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Ten Years of Disseminated Gonococcal Infections in North Carolina: a Review of Cases from a Large Tertiary Care Hospital

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Abstract

Background: The detection and reporting of disseminated gonococcal infection (DGI) has been increasing across the United States (US).

Methods: We conducted a retrospective chart review of DGI case-patients diagnosed between 2010 and 2019 at a large tertiary care hospital in North Carolina.

Results: We identified 12 DGI case-patients (7 males and 5 females, aged 20 to 44 years old) of whom 5 had *Neisseria gonorrheae* isolated from a sterile site (confirmed), 2 had *N. gonorrheae* detected at a non-sterile mucosal site and had clinical manifestations consistent with DGI (probable), and 5 did not have *N. gonorrheae* isolated from any site, but DGI was the most likely diagnosis (suspect). Among the 12 DGI case-patients, the most common manifestation was arthritis or tenosynovitis (n=11); one patient had endocarditis. Half of the patients had significant underlying co-morbidities or predisposing factors, including complement deficiency. Eleven of the 12 case-patients were hospitalized, and 4 required surgical intervention.

Conclusions: This case series highlights the difficulty of making a definitive diagnosis of DGI, which could negatively affect reporting to public health authorities and hinder surveillance efforts to determine the true prevalence of DGI. A high index of suspicion is required and a full diagnostic work-up should be pursued in all cases of suspected DGI.

Summary

In this case series, we summarize clinical manifestations of 12 case-patients with disseminated gonococcal infections diagnosed at a tertiary care hospital between 2010 – 2019 and highlight difficulties diagnosing this infection to inform surveillance.

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Keywords

Disseminated gonococcal infection; gonorrhea; surveillance; sexually transmitted diseases; North Carolina

Introduction

Reports of bacterial sexually transmitted infections (STIs), including gonorrhea, have increased in the United States since 2016.[1] Disseminated gonococcal infection (DGI) is an uncommon, but severe complication of untreated gonorrhea which occurs in 0.5–3% of untreated gonorrhea cases.[2] Clinical manifestations of DGI include septic arthritis, skin lesions, bacteremia, endocarditis, myocarditis/pericarditis, pyomyositis, osteomyelitis, perihepatitis, and meningitis[3,4], frequently requiring hospitalization and surgical intervention.[3,5] In 2019, the Centers for Disease Control and Prevention (CDC) received several reports of DGI, including a cluster of cases in Kalamazoo County, Michigan.[6] This led the CDC to issue a "Dear Colleague" letter, alerting providers and public health officials and providing guidance on diagnosis, management, and reporting of DGI to public health authorities.[7] In 2020, the California Department of Public Health reported a similar uptick in DGI cases;[8] California identified 149 DGI cases statewide through surveillance between July 2020 and July 2021.[9]

In North Carolina, gonorrhea incidence increased by 37% between 2016 and 2020,[10] and the increasing number of DGI cases, driven, at least in part, by delays in diagnosis and treatment of gonococcal infections as a result of the COVID-19 pandemic,[11] led to the issuance of a "Dear Colleague" letter in the state in April 2021.[12] In 2021, North Carolina identified 66 cases of DGI, accounting for 0.23% of all gonococcal infections, but a 164% increase in DGI from the 25 cases diagnosed in 2020.[11] It is unclear whether this represents a true increase in incidence or better detection and reporting.[11] Here, we present a case series from a single North Carolina center, and provide individual patient-level information on clinical presentations and management, illustrate the difficulties in diagnosing DGI, and discuss the implications this has for surveillance.

Materials and Methods

DGI cases were identified by using the i2b2 software[13] to search the Carolina Data Warehouse for Health (CDW-H) system for ICD10 and ICD9 codes associated with DGI diagnosed at a North Carolina public academic medical center between 2010 and 2019. CDW-H is a central data repository containing clinical, research, and administrative data sourced from the University of North Carolina (UNC) Health Care System.[14] The codes included gonococcal infection of the musculoskeletal system, gonococcal endocarditis, meningitis, pneumonia, sepsis, brain abscess, and gonococcal infection of other specified site (Supplementary tables 1 and 2). We also queried the hospital epidemiology department for medical records that included cultures of sterile fluids or sterile sites positive for *Neisseria gonorrheae*. Both searches were limited to the 10-year period between January 2010 and December 2019.

