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CONTRIBUTING PHYSICIANS

Listeriosis:

Clinical recommendations for diagnosis and treatment

Version 1 (5 December 2017):

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Quick Reference Guide – Listeriosis

How does listeriosis present clinically? **Page 8**

- Gastroenteritis (mean incubation <24hrs, range 6hrs-10days).
- Flu-like symptoms in pregnant women, with premature labour and early onset neonatal sepsis (mean incubation 28 days, range 17-67 days).
- Neonatal sepsis, with/without respiratory distress, skin rash, granulomatosis infantiseptica.
- Meningitis with/without brain stem involvement, encephalitis, seizures, coma (mean incubation 10 days, range 0-21 days).

Empiric treatment of acute bacterial meningitis

Page 12

- All cases of neonatal sepsis and all cases of acute bacterial meningitis regardless of age group should be treated according to RSA EML and clinical guidelines for acute bacterial meningitis, with the addition of ampicillin at meningitis doses. See page 12 for doses.
- If an alternative aetiological diagnosis is made, ampicillin should be stopped.
- Where no pathogen is identified and no alternative diagnosis is made, empiric treatment for acute bacterial meningitis should be discontinued after 10 days.

Notification of cases and additional support:

Case investigation forms may be obtained from the NICD website www.nicd.ac.za under the 'Diseases A-Z' tab. Completed forms should be submitted by email to 'outbreak@nicd.ac.za'

Laboratory support: National Institute for Communicable Diseases, Centre for Enteric Diseases: or after-hours, the NICD doctor-on-call 082 883 9920.

When should listeriosis be suspected? **Page 9**

- Listeria should be considered in all cases of suspected acute bacterial meningitis. Epidemiological evidence gathered over 2017 illustrates that *L. monocytogenes* is now the second commonest cause of acute bacterial meningitis in South Africa.
- There is no data regarding the frequency of listeriosis amongst cases of neonatal sepsis, but the number of cases identified in South Africa from January to October 2017 (n=161) suggests that *L. monocytogenes* should be suspected in all neonates with a diagnosis of neonatal sepsis.

Laboratory diagnosis of *Listeria monocytogenes*

Page 9-11

- Neither clinical signs and symptoms, nor a negative CSF cell count or chemistry CSF cell count and chemistry are helpful in excluding the diagnosis of listeriosis.
- However, *L. monocytogenes* is easily cultured from clinical specimens obtained from sterile sites (CSF, abscess fluid, blood).
- *L. monocytogenes* is not routinely cultured on stool specimens – speak to a clinical microbiologist.
- Gram-positive bacilli on CSF are seen in less than 33% of culture positive cases. Therefore a negative Gram's stain does not rule out *Listeria*.
- CSF culture may be negative in cases of listeriosis with rhombencephalitis (brainstem involvement with cranial nerve impairment), or low bacterial loads.
- PCR is sensitive and specific for the diagnosis of Listeria. NICD and private laboratories offer a PCR test for *L. monocytogenes,* and other causes of bacterial/viral

Definitive treatment of acute bacterial meningitis, bacteraemia or sepsis due to *L. monocytogenes*

Page 12-15

Meningitis and bacteriaemia due to listeriosis should be treated according to the EML and South African guidelines for the treatment of acute bacterial meningitis.

The addition of gentamicin in adults with meningitis may be considered but is of uncertain value in improving clinical outcomes.

Contents

1. Introduction

Listeriosis is a bacterial disease caused by the Gram-positive, rod-shaped, motile bacterium, *Listeria monocytogenes*. The bacterium is widely distributed in nature and can be found in soil, water and contaminated food. Animals and food products such as vegetables can become contaminated from these sources. Infection with *L. monocytogenes* is usually asymptomatic or may result in mild to severe febrile gastroenteritis. However, in persons with weak cell-mediated immunity, listeriosis can lead to meningitis (inflammation of the brain and spinal cord membranes) or septicaemia (blood infection). In pregnant women, listeriosis may result in pregnancy loss (abortion) along with sepsis and meningitis of their infant.

In July and August 2017, clinicians and microbiologists at a number of sites in Gauteng Province reported an increase in cases of neonatal sepsis and adult meningitis due to *L. monocytogenes* (Figure 1). In October 2017, 129 culture-confirmed cases of listeriosis were reported to the NICD, and *L. monocytogenes* became the second most common cause of meningitis after *Streptococcus pneumoniae* (Figure 2). In the context of an increasing number of cases of listeriosis identified in the private and public sectors, it became apparent that clinical diagnostic and management algorithms for meningitis did not comprehensively address issues specific to infection with *L. monocytogenes*, and that additions were required.

While the empiric management of acute bacterial meningitis is covered in the South African Essential Medicine List (EML), and comprehensively described in South African guidelines[1], there are specific questions pertaining to the diagnosis and management of listeriosis that have been made more urgent in the current epidemiological context, and that are not addressed in these guidelines. This clinical advisory seeks to address these questions by providing evidence to support responses, and also to put forward a consensus opinion of infectious disease clinicians and clinical microbiologists where evidence is conflicting or insufficient.

