly decreased level of consciousness (Glasgow Coma Scale < 10).
- Papilloedema.
- Unexplained new focal neurological deficit, such as a hemiparesis or dysphasia.
- Isolated cranial nerve palsies are not a contraindication to LP, but caution is advised when co-existent with reduced level of consciousness.
- Unexplained seizures.
- Presence of a ventriculoperitoneal shunt.

In children aged six months to six years, generalised tonic-clonic seizures lasting < 15 minutes are not a contraindication to LP as febrile convulsions are common in this age group[18] (B-1). However, most children with febrile convulsions do not need to have an LP. In all other patients, a first generalised seizure in the preceding week, or changing pattern of seizures in a known epileptic, are a contraindication to LP (C-1).

The level of consciousness at which LP is contraindicated has not been fully evaluated, but an increased relative risk of cerebral herniation with a Glasgow Coma Scale < 8 has been reported.[19] In the absence of robust evidence, it seems reasonable to perform an LP in suspected meningitis in a patient with a Glasgow Coma Scale of 10 or higher (C-1).

The consensus opinion is that the risk of promoting transtentorial or cerebellar herniation is probably outweighed by the benefit to be obtained by the LP if there is a reasonable suspicion of meningitis. Acute meningitis may result in brain swelling and fatal herniation, even in the absence of LP.[20]

CT of the brain should be performed as soon as possible in cases in which LP is delayed for neurological reasons. CT scanning should not delay the taking of blood cultures or immediate commencement of antibiotics.

Contraindications to lumbar puncture after computed tomography head scan

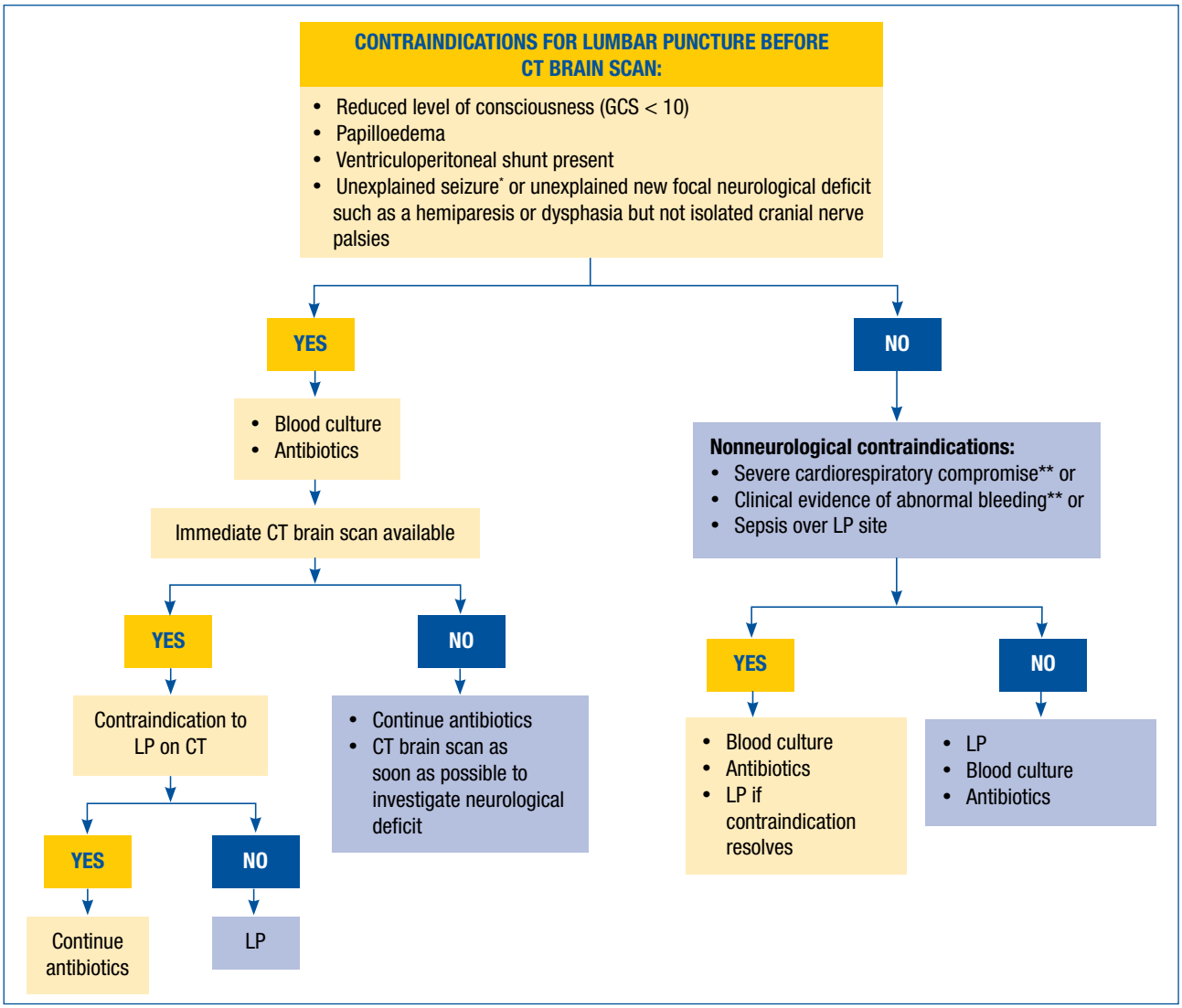
CT features of gross generalised brain swelling or significant hemispheral shift related to a mass lesion are contraindications to LP. However, it is important to note, that a normal CT brain does not exclude the presence of raised intracranial pressure.[20]