Cases of DGI were defined according to CDC case definitions[15] and data was extracted using the CDC's case abstraction form for DGI.[16] Cases of DGI are classified as confirmed if there was isolation of *N. gonorrheae* from a sterile site (i.e. blood, synovial fluid, or cerebrospinal fluid); probable if there were clinical manifestations consistent with DGI in the setting of isolation or detection of *N. gonorrheae* at a non-sterile mucosal site (i.e. urogenital, rectal, or pharyngeal), but the pathogen was not isolated from a sterile site; and suspected if there were clinical manifestations consistent with DGI in the absence of a more likely diagnosis, but the pathogen was not isolated or detected at any site. Cases of gonorrhea limited to urogenital, pharyngeal, or rectal sites, or pelvic inflammatory disease, were classified as non-disseminated gonorrhea.

For this case series, we reviewed electronic medical records (EMR) for each identified case-patient and described their demographics, sex partner history, drug use, *N. gonorrheae* test results, symptoms, clinical manifestations, STI history, pregnancy status, human immunodeficiency virus (HIV) status, other co-morbidities, and treatment. The study was deemed exempt from full review by UNC's Institutional Review Board (IRB). All the data collected for this study was de-identified.

Results

Using the ICD9–10 codes for DGI and reports from the hospital epidemiologist, we identified 58 unique case-patients during the study period. After reviewing the EMRs, we determined that 12 case-patients met the definition for either confirmed, probable, or suspected cases of DGI. Thirty-two did not have a diagnosis of gonorrhea or had a diagnosis outside of the 10-year study period, and 14 had a diagnosis of non-disseminated gonorrhea (Figure 1).

The DGI case-patients' demographic and clinical data are summarized in Table 1. Of the 12 case-patients, 5 (41.7%) were confirmed cases, with isolation of *N. gonorrheae* by culture at a sterile site (4 from synovial fluid, 1 from blood), 2 cases (16.7%) were probable, with clinical manifestations of DGI in the setting of identification of *N. gonorrheae* by nucleic acid amplification test (NAAT) at a mucosal site (one from the oropharynx, one from urine), and 5 (41.7%) were suspected cases.

The median age was 33 years (range 20–44). Five case-patients (41.7%) were female and 7 (58.3%) were male. The gender of sex partners was known for 6 of the male case-patients; 4 reported sex with women only and two with men only. Of the 5 female case-patients, 4 reported sex with men only, and the gender of the remaining woman's sex partner(s) was unknown. Seven case-patients (58.3%) were White, 3 (25%) African American, 1 (8.3%) Asian, and 1 (8.3%) identified as "other". Four case-patients (33.3%) identified as Hispanic or Latino/a.

Clinical manifestation included mitral valve endocarditis (1 case-patient), septic arthritis (6 case-patients), and tenosynovitis with polyarthralgia or monoarthralgia (5 case-patients). One case-patient reported pustular skin lesions, and 2 had an unspecified rash. In addition to DGI manifestations, 3 case-patients also reported symptoms consistent with

pharyngitis, 2 had symptoms of urethritis, and 1 had vaginitis. Six case-patients (50%) had significant co-morbidities. One had well-controlled HIV and had received a renal transplant; 1 had a history of IV drug use; 1 was receiving chemotherapy for cerebellar astrocytoma; 1 had well-controlled type 2 diabetes and gout and was receiving systemic steroids; 1 had complement deficiency, which is historically a known risk factor for invasive *Neisseria* species infections;[17] the case-patient with gonococcal endocarditis had underlying congenital heart disease. No case-patients were receiving therapy with complement inhibitors such as eculizumab or ravulizumab. None of the case-patients were pregnant. Two case-patients had a prior history of uncomplicated gonococcal infection, based on clinical records. No case-patients were diagnosed with chlamydia co-infection based on nucleic acid amplification testing (NAAT). Of the 12 case-patients in this series, 9 were tested for HIV (and one who was already known to be living with HIV), 8 were tested for syphilis via rapid plasma reagin (RPR), 4 were tested for hepatitis C, 3 were tested for hepatitis B, and none were tested for hepatitis A. None of the case-patients who were tested for other STIs or viral hepatitis had positive results.

