Wolters Kluwer

Diagnosis of meningococcal infection

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INTRODUCTION

Neisseria meningitidis is the second most common cause of community-acquired adult bacterial meningitis in the United States [1]. Since routine vaccination of infants with the *Haemophilus influenzae* type b capsular conjugate vaccine was introduced, *N. meningitidis* has become the leading cause of bacterial meningitis in children and adolescents in the United States. (See "Bacterial meningitis in children older than one month: Clinical features and diagnosis", section on 'Causative organisms'.)

The clinical manifestations of meningococcal disease can be quite varied, ranging from transient fever and bacteremia to fulminant disease with death ensuing within hours of the onset of clinical symptoms. (See "Clinical manifestations of meningococcal infection".)

The diagnosis of meningococcal infection will be reviewed here [2-4]. The gold standard for the diagnosis of systemic meningococcal infection is the isolation of *N. meningitidis* from a usually sterile body fluid, such as blood or cerebrospinal fluid, or, less commonly, synovial, pleural, or pericardial fluid.

The microbiology, pathogenesis, epidemiology, treatment, and prevention of *N. meningitidis* infection are discussed separately. (See "Microbiology and pathobiology of Neisseria meningitidis" and "Epidemiology of Neisseria meningitidis infection" and "Treatment and prevention of meningococcal infection".)

MICROBIOLOGIC DIAGNOSIS

It is important to isolate the organism not only to confirm an etiology of infection but also to perform antibiotic susceptibility testing. Meningococci with increasing resistance to the penicillins, chloramphenicol, and cephalosporins have been reported [5-10].

Blood culture — The frequency of positive blood cultures is 50 to 60 percent, a much lower rate than the frequency of positive cerebrospinal fluid (CSF) cultures (80 to 90 percent), even in patients without

overt meningeal signs [11-16].

Cerebrospinal fluid — The first step in the evaluation of the CSF in a patient with suspected bacterial meningitis is a Gram stain. Gram stain is valuable, even in partially treated meningitis [17]. Bacterial counts in the CSF from patients with meningococcal meningitis have ranged from 1.5 x 10^2 to 6 x 10^7 organisms (mean 1.3 x 10^5) [18].

Chemistry and cytologic findings suggestive of bacterial meningitis include a CSF glucose concentration below 45 mg/dL (2.5 mmol/L), a CSF:serum glucose ratio of <0.4, a protein concentration above 500 mg/dL, and a white cell count above 1000/microL. However, one or more of the classic findings is often absent. (See "Clinical features and diagnosis of acute bacterial meningitis in adults", section on 'Cerebrospinal fluid analysis'.)

Antibiotic therapy should **not** be delayed waiting for completion of the lumbar puncture. Blood cultures should be drawn, and plans to institute antibiotic and supportive therapy should begin as soon as the diagnosis of bacterial meningitis is seriously considered [19]. (See "Treatment and prevention of meningococcal infection", section on 'Treatment of meningitis and sepsis' and "Clinical features and diagnosis of acute bacterial meningitis in adults".)

Pretreatment with antibiotics can substantially diminish the probability of a positive CSF culture [20-22], and the time interval between antibiotic administration and negative CSF cultures in children with meningococcal meningitis may be shorter than appreciated. This was illustrated in a study in which lumbar puncture (LP) was performed after antibiotics were given or serial LPs were performed [21]. Among children with meningococcal meningitis who were treated with a parenteral dose of an extended-spectrum cephalosporin, three of nine LPs were sterile within one hour (one as early as 15 minutes), and all were sterile by two hours. Sterilization of the CSF was substantially slower with pneumococcal (4 to 10 hours) and group B streptococcal infection (more than 8 hours).

In contrast with the rapid clearance of meningococcus from the CSF, a small study that assessed the utility of Gram stain and culture from skin biopsies found no correlation between the yield of skin biopsies and previous antibiotic treatment, suggesting slower clearance than from the CSF [23].

Skin biopsy — Skin biopsy may play a role in the diagnosis of meningococcal infection. This issue was addressed in a prospective study of the use of Gram stain and culture from biopsies of skin lesions in 31 patients with suspected meningococcal infection and 12 controls [23]. The sensitivity of cultures of blood, CSF, and skin biopsies was 56, 50, and 36 percent, respectively. When culture and Gram stain were combined, the sensitivity was 56, 64, and 56 percent, respectively. In three patients, the diagnosis of meningococcal infection was based solely upon positive skin biopsy results.

Thus, Gram stain and culture of a skin lesion can increase the diagnostic yield. However, negative results do **not** exclude the diagnosis of meningococcal infection.

CEREBROSPINAL FLUID ASSAYS

Antigen detection — Commercial kits utilizing latex beads coated with antibodies to meningococcal capsular antigens are available for use in body fluids other than blood (eg, cerebrospinal fluid [CSF] and urine) [24,25]. These kits can detect agglutination of five capsular types: A, B, C, Y, and W135. The sensitivity for serogroup B is low, and false-negative results can occur [26]. This potential deficiency of the test is especially important because serogroup B has been common in infections in the United States and western Europe. False-positive results have also been reported [27].