Non-neurological contraindications to lumbar puncture

Non-neurological contraindications to lumbar puncture are:

- Severe cardiorespiratory compromise.
- Severe coagulopathy.
- Local sepsis overlying the LP site.

The degree of cardiorespiratory compromise that constitutes a contraindication to LP is not clearly defined and absolute



*: Excluding simple febrile seziures, **: See text for definitions

CT: computed tomography, GCS: Glasgow Coma Scale, LP: lumbar puncture

Figure 1: Investigations of patients with acute meningitis

values are age-dependent. In general, any patient who is shocked or unable to be positioned for an LP should have the procedure delayed until this has been corrected. There are very limited data regarding the level of coagulopathy at which an LP is contraindicated. In a clinical 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 until laboratory findings are confirmed. Despite limited controlled data, consensus opinion suggests that LP is safe when platelet count > 40 000/mm and international normalised ratio is < 1.53[3,21,22] (C-I). Otherwise these parameters should be corrected prior to LP.

Diagnostic tests

CSF and blood tests required in all cases:

- CSF differential cell count, glucose, total protein, Gram stain, bacterial culture and sensitivity.
- Opening CSF pressure (see Table V).
- Serum glucose.
- Peripheral white cell count and differential.
- Blood culture.
- Serum procalcitonin [C-reactive protein (CRP) if unavailable].

Table V: Measurement of cerebrospinal fluid pressure if manometer is unavailable

Cut the drop chamber from a standard intravenous administration set:

- Attach the Luer lock to the lumbar puncture needle when CSF begins to flow.
- Hold the tubing vertically until the CSF level settles: usually several minutes.
- Measure the height of CSF with a tape measure, measured from the level of the LP needle.*

*: Cerebrospinal fluid pressure measurement is unreliable in crying children and when assistants require force in flexing the patient's head and/or legs

CSF: cerebrospinal fluid, LP: lumbar puncture

Other tests that should be performed for specific indications include:

- *CSF herpes simplex virus PCR:* Fulfils case definition for encephalitis.
- *CSF CMV PCR:* HIV-infected, CD4 < 100 cells/mm^3 with encephalomyelitis.
- *CSF measles PCR:* During a measles outbreak or suggestive clinical features.
- *CSF enterovirus PCR:* During an outbreak of aseptic meningitis.
- CSF cryptococcal latex antigen (CLAT): HIV-infected and > 5 years of age (see below).
- *CSF mycobacterial culture/GeneXpert® M. tuberculosis-resistance to rifampicin:* Uncertain length of history, or other reason to suspect tuberculosis meningitis.
- *Rabies PCR from saliva or nuchal biopsy (CSF PCR has lower sensitivity):* Animal exposure or mucous membrane licks.
- *Serum leptospirosis immunoglobulin M:* Risk exposure for leptospirosis.
- *Serum rickettsial serology:* Poor sensitivity and specificity for tick bite fever. Treatment based on clinical criteria and likely exposure to tick bites.
- *Serum and CSF testing* for syphilis according to protocol of local laboratory: Risk factor for syphilis.

CSF tests that should not be performed routinely as they are unlikely to alter future management of the patient include:

- Bacterial latex antigen tests.
- Lactate.
- Chloride.
- Adenosine deaminase.