All but one of the case-patients were hospitalized. Among the 11 case-patients who were hospitalized, the median length of stay was 4 days (range 2–33). Four case-patients (33.3%) required surgical intervention: the case-patient with endocarditis required mitral valve replacement and 3 case-patients with septic arthritis required joint incision and drainage or washout. All case-patients received an initial treatment of ceftriaxone with or without oral azithromycin, except for one, who received ceftriaxone and doxycycline, consistent with treatment guidelines at the time, though azithromycin is no longer recommended.[18] The duration of treatment was 7, 10, or 14 days for all case-patients, except for the one with endocarditis, who was treated for 6 weeks with intravenous (IV) ceftriaxone following valve replacement. All patients survived and experienced complete resolution of symptoms.

Case Presentations

Confirmed Cases

Case 1.—A 38-year-old male with a history of well-controlled type 2 diabetes and gout presented with left wrist swelling and pain, as well as fever. Culture of his wrist aspirate grew *N. gonorrheae*. Pharyngeal swab NAAT was positive for *N. gonorrheae*. He had reported sex with 1 female partner only. Serology for HIV, hepatitis B and C, and RPR were negative. He was treated with IV ceftriaxone followed by oral cefixime for a total of 14 days and received 1 dose of oral azithromycin.

Case 2.—A 30-year-old male with a history of HIV on antiretroviral therapy, HIV-related cardiomyopathy, and HIV-associated nephropathy necessitating a kidney transplant presented with right elbow, wrist, and shoulder pain. His viral load was undetectable and his CD4 count was 142 (22%) 6 months prior. Gram stain of the right elbow aspirate demonstrated gram negative diplococci, and *N. gonorrheae* grew on the culture. He underwent surgical washout of the right elbow and shoulder and was treated with ceftriaxone for 10 days.

Case 3.—A 36-year-old female with a history of atrial septal defect and persistent right to left shunt presented with fevers and shortness of breath and progressed to hypoxic respiratory failure. Blood cultures grew *N. gonorrheae*, and she was found to have a 1 × 0.2 cm mitral valve vegetation. NAAT for gonorrhea and chlamydia at mucosal sites was not performed. She reported having a sexual encounter shortly prior to the onset of symptoms, but the partner's gender was not specified. Of note, she presented with left sided abdominal pain a month earlier and was found to have a splenic infarct a month prior and was started on apixaban. She underwent hypercoagulable workup during this hospitalization, which was significant for abnormal lupus inhibitor panel, cardiolipin, and phospholipid antibodies. She underwent mitral valve replacement 2 weeks after admission. Culture of the valve was negative but direct sequencing revealed *Neisseria* species, consistent with gonococcal endocarditis. She was continued on IV ceftriaxone monotherapy for 6 weeks.

Case 4.—A 24-year-old male on HIV pre-exposure prophylaxis (PrEP) presented with a sore throat and left knee pain. Culture of his knee aspirate grew *N. gonorrheae*. NAAT for gonorrhea and chlamydia at mucosal sites was not performed. An RPR test and serology for HIV were negative. He was treated without surgery with IV ceftriaxone for 2 weeks. His sexual history was not available in the medical records.

Case 5.—A 38-year-old female with a history of C5 deficiency and prior gonococcal cervicitis presented with right ankle and left knee pain and swelling. Upon admission, she underwent arthroscopic washout of both joints, and joint cultures grew *N. gonorrheae*. NAAT for gonorrhea and chlamydia of mucosal sites was not performed. Serology for HIV and hepatitis C, as well as an RPR test, were negative. She was sexually active with one male partner. She was treated with IV ceftriaxone for 14 days and given a single dose of oral azithromycin.

Probable Cases

Case 6.—A 40-year-old male presented with polyarthralgia involving both knees and ankles, tenosynovitis, rash, fevers, and chills. He had recent condomless oral sex with a male partner and reported a total of 3 sexual partners over the previous 2 months. Blood cultures were negative. NAAT of pharyngeal swab was positive for *N. gonorrheae*. Serology for HIV and an RPR test were negative. No joints were aspirated. He was treated with IV ceftriaxone for 7 days and a single dose of oral azithromycin.