Latex agglutination tests are not routinely recommended because of the limitations described above and because results do not appear to modify the decision to administer antimicrobial therapy [28]. However, other rapid diagnostic tests are being developed [29-31]. As an example, a validation study showed a high sensitivity and negative predictive value for an immunochromatographic rapid detection test for identification of meningococcal antigens, which might be useful in low-income countries in the meningitis belt with few laboratory facilities [29,30], but more data are needed.

Polymerase chain reaction — The polymerase chain reaction (PCR), which detects small quantities of bacterial DNA, has the potential to be an important tool in the rapid diagnosis of meningococcal infection. PCR has a number of advantages compared with culture for the diagnosis of meningococcal infection [22,32-39]:

- It can establish the diagnosis more rapidly when available as an in-hospital test. PCR results are often available on the day of presentation compared with one or two days or more for culture confirmation [22].
- Since viable bacteria are not required, sensitivity is not affected by prior antibiotic administration, which can sterilize the CSF within one to two hours [21].
- It can rapidly type strains, a useful adjunct in situations that appear to be an epidemic in evolution [38,39].
- Multiplex PCR permits simultaneous testing for meningococcal, pneumococcal, and *H. influenzae* infection [40].

The performance of real-time PCR was assessed in a report of 24 patients with meningococcal infection [22]. The sensitivity and specificity were 96 and 100 percent; in contrast, the sensitivity of CSF or blood culture was only 63 percent. In all nine patients in whom blood was tested more than once, PCR remained positive longer than culture after the initiation of antibiotic therapy; in three patients, more than 72 hours longer.

Bacterial load of *N. meningitidis* DNA level by real-time PCR has been associated with mortality, development of permanent sequelae (eg, limb loss, skin grafting), and prolonged hospitalization [41]. Infections caused by serogroup C were associated with a higher bacterial load and an increased risk of death.

The TaqMan array card is a rapid diagnostic real-time PCR assay that allows simultaneous detection of many viral, bacterial, and parasitic pathogens in blood or CSF [42,43]. It has been used to rapidly identify patients infected with meningococcus in an outbreak in Liberia [44].

Despite these benefits, PCR has not replaced traditional culture methods because it cannot be used to determine antimicrobial susceptibility and is not routinely performed by many hospital laboratories. Another limitation is that false-negative results can occur with *N. meningitidis* isolates that possess gene polymorphisms, particularly when a single gene is targeted [45,46].

Loop-mediated isothermal amplification — Loop-mediated isothermal amplification (LAMP) is a promising rapid assay for diagnosis of meningococcal infection in high-risk patients [47,48] and is highly accurate when compared to quantitative PCR and culture. The test is relatively simple to perform in an emergency room setting; the median time from sample collection to result is approximately 90 minutes [47,48].

Studies have shown that LAMP can detect fewer copies of DNA than standard PCR studies [49]. A systematic review that included three studies evaluating 2243 tests on 1989 children using CSF, blood, or naso/oropharyngeal swabs found that LAMP testing is highly accurate (sensitivity 84 to 100 percent and specificity 94 to 100 percent) when compared with quantitative PCR or culture [50].

LAMP systems that can discriminate different meningococcal capsular serogroups have also been developed [51].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bacterial meningitis in adults" and "Society guideline links: Meningococcal infection" and "Society guideline links: Bacterial meningitis in infants and children".)

SUMMARY AND RECOMMENDATIONS

- The gold standard for the diagnosis of systemic meningococcal infection is the isolation of *Neisseria meningitidis* by culture from a usually sterile body fluid, such as blood or cerebrospinal fluid (CSF), or, less commonly, synovial, pleural, or pericardial fluid. (See 'Introduction' above.)
- Isolation of the organism by culture confirms an etiology of infection and permits antibiotic susceptibility testing. (See 'Blood culture' above.)
- Gram stain and culture of a skin lesion can increase the diagnostic yield, although a negative result does not exclude the diagnosis. (See 'Skin biopsy' above.)
- Antibiotic therapy should **not** be delayed waiting for performance of lumbar puncture. Blood cultures should be drawn, and plans to institute antibiotic and supportive therapy should begin as soon as the diagnosis of bacterial meningitis is seriously considered. (See 'Cerebrospinal fluid' above.)
- Chemistry and cytologic findings suggestive of bacterial meningitis include a CSF glucose concentration below 45 mg/dL (2.5 mmol/L), a CSF:serum glucose ratio <0.4, a protein

concentration above 500 mg/dL, and a white cell count above 1000/microL. However, one or more of the classic findings is often absent. (See 'Cerebrospinal fluid' above.)

- Commercial latex agglutination kits, which utilize latex beads coated with antibodies to meningococcal capsular antigens, are available for use in body fluids such as CSF and urine. These kits can detect agglutination of five capsular types: A, B, C, Y, and W135, but the sensitivity for serogroup B is low. Other rapid antigen detection tests are being investigated. (See 'Antigen detection' above.)

- The polymerase chain reaction (PCR) is a sensitive and rapid tool for diagnosing meningococcal infection. However, PCR has not replaced traditional culture methods because it cannot be used to determine antimicrobial susceptibility and is not routinely performed by most hospital laboratories. (See 'Polymerase chain reaction' above.)

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