Disseminated Gonococcal Infection Complicated by Prosthetic Joint Infection: Case Report and Genomic and Phylogenetic Analysis

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Since its nadir in 2009, the rate of Neisseria gonorrhoeae infections have been increasing globally, with prevalence rising across age groups [1]. This rise has coincided with joint replacements taking place at younger ages. In this study, we report a case of disseminated gonococcal infection (DGI) involving a prosthetic joint, and we use whole-genome sequencing to characterize resistance genes, putative virulence factors, and the phylogenetic lineage of the infecting isolate. We review the literature on sequence-based prediction of antibiotic resistance and factors that contribute to risk for DGI. We argue for routine sequencing and reporting of invasive gonococcal infections to aid in determining whether an invasive gonococcal infection is sporadic or part of an outbreak and to accelerate understanding of the genetic features of N. gonorrhoeae that contribute to pathogenesis.

CASE REPORT

In fall 2019, a 59-year-old white man with a history of left knee replacement 8 years ago presented to the emergency department of a hospital in Pennsylvania with a 2-day history of pain and swelling involving multiple joints. He first noticed pain, swelling, and redness over the dorsum of his left hand, followed by similar symptoms in the right wrist, shoulders, right hip, and left knee. The joint pain was exacerbated by movement and limited weight-bearing. He reported no pain on micturition or penile discharge. He reported he was monogamous. On exam, he appeared uncomfortable. His temperature was 36.9°C. Joint exam revealed tenderness in his shoulders and left 2nd to 5th metacarpophalangeal joints, swelling and erythema of the dorsum of the left hand, and decreased range of movement in his shoulders, knees, and right hip. Laboratory work revealed white blood cell count (WBC) of 15.9 × 10^3 cells/mL, with 89% neutrophils. The erythrocyte sedimentation rate was greater than 130 mm/hr and C-reactive protein was 33 mg/dL. Human immunodeficiency virus and rapid plasma reagin were negative. Arthrocentesis of the left knee yielded purulent fluid, with a WBC of 162 000 cells/mL, 89% neutrophils, and red blood cell count of 5000 cells/mL.

The differential diagnosis included joint infection due to commonly encountered pathogens, such as staphylococci, DGI, and migratory polyarticular arthritis secondary to a rheumatological disease. He was started empirically on vancomycin and cefepime, pending culture results, and changed to vancomycin and ceftriaxone after infectious disease consult. After culture from the knee aspirate fluid grew N. gonorrhoeae, he acknowledged multiple recent unprotected heterosexual encounters.

E-test of the N. gonorrhoeae isolate showed an azithromycin minimum inhibitory concentration (MIC) of 0.38 µg/mL, ceftriaxone MIC of <0.016 µg/mL, and ciprofloxacin MIC of 0.003 µg/mL. Management included irrigation and debridement of the left knee with synovectomy and polyethylene liner exchange, arthroscopic irrigation and debridement of the right hip, as well as 4 weeks of intravenous ceftriaxone and a single 1-gram dose of oral azithromycin. He then received 300 mg of cefdinir twice a day for four and a half months, given concern for PJI. His recovery was complicated by tenosynovitis of the left 2nd and 4th compartment with a torn extensor pollicis longus tendon, requiring tendon transfer and repair. He has had no reported recurrence of symptoms.

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The *N. gonorrhoeae* isolate, which appeared piliated and opaque on culture, underwent genome sequencing on the Illumina platform and analysis for resistance mutations and loci postulated to be associated with invasiveness [3–6] (see Supplemental Material). Analysis confirmed the absence of known antibiotic resistance determinants for ceftriaxone, with no known resistance variants in *penA*, *rpoB*, or *rpoD* [3, 6]. Likewise, no variants in *gyrA* or *parC* that confer resistance to ciprofloxacin were observed [3]. The isolate’s mosaic *mtrD* with a K823E mutation and the A39T mutation in *mtrR* can increase the azithromycin MIC by altering the MtrCDE efflux pump and increasing its expression, but do not on their own increase the MIC above clinical thresholds for resistance [3, 4]. No other known azithromycin resistance conferring mutation was observed, with no resistance variants in the 23S rRNA or *rplD* genes [5].