Human immunodeficiency virus testing

HIV status should be determined by a rapid antibody test in all patients not known to be HIV-infected. If informed consent cannot be obtained because of reduced level of consciousness or the unavailability of relatives or caregivers, testing should still be performed in the patient's best interests as it will inform appropriate management.

Fourth-generation enzyme-linked immunosorbent assay incorporating p24 antigen testing and HIV-PCR testing, if necessary, is indicated in adults with features of HIV seroconversion illness (maculopapular rash, lymphadenopathy and a sore throat) and a negative HIV antibody test.

Children < 18 months of age with a positive rapid antibody test should be tested by HIV DNA-PCR as per national guidelines.

Cerebrospinal fluid volume

A minimum of 1 ml of CSF is adequate for routine microscopy, culture and biochemistry, but larger volumes should usually be taken to allow for extra tests. The sensitivity of tuberculois culture is directly related to the volume of CSF tested, so a large volume (maximum 10 ml) should be submitted if tuberculosis meningitis is suspected[23] (B-1). If CSF tuberculosis culture is required in children, smaller volumes can be taken, although the potential risks of repeat lumbar puncture and diagnostic delay if inadequate volumes are removed should also be considered. If sufficient volume of CSF is available, it should be stored at 2-4°C for additional tests, depending on the clinical course of the patient and CSF findings.

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 with different aetiologies. An algorithm for making treatment decisions after the first dose of antibiotics, based on the availability of test results over time, is presented in Figure 2.

When to stop all antibiotics

Serum CRP < 20 mg/l has a negative predictive value (NPV) for bacterial meningitis of 99% in children (≥ 3 months)[24] and adults[25] (A-1). Serum procalcitonin < 0.5 ng/ml has a NPV for bacterial meningitis of 99%[26-27] (A-1). Bacterial meningitis can be excluded and antibiotics stopped if initial cell counts, protein, serum/CSF glucose ratio, and PCT (or CRP) are all normal (B-1). Age-specific normal ranges are shown in Table IV.

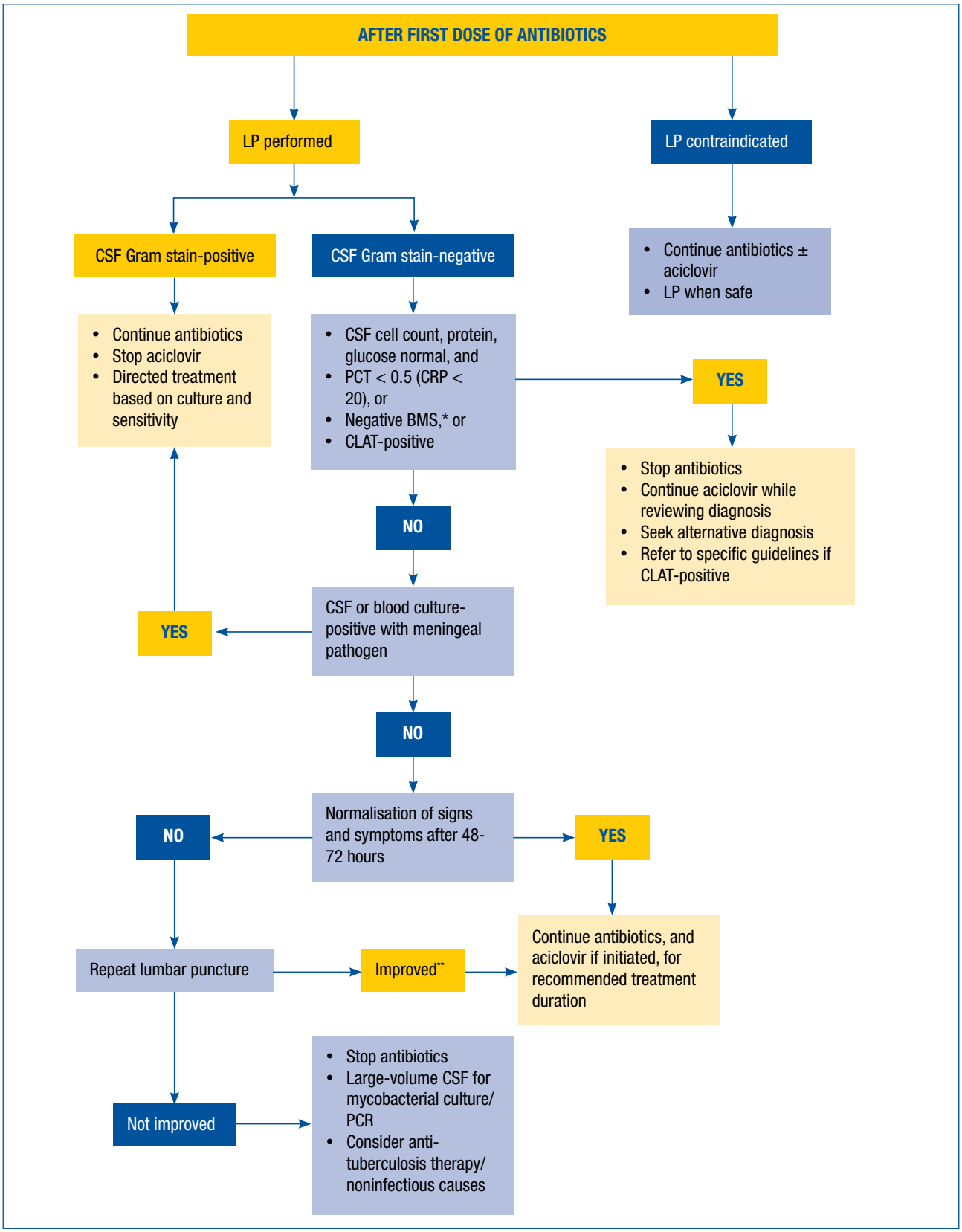
In patients with a positive CLAT, antibiotics can safely be stopped unless there is strong evidence of dual infection with bacteria. Refer to cryptococcal meningitis guidelines for further management.[3] Note that CLAT may be positive in a patient with recently treated cryptococcal meningitis and is not a reliable predictor of disease in these circumstances.