Figure 1. Number of laboratory-confirmed cases of *L. monocytogenes* reported to the NICD in private (blue) and public (orange) sector patients from all provinces of South Africa, January to October 2017

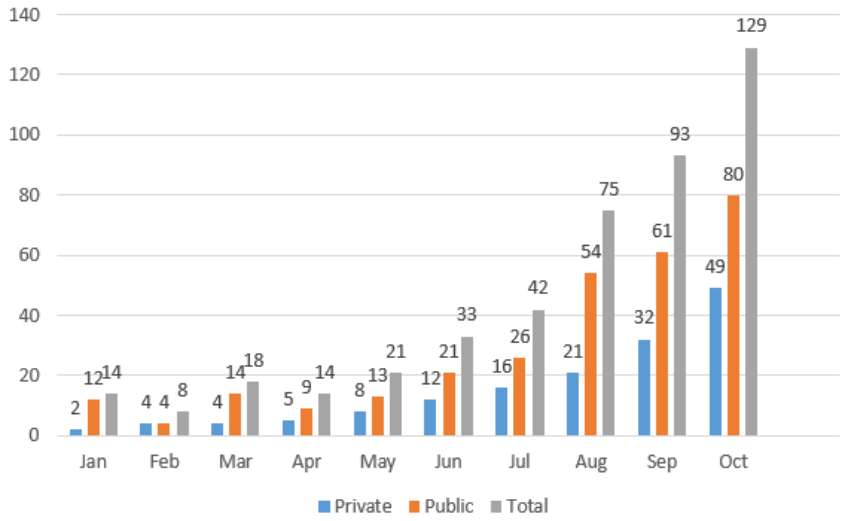
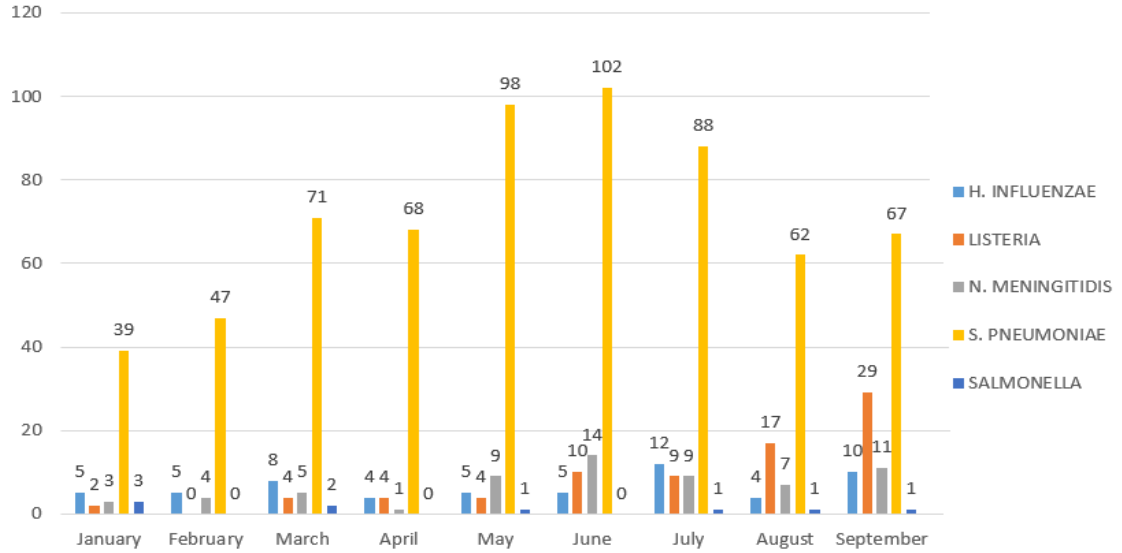


Figure 2. The number of cases of culture-confirmed bacterial meningitis (public and public sector) reported to the GERMS-SA laboratory network by month of 2017.



2. Objectives of this clinical advisory

The objectives of this clinical advisory are to provide clinicians with available evidence in support of responses to the following clinical, diagnostic and management questions:

1. What are the clinical presentations of listeriosis, and when should listeriosis be suspected?
2. When should empiric treatment for acute bacterial meningitis include cover for *L. monocytogenes*?
3. How sensitive and specific are diagnostic tests for *L. monocytogenes*, including Gram's stain, culture, latex agglutination and polymerase chain reaction (PCR)?
4. To what degree does pre-treatment with antibiotics affect diagnostic tests for *L. monocytogenes*?
5. Is there a place for detection of *L. monocytogenes* in stool?
6. When can empiric treatment for acute bacterial meningitis, which includes cover for *L. monocytogenes* be discontinued?
7. What specific antibiotic treatment should be given for meningitis, bacteraemia, neonatal sepsis and gastro-enteritis caused by *L. monocytogenes*?
8. What is the duration of treatment of bacterial meningitis, and bacteraemia due to *L. monocytogenes*?

