Gonorrhea—Shrinking treatment options

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Gonorrhea is a relatively common infection among men who have sex with men, but it is becoming more common in heterosexual people. It is caused by the bacteria *Neisseria gonorrhoeae*. This infection is transmitted via unprotected anal, oral and vaginal sex and can quickly be treated with antibiotics, but, if left untreated, gonorrhea can lead to serious problems. Such problems can occur because gonorrhea-causing germs move from the anus, penis or vagina toward the ovaries and testicles or these germs spread through the bloodstream to the skin, joints, heart or brain. Gonorrhea not only causes pain and suffering but, like many sexually transmitted infections (STIs), it can cause inflammation in delicate ano-genital tissue. Such inflammation makes it easier to acquire or transmit HIV.

For the past decade in high-income countries such as Canada, commonly used treatments for gonorrhea have been the antibiotics cefixime (Suprax) taken orally or ceftriaxone given as an injection into muscle. During this same time in East Asia, reports of gonorrhea resistant to these therapies have gradually been emerging. Now such cases are also appearing in Western Europe. With the availability of relatively cheap air travel and tourism, some STI researchers expect that cases of drug-resistant gonorrhea can only increase in the years ahead.

Gonorrhea that is resistant to cefixime or ceftriaxone is particularly troubling because there are no cheap, easy-to-administer alternative antibiotics waiting in the wings. Also, there is no effective vaccine for gonorrhea. Therefore, revisions to gonorrhea treatment guidelines are being planned or considered in Canada, the UK and other high-income countries. In this *CATIE News* bulletin, we explore some treatment options that researchers are discussing in light of the emergence of multi-drug-resistant strains of gonorrhea. But first we present some background information about gonorrhea transmission, symptoms, testing, current treatment options and the history of gonorrhea’s resistance to antibiotics.

**Transmission**

Gonorrhea results from inflammation caused by infection with *N. gonorrhoeae* bacteria. These germs can be spread in the following ways:

- unprotected contact with the anus, penis, throat or vagina
- from an infected mother to child during birth

The bacteria that cause gonorrhea can infect the wet tissues of the mucosa in the genitals and throat, causing inflammation. If left untreated, gonorrhea can cause serious complications. That is why it is important for sexually active people to engage in safer sex and to have regular checkups.

**Symptoms**

Gonorrhea germs can cause similar and yet different symptoms and complications in men and women.

**Men and women—uncomplicated genital infection**

Gonorrhea germs can cause inflammation of the urinary tract within 10 days after initial exposure. Symptoms can include the following:

- painful urination
leakage of a thick pus-like fluid from the tip of the penis or vagina

Women—uncomplicated genital infection

In most women, gonorrhea-causing germs can infect the opening of the womb. Some infected women do not initially develop symptoms of genital gonorrhea. Among those who do, these symptoms usually occur within 10 days of exposure and can include the following:

- a thick fluid oozing from the vagina
- painful urination
- pelvic inflammatory disease (PID)

Researchers estimate that between 10% and 20% of women with gonorrhea can develop PID as the gonorrhea germs spread into the reproductive tract and organs, causing inflammation and damage. A range of symptoms can subsequently develop, as follows:

- fever, chills
- lower abdominal pain
- cervical pain
- increased bleeding or cramps during periods
- bleeding between periods
- urinating frequently
- painful urination
- lower back pain

If left untreated, PID can cause chronic pelvic pain, infertility and other complications.

Men and women—rectal infection

Gonorrhea in the rectum can occur in cases of unprotected anal intercourse following penetration or potentially oral-anal sex. Rectal gonorrhea can be symptom free or may be accompanied by any of these symptoms:

- anal itching
- rectal pain during bowel movements
- a thick fluid oozing from the anus
- rectal bleeding

Men and women—throat infection

In cases of oral sex with an infected partner, the throat can become infected (pharyngeal gonorrhea), with symptoms such as the following:

- difficulty swallowing
- fever
- swollen lymph nodes in the neck

However, pharyngeal gonorrhea can occur without any obvious symptoms.

