

Literature Review

National STD Curriculum Podcast

Can Gonorrhea, Chlamydia, or Mgen Spontaneously Clear?

February 15, 2024

Season 4, Episode 5

This episode reviews five articles regarding spontaneous clearance of *Neisseria gonorrhoea*, *Chlamydia trachomatis*, and *Mycoplasma genitalium* without the use of antibiotics.

Topics:

- Chlamydia
- Gonorrhea
- Mgen
- STIs
- STDs
- spontaneous clearance

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No Disclosures

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[introduction](#)[00:00] **Introduction**

Hello everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STD [sexually transmitted disease] literature review for health care professionals who are interested in remaining up-to-date on the diagnosis, management, and prevention of STDs.

[background](#)[00:22] **Background**

A recent question that came up was whether an STI pathogen would clear on its own. Let's say if the patient doesn't have any symptoms. Do they need antibiotics, or would their immune system be able to clear the infection without antibiotics? Now, in the setting of increasing antimicrobial resistance in several STI pathogens, as well as the need for better antimicrobial stewardship, this topic has come up in the published literature. Now, in the clinical setting, patients have asked about this, especially if an antibiotic to treat an STI pathogen isn't available or is just difficult to obtain in the U.S., which can happen with multidrug-resistant *Mycoplasma genitalium*. It does seem that some STI pathogens can spontaneously clear, but what we don't know is in what percentage of infections this occurs, the length of time from the infection to clearance, factors that might be associated with spontaneous clearance, and whether it differs for specific pathogens or the anatomical sites that are involved. I'd like to review some articles on this topic and a few more than I usually do in other episodes because I think they connect nicely with each other.

[paper-1](#)[01:34] **Paper #1**

Teker B, de Vries H, Heijman T, et al. Spontaneous clearance of asymptomatic anogenital and pharyngeal *Neisseria gonorrhoeae*: A secondary analysis from the NABOGO trial. *Sex Transm Infect.* 2023 Jun;99(4):219-225. [[PubMed Abstract](#)]

This first article for review was published in *Sexually Transmitted Infections* in June of 2023, and it was published by Dr. Teker and colleagues and is titled "Spontaneous clearance of asymptomatic anogenital and pharyngeal *Neisseria gonorrhoeae*: A secondary analysis from the NABOGO trial." So, the interesting feature of this study is that the NABOGO trial was a randomized controlled trial, and it was evaluating alternative antibiotics for the treatment of uncomplicated gonorrhea. And in this particular study, the authors assessed spontaneous clearance of anogenital and pharyngeal gonorrhea between two different testing visits before antibiotics were given, and the time between testing visits had a median of about seven days.

1. They included 241 patients in the analysis, and what they found is that spontaneous clearance was observed in 15% of patients with anal gonorrhea infection, 19% with pharyngeal infection, 23% with vaginal, and 32% with urethral infection.
2. In the multivariable analysis, the authors found that the odds of spontaneously clearing *Neisseria gonorrhoeae* infection was higher for patients with a larger time interval between the two testing visits, and this had an adjusted odds ratio of around 1 per additional day, and that was significant with a *p*-value of 0.011.
3. The anatomic location of infection, HIV status, PrEP use, and age were not associated with spontaneous clearance, although patients with HIV and a CD4 count that was lower, for example, less than 350, were not included in the study.

The authors of this study found that there are a subset of patients who do clear *Neisseria gonorrhoeae* infection at every anatomical site, and this is without antibiotics. And they found that patients with a longer interval of time in between testing were more likely to clear spontaneously. What we don't know is which patients will spontaneously clear and in what timeframe, but bacterial load and a patient's immune system likely plays a role. This study brings up the idea around the optimal frequency of STI screening in MSM and whether less frequent STI screening may allow for spontaneous clearance and improve antibiotic stewardship. On the other hand, untreated infection can have potential complications, like adverse reproductive consequences, transmission to uninfected partners, or eventually produce symptoms, especially if patients are initially asymptomatic. I look forward to seeing further studies on this topic.