3. Epidemiology of listeriosis

Amongst 440 cases of listeriosis identified in South Africa from January to October 2017, the majority were adults (245, 56%) followed by neonates (161, 37%). The age and gender distribution is shown in Figures 3 and 4. Adults >65 years of age comprised 10% (44 cases). Amongst neonates, 114/161 (71%) and 25/161 (16%) presented on day 0 and 1 of life respectively. Amongst those adults in whom HIV status was known, 25/32 (78%) were HIV positive.

Figure 3. Number of *Listeria* cases and gender distribution amongst 5 categories of listeriosis patients reported to the NICD between January to October 2017.

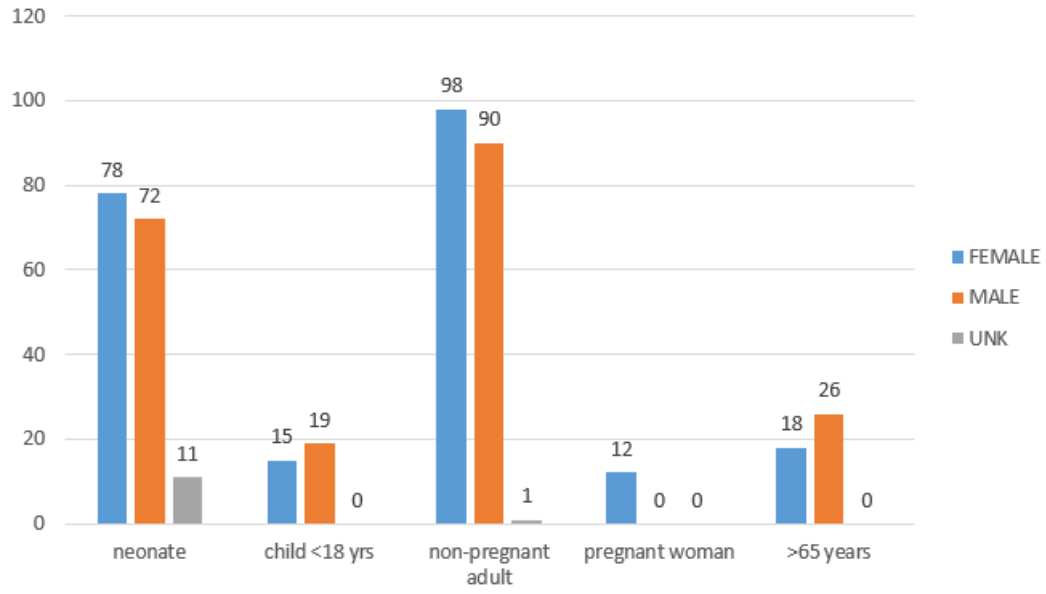
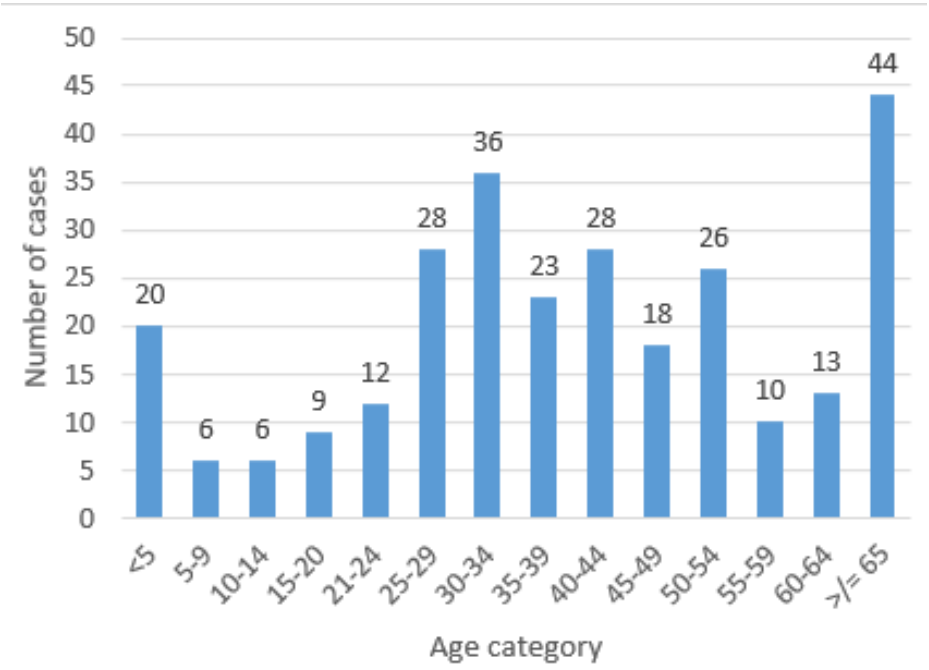


Figure 4. Number of cases of laboratory-confirmed listeriosis in South Africa from January to October 2017 by 5-year age category, EXCLUDING neonates (less than 1 month of age), (n=279)



Listeria has been an uncommon cause of meningitis in South Africa. Amongst 141 cases of adult meningitis in Pretoria Hospital from 1994-1998, no cases due to Listeria were identified[2]. It was established early in the HIV epidemic that the incidence of listeriosis was greater amongst persons infected with HIV. In Los Angeles from 1985-1992, the incidence of listeriosis was 95.8 and 8.8 cases per 100,000 person-years among persons with AIDS and all HIV-infected persons, respectively, but only 1.0 case per 100,000 person-years in the total population[3].