Case 7.—A 30-year-old male presented with fever, right shoulder, knee, and wrist pain and swelling. He had recent condomless sexual intercourse with a female partner. Urine NAAT was positive for *N. gonorrheae*. Serology for HIV and an RPR test were negative. Fluid aspirated from the right wrist had 98,000 white blood cells/mm^3, prompting incision and drainage. Intraoperative culture was negative, but he had already been started on ceftriaxone at this point, and was continued for 7 days.

Suspected Cases

Case 8.—A 27-year-old male with a history of gonorrhea 3 years prior presented with migratory polyarthralgia, tenosynovitis, and pustular skin lesions. He reported sex with

women only and inconsistent condom use. Attempt at aspiration of the right knee was unsuccessful. NAAT for gonorrhea and chlamydia was negative from urine, as well as pharyngeal and rectal swabs. Serology for HIV, hepatitis B and C, and RPR were negative. Blood cultures were negative. He was treated with daily IM ceftriaxone and oral doxycycline for 7 days.

Case 9.—A 44-year-old female with history of intravenous drug use presented with migratory polyarthralgia. Urine NAAT was negative for *Chlamydia trachomatis* and *N. gonorrheae*. Pharyngeal and rectal swabs were not performed. Blood cultures were negative. Cell count from left ankle aspiration was reportedly consistent with bacterial infection, but culture results were not available. DGI was deemed to be the most likely diagnosis, based on clinical assessment, and the patient was treated with IV ceftriaxone for 5 days, followed by 2 days of oral cefixime at discharge, and experienced clinical improvement on this regimen.

Case 10.—A 41-year-old male presented with migratory polyarthralgia involving both shoulders and wrists, fevers, penile discharge, and tender left inguinal lymphadenopathy after recent condomless sexual intercourse with female partners. None of the joints were amenable to aspiration. Urine, rectal and pharyngeal NAAT for *N. gonorrheae* and *C. trachomatis* were negative. DGI was deemed the most likely diagnosis based on clinical assessment. He was treated with ceftriaxone and a single dose of oral azithromycin, followed by oral cefpodoxime for a total of 7 days.

Case 11.—A 21-year-old female with diffuse astrocytoma presented with purulent vaginal discharge and rash after a condomless sexual encounter with a male partner. She was treated empirically with a single dose of intramuscular (IM) ceftriaxone and oral azithromycin. Urine NAAT for gonorrhea and chlamydia was negative but other sites were not tested. Serology for HIV and an RPR test were negative. Her vaginal discharge improved but her rash did not and her left knee started hurting. She was referred to the infectious diseases clinic, where a presumptive diagnosis of DGI was made. She was treated with IM ceftriaxone for 14 days and her symptoms improved.

Case 12.—A 20-year-old female with polycystic ovarian syndrome (PCOS) presented with migratory polyarthralgia involving her left shoulder, knee, and toes, both ankles and wrists, as well as painful nodules on her fingers. She was sexually active with one male partner. Of note, she noted a tick bite about 3 months prior to presentation with positive serology for *Ehrlichia chaffeensis*, but her symptoms did not improve with doxycycline. Her symptoms improved after 6 days of prednisone therapy but recurred. No joint was amenable to aspiration, and NAATs for gonorrhea and chlamydia at all mucosal sites were negative. Serology for HIV, hepatitis B and C, and RPR were negative. She was started on IV ceftriaxone due to high clinical suspicion for DGI and her symptoms improved. She completed a 7-day course of ceftriaxone.

Discussion

In the 10-year period from January 2010 to December 2019, we identified 12 confirmed, probable, or suspected cases of DGI diagnosed at one tertiary hospital in North Carolina.

A thorough review of state-level surveillance data is needed in order to obtain a more accurate reflection of demographic trends, risk factors, and manifestations of DGI across North Carolina. In this single-center case series, however, we aimed to provide a greater level of detail about individual clinical presentations and management, report the obstacles that hinder confirmation of the diagnosis, and highlight suspected and probable cases, which may not be accurately captured through surveillance. Almost all patients in this series were hospitalized, and a large proportion required surgical intervention. In almost half of the cases, the diagnosis was made based on clinical suspicion alone, as *N. gonorrheae* was not identified from any sterile or mucosal site. This underscores the difficulty of isolating this pathogen, the need for a high index of suspicion, and the importance for effective communication between clinicians and laboratory staff when DGI is suspected. The inability to isolate the pathogen may hinder reporting to public health authorities and lead to underestimation of the incidence of DGI.

