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Newsletter

LANCET LABORATORIES
Ghana

Updates in the Diagnosis of Meningitis and Encephalitis

Compiled by the Microbiologists

Meningitis presents with some combination of neck stiffness, fever, headache, nausea, vomiting and photophobia. Encephalitis is distinguished from meningitis by the presence of abnormal brain function as evidenced by altered mental status, motor or sensory deficits, altered behaviour or personality changes, and speech or movement disorders. When meningeal and parenchymal involvement both occur, there can be a mixed presentation of meningoencephalitis as is often seen with viral infections. Meningitis may be due to bacterial, mycobacterial, fungal (mainly Cryptococcus neoformans) or viral causes. Encephalitis is most frequently associated with a viral infection.

Acute Bacterial Meningitis

The incidence of acute bacterial meningitis (ABM) has decreased in the last decade due to:

- The introduction of *Haemophilus influenzae* type B and conjugated *Streptococcus pneumoniae* vaccines into childhood vaccination programmes. Recently, a conjugated vaccine against *Neisseria meningitidis* strains A, C, Y, W135 has also become commercially available.
- Screening of pregnant women for *Streptococcus agalactiae* (Group B Strep) as advocated by numerous clinical guidelines, with antibiotic prophylaxis being given to women during delivery to decrease the burden of Group B strep neonatal sepsis.

Despite these interventions, it is estimated that 1.2 million cases of bacterial meningitis occur annually worldwide. Bacterial meningitis has a high morbidity (hearing loss, visual impairment, limb loss and cognitive impairment) and mortality if left untreated. Therefore, appropriate antibiotic treatment for the causative pathogen should be started as quickly as possible.

Table 1. The most common community-acquired organisms responsible for ABM

Adults and children > 6 months of age	Infants < 6 months of age
Streptococcus pneumoniae	Group B Strep
Haemophilus influenzae	Listeria monocytogenes
Neisseria meningitidis	Escherichia coli K1
Listeria monocytogenes (in immunocompromised persons)	

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Viral Meningoencephalitis

Many different viruses can infect the central nervous system (CNS). Some are more likely to cause meningitis while others are more likely to cause encephalitis, but often there is a mixed presentation with features of both (meningoencephalitis).

Table 2. Causes of viral central nervous system infections

Herpes viruses: Herpes simplex virus type 1 and type 2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, human herpesviruses 6 & 7
Enteroviruses: Includes coxsackie viruses and echoviruses
Parechovirus
Paramyxoviruses: Mumps virus, measles virus
Respiratory viruses: Adenovirus, influenza virus
Arboviruses: West Nile virus, Rift Valley fever virus, dengue virus, chikungunya virus
Human immunodeficiency virus
Rabies virus

Diagnosis

Clinical manifestations of meningitis are relatively non-specific with regards to aetiology and it is difficult to differentiate bacterial from viral causes. Inflammatory markers such as C-reactive protein and procalcitonin are highly suggestive of a bacterial infection, but neither can definitively establish nor exclude the diagnosis of ABM.

Identification of the causative organism is essential for many reasons. Neisseria meningitidis has public health implications, and close contacts of the patient should be identified and given prophylactic antibiotics. Most of the common organisms responsible for ABM can be treated with Ceftriaxone, except Listeria monocytogenes, which is inherently resistant to the cephalosporin class of antibiotics.

Treatment is available for a number of viral infections of the CNS, most notably HSV-1, HSV-2, and VZV.

Definitive diagnosis involves performing a lumbar puncture (LP), if it is not contraindicated, and submitting the cerebrospinal fluid (CSF) to the laboratory for analysis. The CSF should be examined microscopically for cells (polymorphonuclear cells (PMNs), lymphocytes, and red blood cells). Typical changes of ABM include raised PMNs, but lymphocytes may also be raised in early disease, confounding the diagnosis.

Similarly, PMNs may be raised early in viral infections as well.

