Recent advances in laboratory testing of cerebrospinal fluid improve the care of patients with meningitis

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Meningitis is an uncommon but potentially catastrophic illness. It can kill previously well people within a matter of hours or days. However, early in its course, or when caused by organisms with low virulence, it may be relatively difficult to distinguish from other much more common illnesses.¹

For the patient’s general practitioner the crucial issues are to consider the diagnosis, and to promptly transfer to hospital any patients whose clinical features are consistent with the diagnosis of meningitis. This will inevitably result in the referral to hospital of many patients who turn out not to have meningitis. For hospital doctors assessing patients with a possible diagnosis of meningitis, the crucial issues are to promptly perform those tests which may confirm or exclude the diagnosis of meningitis and identify the infecting organism, and, while waiting for the results of these tests, to start empiric antimicrobial treatment.

In general, effective antimicrobial treatment should be commenced within one hour of the diagnosis of meningitis being considered, and often is started by the referring general practitioner. In the majority of patients, meningitis is not a life-threatening illness, and recovery occurs within a few days, without the need for antimicrobial therapy. Rapid identification of the organism responsible for meningitis can allow many patients to be reassured, have their treatment stopped and be promptly discharged from hospital.

The report by McBride and co-authors, based in the adult infectious diseases department and the microbiology laboratory at Middlemore Hospital, in this issue of the NZMJ, provides information on the aetiology of meningitis in adult patients admitted to their hospital between 2000 and 2009, and the diagnostic tests they found most useful to identify the infecting microbe.²

During the study period the annual rate of admission to hospital for meningitis was approximately 1 in 5000 adults. The patients were relatively young, with a mean age of approximately 35 years, and with equal numbers of men and women. Overall, in 60% of patients no infecting pathogen was identified. However, the increasing use of new diagnostic tests during the study period resulted in a dramatic increase in the proportion of cases with a microbiologically proven aetiology, which doubled from 25% in 2000 to 50% in 2009.

Between 1991 and 2007 New Zealand suffered from a prolonged, severe, epidemic of disease due to Neisseria meningitidis.³ During the study conducted by McBride et al this national epidemic of meningococcal disease was declining, and in 2009, the last year of their study, there were no cases of meningococcal meningitis in adults admitted to Middlemore Hospital. However, N. meningitidis remains an important pathogen to consider in all patients presenting with meningitis because of the extreme rapidity with which it can kill, and because it responds so well to antimicrobial treatment.⁴

Unfortunately, in approximately 50% of patients with meningococcal meningitis the bacteria are not visible in a Gram-stained sample of cerebrospinal fluid (CSF), and in patients who have received antimicrobial treatment prior to lumbar puncture N. meningitidis may fail to grow. In recent years many hospital microbiology laboratories have introduced a polymerase chain reaction (PCR) test to detect N. meningitidis DNA, either in samples of CSF, or in blood from patients with meningococcal septicaemia. This test is extremely reliable at detecting the presence of meningococci, even when CSF has been collected some days after the start of antimicrobial treatment.⁵ In those patients whose episode of meningitis is due to N. meningitidis (6% in the Middlemore Hospital study), intravenous treatment with large doses of penicillin should be continued for a total of 3 days.⁴
The bacterial pathogen most frequently identified in the Middlemore Hospital study was *Streptococcus pneumoniae*. In recent years many microbiology laboratories have used the pneumococcal immuno-chromatographic test (PICT) to detect pneumococcal polysaccharide in CSF. This simple, relatively cheap test can rapidly and reliably determine whether meningitis is caused by *S. pneumoniae*. This information is helpful to the treating clinician because of its impact on decisions about antimicrobial treatment. Approximately 16% of *S. pneumoniae* isolates in New Zealand have reduced susceptibility to penicillin.

Because meningitis due to these relatively resistant strains may respond poorly to treatment with penicillin, patients with suspected or proven pneumococcal meningitis should be treated with penicillin, plus vancomycin either until the episode of meningitis has been demonstrated not to be due to *S. pneumoniae*, or until the infecting strain of *S. pneumoniae* has been shown to be fully sensitive to penicillin. McBride et al found that a negative PICT provided strong evidence that meningitis was not due to *S. pneumoniae*, and used this result as a basis to stop treatment with vancomycin.

A virus was the most frequently identified cause of meningitis in the Middlemore Hospital study. As in other studies, enteroviruses were the most commonly identified viruses (17% of patients), followed by herpes simplex viruses (4% of patients) and varicella zoster virus (3% of patients). PCR testing of CSF provides a rapid, reliable method for detecting these viruses and has largely replaced viral culture, because of advantages in speed, accuracy and availability. Timely identification of one of these viruses as the cause of a patient’s episode of meningitis is beneficial because it allows the patient to be reassured about the expected outcome and antibacterial therapy to be discontinued.

Other microbial causes of meningitis not identified in the Middlemore Hospital study include *Leptospira species* and human immunodeficiency virus (HIV). Leptospirosis remains a relatively common disease in livestock farm workers, particularly dairy farmers, and in meat processing workers in New Zealand. It should be considered in patients who report potential exposures to animal urine, especially if there is associated conjunctival injection, and abnormalities in renal and/or hepatic laboratory tests. A PCR test for leptospira DNA in the patient’s CSF is very reliable but not widely available.

Occasionally, patients who have recently acquired HIV infection will present with the clinical and laboratory features of aseptic meningitis. This diagnosis should be suspected in patients with epidemiological risk factors for HIV infection, and can be confirmed by demonstrating high levels of HIV in the patient’s serum.

Adverse reactions to medications are an occasional cause of aseptic meningitis, and need to be considered in the large proportion of patients in whom a microbial cause is not identified. Sulphonamides, non-steroidal anti-inflammatory drugs, and immune modulating agents such as anti-lymphocyte antibodies, are among the most common causes of drug-induced aseptic meningitis. Occasional patients will suffer repeated episodes of meningitis before the association is recognized.

During recent years medical microbiology laboratories have rapidly embraced a range of innovative technologies that have dramatically increased the speed and precision with which they can identify the organisms responsible for many microbial diseases. Faster and more accurate identification of the infecting pathogen can allow clinicians to promptly adjust treatment, thus improving outcomes for their patients.

The staff of the microbiology laboratory at Middlemore Hospital should be congratulated for their enthusiastic introduction of the new technologies that have resulted in improved diagnostic accuracy in patients admitted with meningitis to their hospital. Hopefully, the report by McBride et al will stimulate clinicians caring for patients with meningitis in other New Zealand hospitals to discuss with their local microbiologists the range of tests their laboratory can provide, and the benefits and costs of introducing new tests.

Clinicians may be surprised by the breadth and impact of recent advances in microbiological testing.
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References