Given the limited number of cases, it is difficult to draw any inferences as to the epidemiology or risk factors for DGI in our state. Nonetheless, it is worth noting that, within our small sample, a large percentage of patients were African American and Hispanic, similar to a recent large study from California, in which more than half of DGI patients identified as Hispanic or Latino/a.[9] This is also consistent with the observation that African American and Hispanic populations experience higher rates of gonococcal disease in general compared to non-Hispanic whites both at the national level and in North Carolina, where the incidence of all gonorrhea infections in 2021 was 824.1/100,00 among African Americans, 148.2/100,000 among Hispanics, and only 65.3/100,000 among non-Hispanic whites.[1,10] Furthermore, African Americans accounted for 69% of North Carolina DGI cases between March 2020 and December 2021, despite making up only 22.3% of the states' population.[11,19] There was a slight male predominance among the cases, and all the cases occurred in adults under 45 years of age. Our findings are consistent with recent literature showing a slight male predominance among DGI cases,[20,21] and a similar trend is evident across the state, where males accounted for 64% of DGI cases between March 2020 and December 2021.[11] This may be due to the fact that the reported incidence of gonorrhea overall is higher among males and people under 45 years of age, both in North Carolina and in the US.[1,10] In 2020, CDC estimated that 34.7% of gonorrhea infections occurred among men who have sex with men (MSM).[1] In our review of DGI in one hospital system, only 2 (17%) case-patients were MSM. Our lower proportion of MSM may reflect differences in the populations impacted by DGI or may be an underestimate, as sexual history was not reported for all cases.

Our case series is limited to one hospital, and the low number of cases may not reflect the true burden of DGI in the state. However, half of the DGI cases identified in this analysis occurred in the last 2 years of the study period, suggesting either an uptick in local DGI incidence or improvements in DGI detection. Similar to what was reported in other outbreaks[6,9] – and consistent with prior observations[20,22] – the most common manifestation of DGI involved the musculoskeletal system, while endocarditis was rare. Unlike the clusters reported in Michigan and California,[6,8,9] drug use was not commonly reported among the reviewed cases.

Diagnosing DGI is particularly challenging, given its non-specific presentation, and requires a high index of suspicion. Growing *N. gonorrheae* in culture is difficult and requires special microbiologic techniques.[3,5,23] While NAAT is the gold standard for detection of *N. gonorrheae*, obtaining synovial fluid samples or positive results from mucosal sites in DGI is not always possible. Thus, the diagnosis is often based only on the clinical presentation, with or without identification of *N. gonorrheae* at non-disseminated sites.[21] In fact, as evidenced in this and other case series,[20,22] only a minority of DGI cases are confirmed by culture. This leads to the necessity of using definitions for "suspected" and "probable" cases, which are not based entirely on objective, universally agreed-upon criteria, as DGI clinical manifestations are often non-specific.[3,5] Thus, using these case definitions has the potential to impose limitations on the accuracy of DGI surveillance.[21]

Another limitation that we noted is that often clinicians do not pursue a full diagnostic evaluation once DGI is deemed the most likely diagnosis and there is clinical improvement with empiric DGI treatment. For example, some of the case-patients in this series were not tested for gonorrhea or joint aspiration was not performed. In other cases, empiric treatment was started before diagnostic samples were obtained, which likely limited the yield of diagnostic testing.[24] Antimicrobial susceptibility data were not available in the medical records of any of the case-patients identified; however there were no apparent treatment failures in instances where the CDC recommended treatment was used for DGI.

Obstacles to accurate reporting and surveillance of DGI remain. Since suspected and probable cases do not have supporting laboratory evidence of a DGI diagnosis, public health authorities may not be able to identify them as such in surveillance data, unless the provider reports it. Furthermore, inconsistencies in the clinical diagnosis of DGI among providers, hospitals, or jurisdictions may lead to nonuniform reporting of DGI. To improve surveillance for DGI, clinician education is needed to encourage a high index of suspicion and more complete diagnostic evaluations. The importance of obtaining a comprehensive sexual history in all cases of suspected gonococcal infections should be emphasized, as well as testing of all mucosal sites, specialized specimen collection procedures, and culture requirements for growth of *N. gonorrheae*. Clinicians should be aware to alert laboratory staff when DGI is suspected, as the organism may not grow under routine culture conditions. A clinical prediction score based on objective history and clinical findings may help to identify DGI cases more consistently.