[paper-2\[04:11\] Paper #2](#)

Barbee LA, Soge OO, Khosropour CM, Haglund M, Yeung W, Hughes J, Golden MR. The duration of pharyngeal gonorrhea: A natural history study. *Clin Infect Dis*. 2021 Aug 16;73(4):575-582. [[PubMed Abstract](#)]

The next article to discuss was published in *Clinical Infectious Diseases* in August of 2021 and it was published by Dr. Barbee and colleagues. It is titled “The duration of pharyngeal gonorrhea: A natural history study.” This was a prospective, longitudinal, cohort study in which participants collected swab samples weekly at home, and then they completed an online survey for around 48 weeks.

1. The authors enrolled 140 MSM; 51% were persons with HIV, and 74% had a gonorrhea, chlamydia, or syphilis diagnosis in the past year.
2. The authors found in the study that in 19 men, 21 pharyngeal gonorrhea infections developed, and this corresponded to an incidence of 32 cases per 100 person-years. The estimated median duration of pharyngeal gonorrhea without treatment was quite long—it was actually at 16 weeks.
3. The authors found that the duration of infection did not significantly vary based on HIV status, recent history of gonorrhea, concurrent pharyngeal chlamydia infection, or smoking status.
4. Overall, the majority of cases were asymptomatic and only in six cases (or 26%) men reported a sore throat in the first or second week of infection.

This study found that pharyngeal gonorrhea infection can persist for a median of 16 weeks without treatment, possibly playing an important role in gonorrhea transmission. The authors found that while 26% of the cases men reported symptoms, most of the cases were asymptomatic.

[paper-3\[05:45\] Paper #3](#)

van Liere GAFS, Hoebe CJPA, Dirks JA, Wolffs PF, Dukers-Muijters NHTM. Spontaneous clearance of urogenital, anorectal and oropharyngeal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in women, MSM and heterosexual men visiting the STI clinic: A prospective cohort study. *Sex Transm Infect*. 2019 Nov;95(7):505-510. [[PubMed Abstract](#)]

Now, what about chlamydia infection? Can chlamydia infection spontaneously clear as well? And the answer is yes. There was an article published in *Sexually Transmitted Infections* in November of 2019 by Dr. van Liere and colleagues. It is titled “Spontaneous clearance of urogenital, anorectal, oropharyngeal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in women, MSM, and heterosexual men visiting an STI clinic: A prospective cohort study.” So, this study took place at an STI clinic in the Netherlands where patients with untreated chlamydia or gonorrhea infection were asked to take a repeat test when returning for treatment. Now, the repeat test was done before they got antibiotics, and we’re going to focus on chlamydia infection reported in this study.

1. They evaluated patients using NAATs [nucleic acid amplification tests] but also determined the chlamydia bacterial load using a PCR [polymerase chain reaction] test to quantify the gene that encodes the major outer membrane protein.
2. The median number of sex partners was 2, and 53% of patients reported urogenital symptoms and 4% had anorectal symptoms.
3. The median number of days between the two testing time points was 10 days for urine, 9 days for vaginal swabs, 8 days for anorectal swabs, and 12 days, so a little bit longer for oropharyngeal swabs.
4. They found that spontaneous chlamydia clearance was 9% for urine, 7% for vaginal swabs, 13% for anorectal swabs, and 57% for oropharyngeal swabs.
5. The authors found that lower bacterial load was associated with clearance in all sample types, although not all individuals with low bacterial chlamydia load did clear their infection.

So, in this study, spontaneous clearance of chlamydia infection can occur, and it ranges between 7 to 57%, depending on the anatomical site of infection. The authors found that chlamydia clearance occurred with a median of 10 days from screening but do point out that the study was not able to tell the exact day of infection or the exact day of clearance from the two testing time points, so more studies are needed in this area. While spontaneous clearance of chlamydia infection can occur, it's important to remember that untreated chlamydia infections can result in significant morbidity, including pelvic inflammatory disease, chronic pelvic pain, and tubal factor infertility, even if asymptomatic.

[paper-4](#)[08:11] Paper #4

Jordan SJ, Wilson L, Ren J, Gupta K, Barnes S, Geisler WM. Natural clearance of *Chlamydia trachomatis* infection is associated with distinct differences in cervicovaginal metabolites. *J Infect Dis.* 2023 Oct 18;228(8):1119-1126. [[PubMed Abstract](#)]

The next article to discuss was published in *The Journal of Infectious Diseases* by Dr. Jordan and colleagues in October of 2023. It is titled "Natural clearance of *Chlamydia trachomatis* infection is associated with distinct differences in cervicovaginal metabolites." So, let's take a minute to provide some background. Immunity to chlamydia in animals is mostly mediated by interferon-gamma. Interferon-gamma works on a pathway to deplete the amino acid tryptophan, which is essential for chlamydia survival. Now, chlamydia, in turn, has some survival mechanisms to deal with tryptophan depletion, including a way to convert indole, which is produced by other bacteria and is a signaling molecule to tryptophan. But there might be some other factors involved in chlamydia clearance or persistence that can help our understanding on how this organism survives in the human host.