In healthy, immunocompetent children, viral meningitis is more common than bacterial. The Bacterial Meningitis Score (BMS) can assist in differentiating bacterial from viral meningitis in children with > 10 leucocytes/mm^3 of CSF.[28-30]

The BMS is negative if all of the following are absent:

- Positive CSF Gram stain.
- CSF neutrophils ≥ 1 000 cells/mm^3.
- CSF protein of ≥ 0.8 g/l.
- Peripheral blood absolute neutrophil count of ≥ 10 000 cells/mm^3.
- History of seizure before, or at the time of presentation.

A negative BMS has a NPV for bacterial meningitis of 99.9%. The use of BMS is limited as it has not been validated in children < 2 months old, those pre-treated with antibiotics, those with critical illness, purpura, ventriculoperitoneal shunt, recent neurosurgery or immunosuppression.



*: Bacterial Meningitis Score only applies to children > 2 months of age
**: Opening pressure, protein, total white cell count and percentage neutrophils reduced. Percentage lymphocytes and cerebrospinal fluid/serum glucose increased

BMS: Bacterial Meningitis Score, CLAT: cryptococcal latex antigen, CRP: C-reactive protein, CSF: cerebrospinal fluid, LP: lumbar puncture, PCR: polymerase chain reaction, PCT: procalcitonin

Figure 2: Algorithm following first dose of antibiotics

When to stop ampicillin

Empiric ampicillin for *L. monocytogenes* can safely be stopped if a positive CSF Gram stain, culture or CLAT confirms an alternative pathogen.

When to stop acyclovir

Herpes simplex virus encephalitis can occur with normal CSF findings and PCR can be negative in early disease (< 3 days), so aciclovir cannot be stopped on this basis alone. Aciclovir can safely be stopped if an alternative cause is found, or if the clinical or radiological picture is no longer suggestive and herpes simplex virus PCR on ≥ 0.5ml of CSF remains negative at least three days after the onset of symptoms. If CSF findings are normal and PCR for herpes simplex virus is not available, the initial indication for aciclovir should be reviewed in conjunction with CT brain results, if available, and aciclovir can be stopped if there is no clinical evidence of encephalitis.

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

In patients with negative CSF and blood cultures, the diagnosis should be reviewed after 48-72 hours of antibiotics. Clinical improvement suggests a bacterial aetiology and ceftriaxone should be continued for 10-14 days and ampicillin for 21 days, if initiated. Clinical improvement cannot be quantified as signs and symptoms vary and are age-dependent, but normalisation of fever and improvement in the majority of symptoms should be sought.

If there has been no clinical improvement or there is doubt about the significance of clinical improvement after 48-72 hours, the LP should be repeated. Effective antibiotic therapy for bacterial meningitis should 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[32] (B-1). Otherwise, alternative diagnoses, particularly tuberculous meningitis, should be considered according to published definitions[33] and a large volume of CSF (maximum 10 ml) should be sent for mycobacterial culture and susceptibility, or PCR if available. This approach has only been validated in adults,[32] but a similar approach is advised in children.