4. Microbiology of *Listeria monocytogenes*

Listeria monocytogenes is a Gram-positive non-spore-forming, facultatively anaerobic bacillus. Its optimum growth temperature is between 30°C and 37°C, but it will grow well at 4°C. The primary habitat of the bacterium is soil and decaying vegetable matter, but it is widely distributed in the environment, and can be found in silage, sewerage, water and animal feed[4]. *L. monocytogenes* is often found contaminating foodstuffs including fresh and frozen poultry, processed meats, raw milk and cheese, and fresh produce including fruit and vegetables. Humans may carry the organism asymptomatically in their gastro-intestinal tract. The organism is non-fastidious and will grow on blood agar.

5. Clinical presentations of listeriosis

Infection with *Listeria monocytogenes* may by asymptomatic, or it may result in a spectrum of clinical presentations including acute non-febrile or febrile gastro-enteritis, sepsis, or meningitis. Sepsis (bacteraemia) in pregnant women often results in placental infection, with subsequent premature onset of labour, and neonatal sepsis, with or without meningitis. Meningitis due to *L. monocytogenes* is acute, and presents similarly to acute bacterial meningitis. Occasionally central-nervous system infection by *L. monocytogenes* in adults may present with encephalitis, rhombencephalitis (brainstem encephalitis), or focal signs suggestive of brain abscess formation. Uncommonly focal infections involving the eye may occur.

5.1. Asymptomatic carriage of Listeria monocytogenes

Colonisation or transient carriage of *Listeria* occurs in approximately 1-5% of heathy adults[5,6]. It is likely that individuals experience multiple exposures per year, with transient carriage – Grif et al detected an average of 2 episodes of faecal carriage in 3 persons studied over one year. Each episode of carriage lasted less than 4 days and was asymptomatic[6]. In addition, contacts of persons with invasive disease due to *Listeria* have a high incidence of faecal carriage, ranging from 20-25%[7].

5.2. Gastroenteritis due to *Listeria monocytogenes*

Gastroenteritis due to Listeria is typically self-limited, and is accompanied by fever (60-100% of cases), non-bloody diarrhoea (33-88%), arthromyalgia (20-100%) and headache (15-88%)[8]. Fever and vomiting are more common amongst children, and diarrhoea and arthralgia are more common in adults[9]. The incubation period for gastroenteritis is usually 24 hours or less, but has ranged from 6 hours to 10 days[8]. The usual duration of symptoms is 1-3 days, but can last for up to one week. Hospitalisation following gastroenteritis due to listeriosis is more common amongst children or the elderly, and amongst these persons, blood cultures may yield *Listeria*[10,11]. In outbreaks of gastroenteritis a proportion of persons may also present with a flu-like illness without gastro-intestinal symptoms[11].

5.3. Listeriosis in pregnancy

Pregnancy is a predisposing factor for the development of invasive disease due to *Listeria*, as underlying risk factors in pregnant women with listeriosis are uncommon[12] . The incubation period for listeriosis in pregnancy has been estimated to be 27.5 days, with a range of 17-67 days[13]. Listeriosis in pregnancy presents with mild flu-like symptoms, with fever, backache and headache[14]. A minority of pregnant women may only have gastrointestinal symptoms, and some may even be asymptomatic[14] but infection can be inferred through development of neonatal sepsis due to

Listeria[15]. Most cases of listeriosis in pregnancy tend to occur during the third trimester[15], but listeriosis does occur at earlier stages of pregnancy, and is associated with poorer neonatal outcomes. Adverse sequelae following infection in pregnant women include spontaneous abortion, still birth, or preterm birth[15]. Neonatal infection with *Listeria* does not follow all cases of maternal infection.

5.4. Neonatal infections due to *Listeria monocytogenes*

Neonatal infection with Listeria is acquired through transplacental infection, or through inhalation of infected amniotic fluid, or following colonization from maternal gastro-intestinal or vaginal carriage[15]. Similar to neonatal group B streptococcal infection, listeriosis in neonates may present with early or late onset disease. Early onset disease presents within 36 hours, and most likely represents transplacental neonatal infection, as more than half of mothers have *Listeria* isolated from their genital tract or blood culture[15]. Neonates present with sepsis (90%), respiratory distress or pneumonia (40%), meningitis (25%), and occasionally with disseminated inflammatory granulomata (so-called 'granulomatosis infantiseptica'). Occasionally a characteristic rash is present with maculopapular or papulovesicular lesions on the trunk or extremities[12]. Microabscesses may be seen on the foetal surface of the placenta[12]. Late onset disease develops between 5-30 days postpartum, and presents with the development of non-specific symptoms, sepsis and meningitis.