In summary, we identified 12 cases of confirmed, probable, or suspected DGI over the previous ten years at a large tertiary care hospital in North Carolina, half of which occurred in the last two years of the study period. The majority of cases lacked microbiologic confirmation, highlighting the need to rely on clinical diagnosis, which could hinder surveillance. Improvements in surveillance and larger studies on DGI are needed to understand how our findings compare to the epidemiology of DGI in other contexts and to better identify risk factors for DGI and trends over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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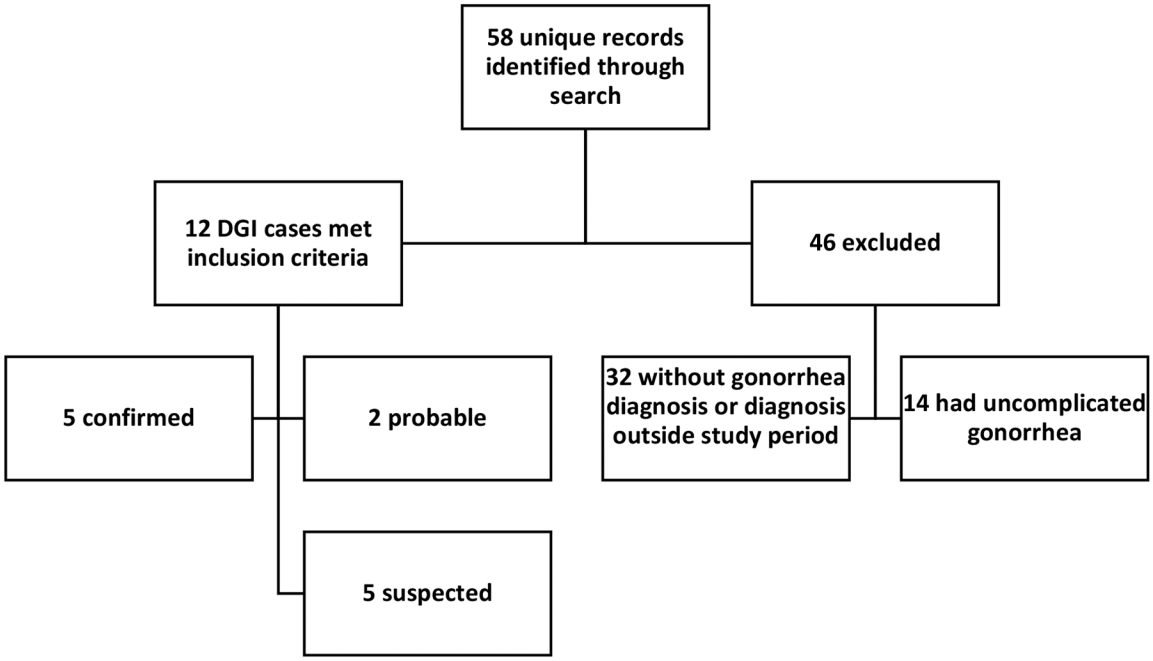

Figure 1.

Summary of medical records search results, with number of cases included in and excluded from the case series, and reasons for inclusion or exclusion.

Table 1.

Summary of DGI cases: Demographic data and clinical syndromes.

	N=12	N (%) or Median (range)
Age (years)		33 (20–44)
Sex		
	Male	7 (58.3%)
	Female	5 (41.7%)
Race		
	African-American	3 (25%)
	White	7 (58.3%)
	Asian	1 (8.3%)
	Other	1 (8.3%)
	Hispanic or Latino/a *	4 (33.3%)
Clinical syndromes		
	Septic arthritis	6 (50%)
	Polyarthralgia/monoarthralgia and/or tenosynovitis	5 (41.7%)
	Endocarditis	1 (8.3%)
	Rash or pustular skin lesions	3 (25%)
Concomitant gonorrhea at mucosal sites		
	Pharyngeal	3 (25%)
	Urethral	2 (16.7%)
	Vaginal	1 (8.3%)
	NAAT not performed or not reported	4 (33.3%)
Required hospitalization		11 (91.7%)
Length of hospital stay (days)		4 (2–33)
Required surgery		4 (33.3%)

* Race and ethnicity are not mutually exclusive