Epidemiology of resistance

An understanding of the epidemiology of antibiotic resistance in South Africa is needed to direct empiric therapy (Table VII).

Directed therapy

Bacteria

De-escalate antibiotics whenever possible (Table VIII). Antibiotic duration has little evidence base. No randomised trials exist in adults to support reduced duration. In children, there are a number of studies, including two smaller studies,[41-42] a meta-analysis[43] and a large multicentre, randomised, placebo-controlled trial,[44] that suggest that short-course therapy of 4-7 days is sufficient for acute bacterial meningitis. The latter study compared five vs. 10 days treatment with ceftriaxone for meningitis due

Table VI: Normal ranges for cerebrospinal fluid and blood parameters related to age

	< 1 month	*1-3 months*	*4-24 months*	*> 2 years*
CSF total leucocyte count (cells/mm^3)	< 20[7]	< 10[7]	< 5 (100% lymphocytes)[7]	< 5 (100% lymphocytes)
CSF/serum glucose	Ratio not useful	> 0.66[7]	> 0.66[7]	> 0.6
CSF protein (g/l)	< 1 (term) < 1.5 (preterm)	< 0.55[31]	< 0.35	< 0.58
Serum CRP (mg/l)	Less useful	< 20	< 20	< 20

CRP: C-reactive protein, CSF: cerebrospinal fluid

Table VII: Prevalence of antibiotic resistance in South Africa among meningitis strains

Bacteria	Antibiotic	MIC (µg/ml)	Prevalence	Time
Steptococcus pneumoniae	Penicillin[34-35]	± 0.12	35% overall < 5 years, 56% ≥ 5 years, 35%	2006-2008
	Ceftriaxone[35]	≥ 1 µg/ml	< 5 years, 15% ≥ 5 years, 6%	2009
	Pencillin and cephalosporin resistance expected to decrease with infant conjugate pneumococcal vaccine use[36-37]			
Neisseria meningitidis	Pencillin[38]	≥ 0.12	6%	2001-2005
	Clinical significance of penicillin intermediately resistant strains unknown. Some guidelines advocate ceftriaxone or cefotamine when MIC ≥ 0.12 (B-I)[39]			
Haemophilus influenzae	Ampicillin[40]		16%. All but one isolate produced ß lactamase	2003-2008

MIC: minimum inhibitory concentration

Table VIII: Recommendations for choice and duration of directed therapy for bacterial meningitis

Pathogen	Antimicrobial	Alternative	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

MIC: minimum inhibitory concentration

to *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*. No differences in survival or neurological outcomes were detected and there were similar numbers of treatment failures in both groups with very few relapses. This evidence suggests that for children who are clinically stable on day five, five days treatment may be sufficient. The recommendations in Table VIII should be considered as a guide only. Duration of therapy should be based on the individual's clinical course and response to therapy. Despite the reported high prevalence of ceftriaxone resistant *S. pneumoniae* isolates, vancomycin should not be added empirically. The majority (> 80%) of isolates tested were intermediately resistant [minimum inhibitory concentration (MIC) = 1 µg/ml] and may still respond to adequate high-dose ceftriaxone or cefotaxime. Vancomycin should be added if MIC ≥ 1 µg/ml is confirmed or there is a poor clinical response after 48 hours. Risk factors for ceftriaxone nonsusceptibility include young age (< 5 years), vaccine serotype, and recent ß-lactam use. Recommended doses are shown in Table IV.

Eradication of nasal carriage of *Neisseria meningtidis* is achieved with single-dose ceftriaxone, but penicillin is not effective in clearing nasal carriage. Therefore, if only penicillin is used for treatment, nasal carriage should be eradicated with single-dose ciprofloxacin or a two-day course of rifampicin if this is unavailable. Resistance by *N. meningitidis* to ciprofloxacin and rifampicin, used for the eradication of nasal carriage and secondary prophylaxis, is rare in South Africa.[38-39]

Avoid the use of ceftriaxone in patients receiving concomitant intravenous calcium-containing fluids, such as Neonatalyte®. Cefotaxime is the preferred alternative to ceftriaxone in all infants < 3 months of age and in patients receiving intravenous calcium-containing fluids.

Herpes simplex virus

If herpes simplex encephalitis is either confirmed by PCR or not excluded on the basis of other tests, aciclovir 10 mg/kg eight hourly intravenously (20 mg/kg in neonates) should be continued for 14-21 days.