5.5. Bacteraemia due to *Listeria monocytogenes*

In adults, bacteraemia due to *Listeria* may or may not be associated other clinical presentations of illness. Bacteraemia due to *Listeria* may follow gastroenteritis[8-10,13], or be associated with pregnancy[14-16] or neonatal infection. Isolated bacteraemia in adults is usually associated with underlying risk factors including HIV infection, steroid use, underling malignancy, chemotherapy or age >65 years.

5.6. Acute bacterial meningitis or invasive neurological disease due to *Listeria monocytogenes*

Listeria has been associated with acute meningitis and encephalitis. In addition, *L. monocytogenes* is associated with rhomboencephalitis - the involvement of the midbrain, pons and/or cerebellum with associated cranial nerve involvement or cerebellar signs (ataxia, tremor), or the development of hemiparesis. The incubation period of meningitis is estimated to be 0-21 days with an average of 10 days[17]. In a study of over 100 cases of neuroinvasive listeriosis, neck stiffness was present in 75% of cases, focal neurological signs in 30%, seizures in 30% and coma in 7%[18]. Focal neurological signs included single or multiple cranial nerve involvement, (most commonly the 6th and 7th cranial nerves) hemiparesis, ataxia and aphasia. Nine cases had rhombencephalitis[18]. Delay in treatment and the presence of seizures were associated with poor outcome.

6. Diagnosis of listeriosis

6.1. Diagnosis of *Listeria* bacteraemia

Listeria monocytogenes is not fastidious and may easily be cultured from blood using standard blood culture techniques and laboratory identification protocols. No additional diagnostic assays are advised.

6.2. Diagnosis of *Listeria* gastroenteritis

Clinical microbiology laboratories do not routinely look for *L. monocytogenes* in stool specimens that have been submitted for microscopy, culture and sensitivity for the following reasons[19]: 1) gastroenteritis due to *L. monocytogenes* is uncommon, and is usually self-limiting in persons without underlying risk factors; 2) the interpretation of positive and negative stool cultures for *L. monocytogenes* is difficult: *L. monocytogenes* has been shown to be transiently present in stool in asymptomatic persons; 3) stool culture may be falsely negative as culture may not be sufficiently sensitive.

However during outbreaks of listeriosis, the isolation of the bacterium from stool may be helpful in the identification of contaminated foodstuffs as febrile gastroenteritis due to *L. monocytogenes* has the shortest incubation period (<48 hours) of all clinical syndromes caused by the bacterium. If clinicians are considering *L. monocytogenes* in their differential diagnosis of acute febrile diarrhoea, they should indicate this on the specimen request slip and should discuss the case with a clinical microbiologist or laboratory technologist.

6.3. Diagnosis of meningitis due to *Listeria* monocytogenes

The diagnosis of meningitis due to *L. monocytogenes* begins with the recognition of acute meningitis. Adults with any two of: 1) headaches; 2) fever >37.5^{o}C; 3) neck stiffness or 4) altered mental status of <7 days' duration should be investigated for meningitis[20]. The presence of Kernig's and Brudzinski's signs are unreliable indicators of meningitis and should not be used[21]. The diagnosis of rhombencephalitis may be suspected in adults with symptoms of acute meningitis or a febrile prodrome with cranial nerve involvement or hemiparesis. In children, the clinical presentation of meningitis is age-dependent (Table 1) which limits the diagnostic accuracy of clinical features, compared to adults[22,23]. Therefore, a lower threshold for suspecting meningitis should be applied to infants and young children, compared with older age groups. Fever, vomiting and altered level of consciousness are common to persons of all ages with meningitis. 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[24]. The signs and symptoms of paediatric acute meningitis merge with those of adults beyond 3-5 years of age[24].

Table 1. Signs and symptoms of acute meningitis specific to various age groups (according to [1])

	Neonates and infants <3 months of age	Infants and young children: 3 months to 3 years	Older children (> 3 years) and adults
Symptoms	Irritability Poor feeding	Headache Neck stiffness	Headache Neck stiffness Photophobia
Signs	Bulging fontanelle Hypothermia or pyrexia		Maculopapular or petechial rash Neck stiffness

Lumbar puncture (LP) is an essential diagnostic procedure for determining the aetiological cause of meningitis. However, when acute meningitis is suspected, LP is contra-indicated in the following circumstances[1]:

- Coma or markedly decreased level of consciousness (Glasgow Coma Scale <10).
- Papilloedema.
- Unexplained new focal neurological deficit such as hemiparesis or dysphasia.
- Unexplained seizures.
- Cranial nerve involvement with altered level of consciousness (isolated cranial nerve involvement is not a contra-indication to LP).
- Presence of a ventriculoperitoneal shunt.
- Severe cardiorespiratory compromise.
- Clinical evidence of abnormal bleeding.
- Sepsis over the LP site.