Although no genetic basis for dissemination or invasive disease in *N. gonorrhoeae* has been well established, several genetic loci have been speculated to be involved in invasiveness and serum resistance, including the gonococcal genetic island [7], the *opa* genes [8], the genes *porB* [9] and *lptA* [10], and the *lgt* operon [11, 12]. The isolate causing this case lacked the gonococcal genetic island and encoded wild-type *lptA* and *porB1b*. The *lgt* operon codes for glycosyl transferases that mediate biosynthesis of lipooligosaccharide (LOS) and several of the genes in this locus are phase variable, thus influencing the nature of the LOS [13]. Assessment of phase variation indicated that *lgtA* and *lgtC* were off and *lgtD* was on; however, the in vitro passaging of the clinical isolate may have resulted in genetic changes in these loci, rendering interpretation of the phase variation at these loci unclear. The 11 *opa* loci in the genome each have 2 hypervariable regions and could not be resolved and typed by the short sequencing reads.

Phylogenetic analysis revealed that the clinical isolate is derived from an internationally circulating lineage of antibiotic-susceptible *N. gonorrhoeae* with NG-MAST 20638 and MLST 11428. No other isolate causing DGI has been reported from this lineage to date. Comparison with recently reported sporadic cases of DGI in a large genomic epidemiology study revealed that the isolates causing those infections derive from distinct genetic lineages (see Figure 1).

### Patient Consent Statement

Patient consent was obtained. Institutional Review Board review is not required for this activity, for, as a case report, this work neither produces generalizable knowledge nor is it an investigation of a US Food and Drug Administration-regulated product.

### DISCUSSION

Disseminated gonococcal infection can present with dermatitis, migratory arthritis, and tenosynovitis [15]. In this case, the patient presented with migratory arthritis and left-hand tenosynovitis. This case of DGI was complicated by PJI, with only one other case to our knowledge reported in the literature [16], and DGI-associated tendon rupture.

The rarity of gonococcal PJI may be due to DGI as an uncommon manifestation of gonorrhea and the low prevalence of joint replacements in the age group of patients at highest risk of gonococcal infection [15, 17]. However, these groups are increasingly overlapping: more people are having prosthetic joint surgeries at earlier ages [17], and rates of gonococcal infections in the United States rose 63% from 2014 to 2018, with cases of gonorrhea in individuals aged 40+ years more than doubling [1].

The recommended treatment for uncomplicated gonococcal infection is single-dose intramuscular ceftriaxone plus...
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chain reaction-based tests for ciprofloxacin resistance [22] 

and growing understanding of the genetic basis of resistance 

to ceftriaxone and azithromycin provide an evidence base for 

development of genotypic assays for predicting phenotypic 

resistance to these antibiotics [23, 24]. In the case presented 

here, the genotype predicted susceptibility to ciprofloxacin, 

ceftiraxone, and azithromycin, in keeping with the observed 

phenotype. Beyond the categorical determination of suscepti-

bility, the variants observed in mtrD and mtrR, each expected 

to slightly increase the azithromycin MIC, were consistent with 

the Etest result. The accuracy of quantitative MIC prediction 

suggests that advances in genotype-to-phenotype models may 

make these assays useful for nuanced clinical decision making.