Special groups

Recurrent bacterial meningitis

The following risk factors should be actively excluded in a patient with a second episode of meningitis: congenital or post-traumatic anatomical defects of the cranium and sinuses, congenital or acquired asplenia, primary immunodeficiencies, e.g. terminal complement deficiency and acquired immunodeficiency, e.g. HIV infection (C-I).

Hospital-acquired infection

Base the choice of empiric antibiotics for hospital-acquired meningitis on likely nosocomial pathogens and local antimicrobial susceptibility patterns (C-I). In patients with CSF shunts, removal of the infected shunt, temporary external CSF drainage and appropriate antimicrobial therapy (vancomycin plus ceftazidime or cefepime) are generally effective[45-46] (A-II).

Base of skull fracture

Give ceftriaxone, pending the results of CSF culture, plus vancomycin if ceftriaxone MIC ≥1 µg/ml is anticipated or confirmed.

Infection control and post-exposure prophylaxis

Meningococcal disease is notifiable by telephone to local health authorities on the basis of a clinical diagnosis alone, or preliminary or confirmed laboratory diagnosis.

Post-exposure chemoprophylaxis should be provided to close contacts of suspected cases of *N. meningitides* and *H. influenzae* serotype b as soon as possible, but may be effective up to 10 days after exposure. Close contacts are people living in

the same house or sharing eating utensils with the index case in the seven days prior to the onset of illness. In an educational setting, these include close friends who may share eating utensils. It may be more difficult to define a close contact among younger children in preschools or crèches. Healthcare workers are not considered to be close contacts unless directly exposed to the patient's nasopharyngeal secretions.

Chemoprophylaxis is also recommended for all contacts of suspected cases of *H. influenzae* type b (Hib) where the following criteria apply:

- Household with any child under four years of age who is incompletely vaccinated or unvaccinated.
- Household with any immunocompromised children, regardless of child's Hib immunisation status.
- Child care centre contacts, when two or more cases have occurred within 60 days.
- For index case (if under two years of age) and treated with a regimen other than cefotaxime or ceftriaxone (prophylaxis is usually provided just before hospital discharge).

Mass chemoprophylaxis is not generally recommended for the control of meningococcal disease outbreaks.

Neisseria meningitides

Ciprofloxacin (500 mg stat for adults and 10 mg/kg stat for children), ceftriaxone (250 mg stat intramuscularly) is an alternative option in pregnancy.

Hib

Daily rifampicin should be given for four days (10 mg/kg/day < 1 month, 20 mg/kg/day > 1 month, maximum 600 mg daily).

Streptococcus pneumoniae

No prophylaxis is required.

Suspected or confirmed cases of *N. meningitidis* or Hib should be placed on standard and droplet precautions (side room and healthcare workers to wear aprons, gloves and surgical masks). Discontinue after 24 hours of therapy, except meningococcal cases treated with penicillin who have not received nasopharyngeal carriage eradication therapy.

Vaccine-preventable meningitis

Inclusion of the measles vaccine, Hib vaccine and more recently, the pneumococcal conjugate vaccine, into childhood immunisation programmes, has altered meningitis aetiology. Similarly, in some settings, meningococcal vaccines may also impact on the epidemiology of meningococcal disease, although they have not yet been included as part of the public immunisation programme in South Africa. The schedule for immunisations targeting meningeal pathogens is shown in Table IX.

Table IX: Immunisation schedule of vaccines targeting meningeal pathogens in South Africa

Haemophilus influenza type b
Hib (combined with DTaP-IPV): 6, 10 and 14 weeks, and at 15-18 months
Streptococcus pneumoniae
13-valent PCV: 6 and 14 weeks, and at 9 months (An additional dose at 10 weeks is proposed for children who are HIV infected)

DTaP-IPV: Diptheria, tetanus, acellular pertussis-inactivated polio vaccine, Hib: *Haemophilus influenzae*, HIV: human immunodeficiency virus, PCV: pneumococcal conjugate vaccine

Although a quadrivalent polysaccharide vaccine is available, conjugate meningococcal vaccines, which may have a role to play in outbreak situations to reduce the risk of pharyngeal colonisation and subsequent transmission within communities, are not yet licensed in South Africa. Other vaccines currently under development include those that protect against *S. agalactiae* (Group B), which has emerged as the most common cause of childhood meningitis in settings in which other conjugate vaccines have been introduced into public immunisation programmes.

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