According to guidelines, blood cultures should always be taken in addition to a LP[1]. Where it is not possible to do a lumbar puncture in persons with signs or symptoms of meningitis, blood cultures should still be taken as these may be helpful in yielding a causative organism[1] and empiric antibiotics should be commenced (see Section 7.1)

If a LP is performed, cerebrospinal fluid (CSF) should be submitted for Gram's stain, cell count, chemistry, cryptococcal latex agglutination test and bacterial culture. Persons with confirmed *L. monocytogenes* meningitis usually present with CSF parameters including cell counts and glucose concentration that are no different to persons with acute meningitis due to other bacteria[18,25,26]. International guidelines agree that CSF parameters such as cell count and chemistry are unreliable factors on which to base aetiological presumptions or treatment decisions, including the addition or cessation of antimicrobial agents. The Gram's stain on CSF of persons with meningitis due to *L. monocytogenes* is less frequently positive compared with other bacterial aetiologies. Most case series report the visualisation of Gram-positive bacilli in less than a third of CSF specimens where *L. monocytogenes* is cultured[18,27,28].

Polymerase chain reaction (PCR) on CSF is sensitive and specific for the diagnosis of meningitis due to *L. monocytogenes*[29,30] and other bacterial and viral pathogens (enterovirus and herpes simplex virus). PCR may be helpful where Gram's stain and culture does not identify bacterial organisms[31]. A real-time PCR for the diagnosis of *Listeria* is currently available in the private sector, and at the NICD (with limited availability for diagnostic testing, personal communication, Prof Anne von Gottberg, Centre for Respiratory Diseases and Meningitis). Both product specifications report and in-house validation have confirmed that the *Listeria* PCR assay has a threshold of detection of 10^3 organisms/mL.

Where Gram's stains are negative, and meningitis is suspected on the basis of clinical presentation and CSF findings, empiric antibiotics should be initiated as described below. CSF may be submitted to the NICD for PCR of bacterial agents causing meningitis including *L. monocytogenes.* However, this should be arranged in consultation with clinicians at the Centre for Respiratory Disease and Meningitis (011-555-0327) as the long turn-around time, and inability to support large numbers of

diagnostic specimens mean that this test may not be helpful for clinical management. Importantly, empiric antibiotic treatment should be continued even if PCR is negative for bacterial pathogens.

Latex agglutination tests for the diagnosis of bacterial meningitis are not recommended by South African or international guidelines[1,28,32]

7. Treatment of listeriosis

7.1. Treatment of gastroenteritis due to *Listeria monocytogenes*

In immunocompetent persons with no risk factors for invasive listeriosis, gastroenteritis due to Listeria monocytogenes has usually resolved by the time the diagnosis is made. Therefore treatment is not usually indicated. However, gastroenteritis due to Listeria in persons with underlying risk factors, such as pregnant women, persons with malignancy, on chemotherapy, the elderly may be treated with oral ampicillin or cotrimoxazole in standard doses for 3-7 days[8].

7.2. Empiric treatment of acute bacterial meningitis

Regarding empiric treatment of acute meningitis, current South African guidelines including the EML advise ceftriaxone (adults, children and infants>1 month of age) and cefotaxime (neonates) as empiric treatment for acute bacterial meningitis[1]. However *L. monocytogenes* is intrinsically resistant to cephalosporin antibiotics because the organism lacks penicillin-binding-proteins that render other bacteria susceptible to cephalosporins[33]. *L. monocytogenes* has *in vitro* susceptibility to a wide range of antimicrobial agents including penicillin, ampicillin, imipenem, gentamicin, macrolides, co-trimoxazole and ciprofloxacin[33]. However, most clinical experience in the treatment of listeriosis is with ampicillin[1,28,32,34]. Therefore, guidelines advise addition of ampicillin in the following circumstances: 1) in neonates; 2) in adults >50 years; 3) in those who are immunosuppressed because of malignancy, immunosuppressive drugs, alcoholism, liver cirrhosis, asplenia, end-stage renal failure or diabetes mellitus. The guidelines expressly indicate that HIV co-infection is not an indication to add ampicillin.

However, in the context of the increased incidence of listeriosis in South Africa in 2017, and until more evidence is available regarding underlying risk factors or exposures, an emergency update of current guidelines for treatment of acute meningitis is required. We advise that that empiric treatment for <u>all cases</u> of suspected acute bacterial meningitis, regardless of age or underlying risk factors should include agents listed in Table 2.

