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# The Brief Case: Disseminated *Neisseria gonorrhoeae* in an 18-Year-Old Female

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## CASE

An 18-year-old previously healthy female presented to a Philadelphia, PA, pediatric emergency department in February for further evaluation of polyarticular arthritis. Two weeks prior, she had presented to an outside hospital with body aches and onset of acute pain in the left arm and leg. The etiology was thought to be cervical radiculopathy, and she was discharged on naproxen and prednisone. She returned to the outside hospital 5 days later without improvement and now with pain and swelling in her left knee, right thumb, right wrist, and bilateral ankles. She had a markedly elevated erythrocyte sedimentation rate (ESR) of 80 mm/h (reference range, 0 to 20 mm/h) and C-reactive protein (CRP) of 76.6 mg/dl (reference range, 0 to 0.9 mg/dl). A workup for autoimmune disease included negative results for antinuclear antibody, rheumatoid factor, and anticyclic citrullinated peptide. Serologic testing for Lyme disease was also negative. Her white blood cell (WBC) count was initially elevated and increased to 23,600 cells/$\mu$l (reference range, 4,400 to 9,700 cells/$\mu$l) in the setting of steroid therapy. Imaging via ultrasound and magnetic resonance imaging (MRI) showed a moderately sized simple left knee effusion with marked surrounding edema. Left knee arthrocentesis was performed, revealing a mildly elevated synovial fluid WBC count of 36,900 cells/$\mu$l (normal below 2,000 cells/$\mu$l), and culture of the collected synovial fluid on sheep blood and chocolate agars incubated in 5% $CO_2$ showed no growth. She was continued on prednisone and received opioid pain medication. After spending a week at the outside hospital, she left against medical advice to seek a second opinion. Upon arrival in our emergency department she was afebrile and had swelling and limited range of motion of her left knee and right thumb. She denied sexual activity, exposure to ticks, or recent trauma. She had traveled to Mexico 1 month prior to her initial presentation. Her ESR remained significantly elevated. The Department of Rheumatology was consulted and recommended testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, and a urine sample was sent for *C. trachomatis*/*N. gonorrhoeae* nucleic acid amplification testing (NAAT). The patient received one dose of azithromycin and was started on ceftriaxone and clindamycin to empirically treat *C. trachomatis*, *N. gonorrhoeae*, and other causes of septic arthritis. The Department of Orthopedics was also consulted and repeated an arthrocentesis, given continued concern for septic arthritis, despite the lack of fevers during her 2 weeks of symptoms. Her synovial fluid WBC count remained elevated at 48,120 cells per $\mu$l (89% neutrophils). A Gram stain of the synovial fluid revealed Gram-negative diplococci in pairs (Fig. 1). Less than 24 h later, growth was observed on the chocolate agar plate of the synovial fluid culture,

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For answers to the self-assessment questions and take-home points, see https://doi.org/10.1128/JCM.00933-17 in this issue.

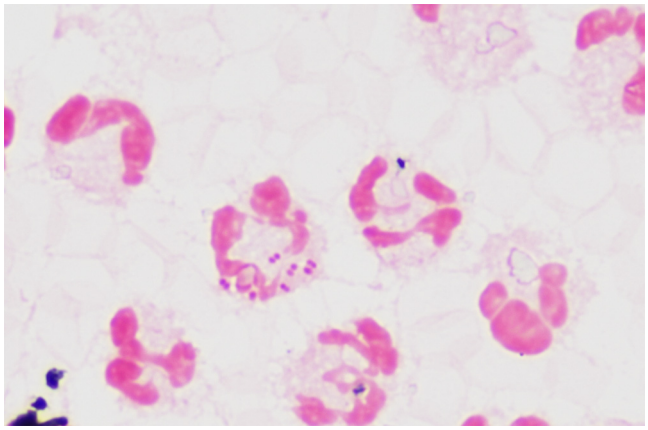

**FIG 1** Gram stain of synovial fluid demonstrating Gram-negative diplococci in pairs suggestive of *Neisseria* species.

which was incubated at 5% $CO_2$ (Fig. 2). The growth was later definitively identified as *Neisseria gonorrhoeae* by carbohydrate utilization and enzyme detection (RapID NH; Remel) and antigen detection (Gonogen; BioConnections), confirming the suspected diagnosis of disseminated gonococcal infection (DGI). Two days later, her urine *C. trachomatis*/*N. gonorrhoeae* NAAT came back positive for both organisms. HIV antibody and syphilis testing (rapid plasma reagin) were also ordered and were negative. The patient was treated with 1 week of parenteral ceftriaxone while admitted to the rehabilitation service for intensive physical therapy. She was discharged 3 weeks later with significant improvement of her left knee's range of motion.