1. And so what this study did is, they evaluated whether interferon-gamma-independent metabolic pathways are associated with spontaneous clearance of chlamydia infection in women.
2. They used mass-spectrometry to record molecular ions found in cervicovaginal lavages from 34 women, 17 women who spontaneously cleared their infection and then 17 women who did not.
3. What the authors found is that spontaneous clearance of chlamydia infection was associated with increased levels of oligosaccharides: trehalose, sucrose, melezitose, and maltotriose; and lower levels of indoline and various amino acids, especially valine, leucine, and isoleucine.

So, overall, the study suggests that amino acids other than tryptophan and interferon-gamma-mediated pathways impact chlamydia survival in humans. They found that distinct differences in cervicovaginal metabolites occurred in women who naturally cleared their infection, and that is important information to understand when thinking about immunity, and in relation to a future chlamydia vaccine. In addition, these metabolites may be influenced by the cervicovaginal microbiota or other bacteria in the cervicovaginal area, and the authors note that this will be a focus of future studies.

[paper-5](#)[10:23] Paper #5

Ring A, Balakrishna S, Imkamp F, et al. High rates of asymptomatic *Mycoplasma genitalium* infections with high proportion of genotypic resistance to first-line macrolide treatment among men who have sex with men enrolled in the Zurich primary HIV infection study. *Open Forum Infect Dis.* 2022 Apr 27;9(6):ofac217. [[PubMed Abstract](#)]

The next study to discuss was published by Dr. Ring and colleagues in *Open Forum Infectious Diseases* in April of 2022. It is titled "High rates of asymptomatic *Mycoplasma genitalium* infections with high proportion of genotypic resistance to first-line macrolide treatment among men who have sex with men enrolled in the Zurich primary HIV infection study."

1. They found that 30 of the 148 participants (or 20%) had at least one *Mycoplasma genitalium* infection

during the study period, which occurred from 2019 to 2020, and this resulted in an incidence rate of around 20 cases per 100 person-years.

2. Only 2 of the 30 participants (or 7%) were symptomatic; 93%, and the majority of patients, were asymptomatic.
3. Authors found that 22 participants had macrolide-resistant infection; one participant had quinolone-resistant infection; and four had resistance to both macrolides and quinolones.
4. They found nine infections (or 30%) were spontaneously cleared by the next testing time point, which was about 3 months later.

The spontaneous clearance of *Mycoplasma genitalium* can occur, and this study showed that most MSM with HIV had asymptomatic *Mycoplasma genitalium* infection. Antimicrobial resistance is a concern and there were high rates of macrolide-resistant infections indicating that treatment with azithromycin alone would not work for the majority of patients in this study.

[summary](#)**[11:56] Summary**

To conclude, I'd like to summarize some key points from this session:

1. Spontaneous clearance of *Neisseria gonorrhoea*, *Chlamydia trachomatis*, and *Mycoplasma genitalium* can occur without antibiotics, although not all patients are able to clear these organisms on their own.
2. The median duration of pharyngeal gonorrhea without treatment was quite long at about 16 weeks, and the majority of cases are asymptomatic. This can potentially lead to the transmission of the organism to uninfected partners.
3. Spontaneous clearance of chlamydia infection can occur, and it ranges from 7 to 57%, depending on the anatomical site of infection, although one needs to keep in mind that untreated chlamydia infection can cause pelvic inflammatory disease and infertility.
4. There are likely interferon-gamma-independent metabolic pathways that are associated with spontaneous clearance of chlamydia infection in women.
5. Further studies are needed in this area to determine factors associated with spontaneous clearance of STIs.

[credits](#)**[13:04] Credits**

This podcast is brought to you by the National STD Curriculum, the University of Washington STD Prevention Training Center, and is funded by the Centers for Disease Control and Prevention.

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[spontaneously-clear](#)