Table 2. Revised empiric antibiotic treatment for acute meningitis following the recognition of *Listeria monocytogenes* as the second most common cause of bacterial meningitis in South Africa (October 2017 and onwards until further information becomes available) (dosages/regimens are provided as a guide – dose modification where applicable is advised)

	Adults	Age category	Neonates and children Ampicillin (ivi)[#]	Cephalosporin (ivi)
Recommended treatment	Ceftriaxone 2g iv 12 hourly **PLUS** ampicillin 3g iv 6-hourly	Neonates < 7 days and <2000g	100mg/kg/day in 2 divided doses	Cefotaxime 50 mg/kg/dose given 6-hourly
		Neonates < 7 days and >2000g	150mg/kg/day in 3 divided doses	
		Neonates 8-31 days and <2000g	150mg/kg/day in 4 divided doses	
		Neonates 8-31 days and >2000g	200mg/kg/day in 4 divided doses	
		Infants >31 days and children	300mg/kg/day in 4-6 divided disease with a maximum of 12g/day	Ceftriaxone50mg/kg 12 hourly
			Co-trimoxazole (ivi)	**Cephalosporin (ivi)**
Treatment in the presence of confirmed penicillin allergy	Ceftriaxone 2g iv 12 hourly **PLUS** Co-trimoxazole 20mg TMP/kg/day in divided doses 8 hourly*	Neonates <31 days	Co-trimoxazole 8-12mg TMP/kg/day in divided doses 8 hourly*	Cefotaxime 50 mg/kg/dose given 6-hourly
		Infants >31 days and children	Co-trimoxazole 8-12mg TMP/kg/day in divided doses 8 hourly*	Ceftriaxone 50mg/kg 12 hourly

*Frequent, smaller doses of co-trimoxazole are advised (i.e. 6hrly) to minimize toxicity[35]; however 6hrly dosing is impractical in resource-poor settings. Eight hourly dosing is recommended as a compromise.
#ampicillin dose according to reference [36]

Empiric treatment of acute meningitis may commence before transfer to hospital and according to the above guidelines[1]. Following transfer to hospital, and if no contra-indication to LP is present, LP and blood culture should be done immediately, followed by initiation (or continuation) of empiric antimicrobial therapy. If LP is contra-indicated, blood cultures should be collected, following by initiation/continuation of empiric antimicrobial therapy and CT scan of the brain.

Empiric treatment for bacterial meningitis should be continued until a definitive diagnosis is made. When a definitive diagnosis is made, treatment specific for that aetiology should be commenced and empiric treatment for listeriosis stopped. In the event that a diagnosis is not made, international guidelines for the treatment of acute bacterial meningitis recommend that antibiotic therapy may be ceased after 10 days of treatment if there has been a favourable clinical response to such treatment [28,32,34]. In the absence of evidence to support an alternative approach, we advise the same. However, in the context of an outbreak of listeriosis, clinicians may elect to continue antibiotics for 21 days if the diagnosis is suggestive of rhombencephalitis, or if they has other reasons to suspect meningitis due to *L. monocytogenes*.

7.3. Definitive treatment of invasive *Listeria monocytogenes* infection in neonates, children and non-pregnant adults

Ampicillin has good activity against *L.monocytogenes*, and is the recommended antimicrobial agent for the treatment of bacterial infections due to *Listeria*[1,28,32]. While numerous antibiotics are active against *Listeria* (Table 1), clinicians have most experience with ampicillin over the years[37,38]. There are theoretical reasons why this choice is surprising as ampicillin is bacteriostatic *in vitro*, has relatively poor CSF penetration (<15%), and relatively low intracellular concentrations[39]. However, animal studies and human case-series demonstrate efficacy[38]. *In vitro*, ampicillin inhibits production of the virulence factors listeriolysin and beta-galactosidase, which may permit cell mediated destruction of the organism, and facilitate cure[38].

Table 3. In vitro activity and CSF penetration of selected antibiotics active against *Listeria*[33,39]

Antibiotic	MIC range	Comments	CSF penetration (CSF: blood ratio, %)[39]
Ampicillin	0.06-0.5 (susceptible)	Bacteriostatic *in vitro*	13-14%
Gentamicin	0.06-4 (susceptible)	Bactericidal *in vitro*	0-30%
Rifampicin	0.04-0.25 (susceptible)	Bacteriostatic *in vitro*	7-56%
Co-trimoxazole	0.06-0.5 (susceptible)	Bactericidal *in vitro*	<41%

The addition of gentamicin has unclear impact on mortality amongst listeriosis. Gentamicin and ampicillin are synergistic *in vitro*, and the combination may be effective against extracellular bacilli[38]. However, penetration of gentamicin into CSF is poor[39], and the use of gentamicin is limited by toxicity. Gentamicin has high intracellular concentrations, but it is contained exclusively within the lysosome where the pH renders gentamicin into its protonic isoform, which is completely inactive[38]. Further, mouse models have not shown benefit of ampicillin/gentamicin vs ampicillin alone. Four studies (three retrospective record reviews and a single prospective study) have compared clinical outcomes of listeriosis when treatment with combination therapy (ampicillin with gentamicin) with ampicillin alone and report the following findings:

- Mitja et al[40] reviewed 102 cases in adults treated in Spain from 1983-2006 and looked at the relationship between early mortality (>48 hrs until day 14 after presentation) or late mortality (>14 days) with administration of combination antibiotic therapy vs ampicillin alone, and observed that ampicillin monotherapy was protective against death within 14 days (4.3% vs 11.8%, p=0.003). Further, gentamicin combination therapy tended towards an increase early mortality, aOR=3.9 (0.78-19.4, p=0.09).
- Thonnings et al[41] reviewed 229 patients in Denmark, including adults and children, from 1997-2012 and observed that persons treated with combination therapy (ampicillin plus gentamicin) were more likely to survive but this was not statistically significant. However, there were significant analytical problems as authors did not differentiate adults from neonates, nor eliminate deaths within 48 hours nor deaths post treatment completion.
- Arslan et al[18] did not observe any association between the addition of gentamicin to ampicillin in adults and poorer outcome including death or neurological sequelae amongst 100 patients with neuroinvasive listeriosis.

- Charlier et al[42] in the MONALISA prospective study of listeriosis in France over a 4-year period (July 2009-November 2013) identified in multivariable analysis that the addition of aminoglycoside therapy was protective against 3-month mortality (OR 0.6, 95% CI 0.38-0.94, p<0.024) amongst 679 cases of bacteraemia and neurolisteriosis.

All studies that have attempted to examine the relationship between combination therapy (ampicillin plus gentamicin) have methodological flaws such that definitive conclusions cannot be made based on their findings. These include retrospective data collection, differing (or absent) inclusion criteria, non-standardised dosing regimens and different mortality end-points. Therefore it is not possible to identify a superior antibiotic treatment regimen from this evidence base. Therefore, we advise that treatment of listeriosis should include ampicillin with or without gentamicin at the discretion of the attending physician. Factors such as the age of the patient, the presence of co-existing renal impairment, the ability to monitor renal function and disease severity may support a decision to omit or include gentamicin.

Most international clinical guidelines advise that *Listeria* meningitis and bacteraemia be treated for 21 days[1,28,32,34]. However, it is acknowledged that there is no evidence base for this[43]. The duration of antibiotic therapy is based on theoretical grounds related to the poor CSF penetration of ampicillin and gentamicin, the underlying risk factors amongst many persons with *Listeria*, and potential for intracranial spread. If gentamicin is co-administered with ampicillin, it need only be given for up to 7 days.

Dexamethasone or other steroids are not indicated in the treatment of meningitis due to *Listeria*[28,44].

Table 3. Antibiotic treatment for invasive infection due to *Listeria monocytogenes* (dosages/regimens are provided as a guide – dose modification where applicable is advised)

	Adults	**Neonates and children**		
		Age category	**Ampicillin (ivi)#**	**Gentamicin (ivi)**
Recommended treatment	Ampicillin 3g iv 6-hourly for 21 days with or without gentamicin# 3mg/kg/day ivi in three divided doses	Neonates < 7 days and <2000g	100mg/kg/day in 2 divided doses	2.5mg/kg/dose every 12 hours
		Neonates < 7 days and >2000g	150mg/kg/day in 3 divided doses	
		Neonates 8-31 days and <2000g	150mg/kg/day in 4 divided doses	2.5mg/kg/dose every 8-12 hours
		Neonates 8-31 days and >2000g	200mg/kg/day in 4 divided doses	2.5mg/kg/dose every 12 hours
		Infants >31 days and children	300mg/kg/day in 4-6 divided disease with a maximum of 12g/day	Gentamicin 7.5mg/kg per day in 3 divided doses
Treatment in the presence of confirmed penicillin allergy	Co-trimoxazole^ 20mg trimethoprim /kg/day in divided doses 8 hourly* for 21 days		**Co-trimoxazole (ivi)**	
		Neonates <31 days	Co-trimoxazole 8-12mg trimethoprim /kg/day in divided doses 8 hourly*	
		Infants >31 days and children	Co-trimoxazole 8-12mg trimethoprim /kg/day in divided doses 8 hourly*	

*Frequent, smaller doses of co-trimoxazole are advised (i.e. 6hrly) to minimize toxicity[35]; however 6hrly dosing is impractical in resource-poor settings. Eight hourly dosing is recommended as a compromise.
#ampicillin dose according to reference [36]

#Most international guidelines include gentamicin at the discretion of the attending physician[28,32]; gentamicin dose and dosing interval based on reference [27,38]; gentamicin is contraindicated in pregnant women
^Cotrimoxazole should be used with caution in pregnant women

7.4. Treatment of *Listeria monocytogenes* in pregnant women

Listeriosis in pregnant women has potential to cause adverse fetal outcomes, however, early treatment may lead to cure[45,46]. Therefore a high index of suspicion should be maintained by clinicians when managing pregnant women, particularly in the context of an outbreak. Women who experience gastro-enteritis followed by flu-like symptoms, or flu-like symptoms with or without fever should be investigated for listeriosis by taking of blood cultures. The value of stool cultures in these patients is unclear[19]. Pre-emptive treatment with ampicillin is reasonable in febrile pregnant women when the index of suspicion is high, and blood culture results are pending[19]

8. References

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