## DISCUSSION

*Neisseria gonorrhoeae* is the 4th most common sexually transmitted infection in the United States. As the majority of infections are asymptomatic, routine screening for *N. gonorrhoeae* (and *C. trachomatis*) via NAAT is recommended for sexually active females under the age of 25, while risk-based screening is recommended for women over the

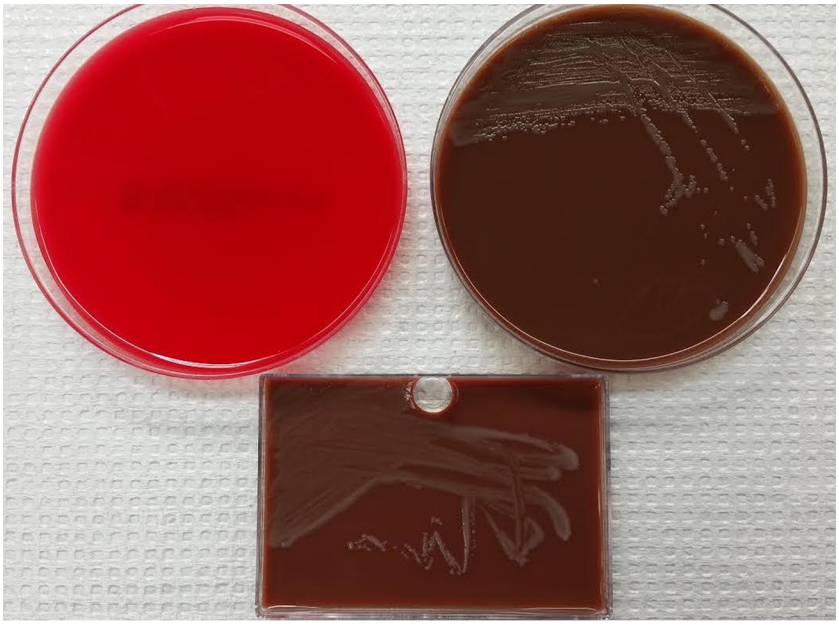

**FIG 2** Growth of *Neisseria gonorrhoeae* on microbiologic culture media. Note the lack of growth on sheep blood agar (top left) and visible colonies on chocolate agar (top right) and the *Neisseria* sp.-selective Martin-Lewis agar (bottom).

age of 24 and sexually active males (1). The most frequent clinical manifestations of *N. gonorrhoeae* infection include cervicitis and pelvic inflammatory disease in females and urethritis and epididymitis in males. Extragenital infections are common, and clinical manifestations include pharyngitis, proctitis, and conjunctivitis, dependent on the site of inoculation. Only 0.5 to 3% of *N. gonorrhoeae* infections from any site lead to dissemination. Females are at a 4-fold-higher risk for dissemination than males, particularly if they are menstruating or pregnant. Individuals with a complement deficiency are also at increased risk. DGI classically presents with arthritis and dermatitis early in the course of disease. Skin lesions can be seen in more than 40% of patients with DGI paired with migratory arthritis and/or tenosynovitis and/or fever (2). If untreated, progression to pyogenic septic arthritis occurs in less than a third of patients. Despite a large degree of clinical overlap with common causes of septic arthritis, involvement of distal joints and polyarticular arthritis are specific to DGI septic arthritis and can help steer the differential. Further, synovial fluid cell counts tend to be an order of magnitude lower in cases of *N. gonorrhoeae* septic arthritis than in cases of other common bacterial causes (2), consistent with the case presented. While DGI is reported as the leading cause of infectious arthritis in sexually active young adults without preexisting joint disease, unpublished data from our institution show Lyme disease (*Borrelia burgdorferi*) to be at least 5-fold-more common in this age group, as we are in an area of Lyme endemicity. Nonetheless, DGI should always be considered in adolescents presenting with joint pain with no alternative explanation (i.e., trauma). The lack of consideration of DGI during the patient's first and second hospital visits led to a delayed diagnosis, significant joint impairment, and, as a result, a lengthened hospital stay.

Laboratory testing for DGI is limited to indirect testing of urogenital (and/or rectal and/or pharyngeal) sites of primary mucosal infection by NAAT and, if possible, Gram staining and culture from sites of dissemination. Blood cultures have less than 10% sensitivity, with slightly higher yields during the early stages of dissemination (2). This is likely partially due to the blood culture anticoagulant additive sodium polyanethole sulfonate (SPS), which is well known to inhibit the growth of *Neisseria* species (3) and may have more impact when bacteremia levels are low during later stages. In the case presented, 2 sets of blood cultures drawn 12 to 13 days after symptom onset were negative. Culture of the implicated joint's (or joints') synovial fluid is maximally 50% sensitive for DGI septic arthritis, and the corresponding Gram stain is estimated to be less than 10% sensitive. Despite evidence that *N. gonorrhoeae* directly invades the skin, manifesting in lesions, culture of punch-biopsied material is not recommended, as the yield is close to 0% (4).