The factors that influence the likelihood of invasive gono-
coccal disease remain incompletely understood. Host factors 
predisposing to disseminated disease include innate or acquired 
complement deficiency [25, 26]. The pathogen factors contribut-
ing to invasiveness have been more challenging to establish, 
because they have been based on small numbers of cases. An 
outbreak of DGI in the late 1970s and early 1980s was caused by 
an auxotype requiring arginine, hypoxanthine, and uracil (the 
AHU auxotype) [27–31], raising suspicion that this auxotype-
defining lineage carried genetic determinants that promoted 

invasiveness. However, this auxotype seems to have stopped cir-
culating, and further genomic and phenotypic characterization 

of this lineage remains to be done. Other genetic loci speculated 
to be virulence factors include the gonococcal genetic island 
[7], the opa genes [8], the genes porB [9] and lptA [10], and the 
lgt operon [11, 12], with several of these loci contributing to 

escape of complement-mediated killing [32]. Recent outbreaks, 
including one among heterosexuals in Michigan, have renewed 
questions about the genetic predisposition of particular lineages 
to invasiveness [2, 33].

Routine reporting of genome sequences of invasive N. 
gonorrhoeae isolates together with the clinical contexts can aid 
in the effort to define the genetic basis for gonococcal viru-

ence and represent an important complement to in vitro and 
animal-model studies. For comparison, recent studies using se-
quence data from isolates collected over many years and coun-
tries has expanded our knowledge of the genetic modulators of 
antimicrobial resistance in clinical isolates of N. gonorrhoeae as 
well as its adaptation to anatomical sites of infection [4–6, 34, 
35]. Likewise, the genome sequences of Neisseria meningitidis 
isolates causing sporadic cases and outbreaks of urethritis have 
aided in understanding the genetic basis of meningococcal ad-
aptation to the urogenital niche and in clarifying the impor-
tance of putative virulence loci [34, 36–38].

Although N. gonorrhoeae genome sequencing has primarily 

relied on cultured specimens, recent advances demonstrated 
the potential of sequencing directly from patient specimens 
[39, 40]. The most likely near-term use of these technologies 

includes point-of-care prediction of antibiotic susceptibility 
based on genome sequence either by direct assessment of one 
or more loci [23, 39, 40] or by phylogenetic-neighbor typing 
methods [41]. The use of long-read platforms to sequence di-
rectly from patient specimens also contributes to efforts to iden-
tify loci that contribute to invasiveness. This approach will allow 
for querying phase-variable sites (such as in the lgt operon) di-
rectly, thereby eschewing the confounding phase alterations 
that may arise during in vitro passage. In addition, long-read 
sequencing will allow for the comprehensive characterization 
of the Opa repertoire that is challenging to do with short-read 
sequencing platforms.

CONCLUSIONS

Reporting of sporadic and outbreaks of DGI cases together 
with genome sequence data and host risk factors can inform 
and enable similar efforts to combine data and uncover the 
N. gonorrhoeae genetic contributors to invasiveness as well 
as understand the extent to which cases reflect gonococcal 
lineages with a higher risk of invasion. At least 10 individual 
cases of DGI and one DGI outbreak have been published and 
indexed on PubMed over the past year [2, 42–52]. Sequences 
from these isolates would address several key questions. First, 
to what extent are DGI cases sporadic, and to what extent do 
they represent a lineage's propensity to cause invasive disease? 
For example, of the isolates from DGI cases in Australia [14] 
included in the phylogeny, some isolates are clustered and 
others appear sporadic (Figure 1). Adding more isolate 
genomes to this phylogeny will help assess whether the clustered 
cases represent outbreaks, and additional outbreak lineages 
will provide statistical power to identify the genetic basis for 
invasiveness. Second, although disseminated infection remains 
rare and rates appear to have declined over the past several dec-
ades [53], is the lower rate attributable to changes in circulating 
strains? Third, if there is a DGI cluster, how geographically and
demographically widespread is it? For example, the reporting of genome sequences from the recent Michigan DGI outbreak will inform on whether the case reported here reflects spread of an invasive lineage and inform efforts for surveillance.

The number of genome sequences from clinical N. gonorrhoeae isolates in public databases is over 13,000 and steadily growing. Just as the subset of these isolates for which antibiotic resistance data has helped expand our understanding of the genetic basis of resistance [4, 5, 34], routinely sequencing and reporting invasive strains will increase the statistical power to address critical questions of N. gonorrhoeae virulence and help inform public health surveillance and interventions.

Supplementary Data
Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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