Chemistry of the CSF in ABM typically demonstrates low glucose compared to serum glucose and high total protein % 0.45 g/mL. Isolation of the organism by culturing the CSF was traditionally the "gold standard" of diagnosis. Some of the organisms responsible for ABM have fastidious culture requirements and the chance of a positive culture also decreases with prior antibiotic treatment. Thus, sensitivity of culture may be low. Streptococcus pneumoniae has autolytic enzymes which causes rapid death of the organism, especially at lower temperatures which may occur on transport of the specimen to the laboratory. Similarly, Gram staining the CSF also has poor sensitivity (approximately 40%) when prior antibiotic treatment has been administered.

Immunological tests, such as particle latex agglutination, directly on the CSF sample has traditionally been a useful adjunct to the diagnosis of ABM when there are abnormal findings on CSF microscopy and chemistry. Blood stained CSF may however cause false-positive results on the latex agglutination test. Studies have shown that the latex agglutination test has a low sensitivity in patients who have received any antibiotics prior to sampling. However, Cryptococcal antigen testing continues to be the diagnostic standard for diagnosis of Cryptococcal meningitis.

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PCR detection methods are more sensitive than conventional culture or immunological latex antigen tests, and may detect organisms that are non-viable or unculturable. CSF is normally a sterile body site where any evidence of a micro-organism is likely to represent infection, and infections are typically monomicrobial. For these reasons, molecular methods are well suited for the diagnosis of CNS infections.
The risks of contamination necessitate the need for strict adherence to aseptic collection policies (e.g. the use of sterile gloves and a surgical mask) during the LP procedure. Individuals with active respiratory infections (rhinovirus may cross-react with enterovirus), active/latent herpes simplex virus infection (i.e. cold sores), and asymptomatic shedders of S. pneumoniae, H. influenzae or other organisms, may contaminate samples and thus cause false-positive results.
PCR panels that include detection of cytomegalovirus (CMV) and human herpesvirus-6 (HHV-6) do not distinguish between latent/chromosomally integrated, secondary reactivation, or active infections - positive results should be carefully interpreted in conjunction with other clinical, laboratory, and epidemiological information.

A negative PCR result does not exclude the possibility of CNS infection and should not be used as the sole basis for diagnosis, treatment, or other management decisions. There is a risk of false-negative results due to the presence of sequence variants or rearrangements in the gene targets of the assay, procedural errors, inhibitors in specimens, technical error, sample mix-up, low pathogen load, or infection caused by an organism not detected by the panel used. Low viral load in CSF for certain viruses (e.g. herpes simplex virus), especially in the first 3 days after symptom onset, may warrant additional testing with an alternative singleplex assay, testing alternate sources (e.g. blood) or repeating the LP procedure after a few days for follow-up testing.

Lancet Laboratories offers both bacterial and viral PCR panels to provide the most sensitive test methodology and thus the most useful result for the management of your patients with meningitis /encephalitis. The bacterial PCR detects the most common causes of community-acquired
bacterial meningitis, including Listeria monocytogenes which is unavailable as a latex
agglutination test. The main limitations of bacterial PCR testing are that not all organisms are
included in the test, and antibiotic sensitivity is not yet done with molecular testing. Therefore, culture of the CSF with sensitivity testing should remain a part of the testing algorithm. Bacterial PCR testing will replace the latex agglutination (bacterial antigen) test. Viral PCR testing will only be performed if requested specifically.

Table 3. Organisms included in the Multiplex PCR panels

Bacterial multiplex PCR	Viral multiplex PCR	
Neisseria meningitidis	Herpes simplex type 1	Human herpesvirus 7
Haemophilus influenzae	Herpes simplex type 2	Enterovirus
Streptococcus pneumoniae	Varicella zoster virus	Parechovirus
Streptococcus agalactiae	Cytomegalovirus	Mumps virus
(group B strep)	Epstein-Barr virus	Adenovirus
Listeria monocytogenes	Human herpesvirus 6	
Escherichia coli K1		

Mortality rates of ABM are still high, as much as 5% – 10%, despite intensive care and antibiotic therapy. The risk of neurologic sequelae in survivors of ABM is reported to be 20%. ABM is a medical emergency and molecular testing has a dramatic impact on diagnosis and management, whereby rapid identification of a pathogen can result in prompt initiation of appropriate antibiotics, which is life-saving.

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