NAAT for *N. gonorrhoeae*, via any of the FDA-cleared platforms, is not approved for synovial fluid or blood. There are few reports of laboratory-developed molecular testing for *N. gonorrhoeae* from synovial fluid, as the matrix is thought to be inhibitory to amplification. One study used a nested-PCR approach to increase sensitivity, with a reported 78.6% sensitivity when 10 culture-negative samples were tested from patients with probable DGI (5). As FDA-cleared platforms do not employ nested PCR, it is difficult to extrapolate these findings to commonly used NAAT platforms for *N. gonorrhoeae*. Thus, NAAT testing should be performed on FDA-cleared or validated sources, such as urine, vaginal swabs, and pharyngeal and/or rectal swabs, as supportive evidence for DGI and to rule out coinfection with *C. trachomatis*. Importantly, rectal and pharyngeal sources are also not yet FDA cleared by any of the commercially available platforms but have been validated by numerous clinical laboratories for the detection of *C. trachomatis*/*N. gonorrhoeae*.

*Neisseria gonorrhoeae* grows readily on chocolate agar and even some formulations of blood agar (Fig. 2). Specialized agar for the selection of *Neisseria* species should be included for culture, particularly from nonsterile sources (Fig. 2). This medium is referred to as modified Thayer-Martin or Martin-Lewis agar and typically includes vancomycin, colistin, trimethorprim, and anisomycin or nystatin to inhibit normal flora and most nonpathogenic (saprophytic) *Neisseria* species. Care should be taken with positive growth from pharyngeal cultures, as *Neisseria meningitidis* can be incidentally isolated. Colonies suspicious for *Neisseria gonorrhoeae* (oxidase-positive, Gram-negative diplococci) require confirmation by biochemical and/or enzymatic analyses. Testing

should be performed from colonies isolated on the *Neisseria* selective agar mentioned above to limit possible false-positive interpretations for *N. gonorrhoeae*. More than one method of confirmation may be necessary, as no test is 100% specific. The carbohydrate utilization test analyzes differential fermentation between 4 sugars: glucose, maltose, lactose, and sucrose. *N. gonorrhoeae* should ferment only glucose, while other *Neisseria* species should ferment 2 or more sugars. Enzymatic testing looks for the presence of proline-iminopeptidase, which should be specific for *N. gonorrhoeae*. Identification of *N. gonorrhoeae* by matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry may be validated by individual laboratories but is not currently FDA approved/cleared for commercially available systems as a stand-alone identification. Molecular confirmation of isolated colonies by one of the NAAT platforms used for primary specimen screening has also been reported. Finally, sequencing of the first 500 bp of the 16S ribosomal gene, widely used for bacterial identification, may not provide enough resolution to call an isolate of *Neisseria* to the species level, and results should be interpreted with caution.

Despite limited sensitivity compared to that of molecular testing, culture is still recommended to generate isolates for susceptibility testing (and for medicolegal purposes). While routine susceptibility testing is not recommended, it may be useful in cases of treatment failure and dissemination. The majority of clinical isolates are resistant to penicillin, tetracyclines, and fluoroquinolones; thus, these drugs are no longer recommended for treatment (6). Susceptibility testing now focuses on emerging resistance to cephalosporins and azithromycin. In 2012, the CDC revised treatment recommendations, due to increasing oral cephalosporin resistance, to now recommend only dual therapy with 1 injection of high-dose ceftriaxone (250 mg) plus a single dose of azithromycin. For disseminated infections, treatment with parenteral ceftriaxone (1 g) for a duration of 7 to 14 days is recommended along with a single dose of azithromycin for combination therapy and to treat possible *C. trachomatis* coinfection (6). In these cases, treatment may be switched to an oral 3rd-generation cephalosporin, such as cefixime or cefpodoxime, if susceptibility can be confirmed. Most clinical laboratories do not have the capacity to perform susceptibility testing on *N. gonorrhoeae* isolates, as agar dilution is the gold standard. Clinical laboratories should contact their public health laboratory to coordinate testing as needed.

## SELF-ASSESSMENT QUESTIONS

1. Which of the following specimens is recommended and FDA cleared for nucleic acid amplification testing (NAAT) in suspected cases of disseminated *Neisseria gonorrhoeae*?
   A. Whole blood
   B. Urine
   C. Synovial fluid
   D. Serum
2. What is the estimated sensitivity of aerobic culture for the detection of *N. gonorrhoeae* in synovial fluid?
   A. ~10%
   B. ~25%
   C. ~50%
   D. ~90%
3. Which of the following is the recommended treatment for disseminated gonococcal infection?
   A. Cefpodoxime plus azithromycin
   B. Ceftriaxone plus doxycycline
   C. Cefixime plus doxycycline
   D. Ceftriaxone plus azithromycin

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