Men and women—eye infection

Gonorrhea can cause painful eye inflammation. Usually this happens in people who have genital gonorrhea and who touch their eyes right after touching the genital area.

Men and women—perihepatitis

This complication is rare. However, in some cases, gonorrhea-causing germs can spread from the genitals, perhaps through the lymphatic system, to the liver, causing inflammation in that organ. Affected people can have pain and tenderness in their upper right abdomen (where the liver is). In some cases, blood tests may detect increased levels
of liver enzymes in the blood, suggestive of liver inflammation.

**Lab and other tests**

Gently scraping or swabbing a sample of mucous from the genitals, rectum or throat can be useful in growing and identifying *N. gonorrhoeae* in the lab. This type of testing is called culturing. However, culture for gonorrhea is not available in some parts of Canada. Instead, a different type of test called NAAT (nucleic acid amplification test) is used. NAAT is very useful in finding gonorrhea-causing germs because it can also be done on the urine. However, a drawback of NAAT is that it cannot detect potential resistance to antimicrobials.

In some cases of PID or perihepatitis, doctors may insert a tiny tube with a miniature camera at the end into an incision just below the belly button. This is helpful when trying to examine tissues such as the ovaries, fallopian tubes and uterus. A general anaesthetic is given to women during this procedure to minimize pain.

**Treatment**

The Public Health Agency of Canada (PHAC) has facilitated the development of guidelines for STI detection and treatment. In these guidelines, the preferred treatment for uncomplicated gonorrhea affecting the penis, rectum, throat or vagina is a single dose of cefixime (Suprax) 400 mg taken orally.

If for some reason cefixime cannot be used, PHAC suggests alternatives, including these:

- ceftriaxone 125 mg given in a single intramuscular injection
- spectinomycin 2 grams given in a single intramuscular injection
- azithromycin 2 grams in a single oral dose

**Notes**

In order to obtain spectinomycin, physicians must contact Heath Canada’s Special Access Program (SAP). Contact information appears later in this bulletin.

Azithromycin at such a high dose carries a significant risk of nausea and vomiting, especially for low-weight patients, and should be taken during a meal. Some patients find that taking an anti-nausea drug such as dimenhydrinate (Gravol) is also useful when taking azithromycin. Also, reports of gonorrhea (and syphilis) resistant to azithromycin have emerged.

**Trends in resistance**

In the 1940s when penicillin was first introduced, small doses were highly effective in curing gonorrhea. However, these bacteria gradually mutated and began to develop resistance to penicillin. Indeed, by the late 1960s the recommended dose of penicillin was 40-fold greater than what was initially needed to cure gonorrhea.

In the mid-1970s, penicillin resistance became such a problem that some doctors switched to another antibiotic, spectinomycin given by injection.

In the 1980s, the oral antibiotic ciprofloxacin (Cipro) became available and proved highly effective as a treatment for gonorrhea. Also in the 1980s, another antibiotic, tetracycline, was used for gonorrhea treatment but then reports of gonorrhea resistant to this antibiotic emerged.

By the year 2000, reports of ciprofloxacin-resistant gonorrhea became more frequent. And, in 2008, treatment in most high-income countries had changed and it was generally recommended to take cefixime orally or ceftriaxone by injection. These two drugs belong to a class of antibiotics called cephalosporins.

**The present problem**

Reports of gonorrhea resistant to treatment with cephalosporins in East Asia have increased in the past decade. This is particularly troubling because in such cases gonorrhea is usually resistant not just to cephalosporins but likely to other antibiotics as well. This makes these cases of gonorrhea expensive and hard to treat. Furthermore, should multi-drug-resistant gonorrhea become widespread, few well-studied alternative antibiotics are available. We
now briefly highlight some cases of drug-resistant gonorrhea in several high-income countries.

**In Japan**

In this country, researchers have stated that *N. gonorrhoeae* has developed resistance to “multiple classes of [antibiotics],” including penicillin and several of its derivatives, tetracyclines and ciprofloxacin (and similar drugs). Therefore, the preferred treatment there is injectable ceftriaxone or spectinomycin.

In January 2009, a 31-year-old woman visited an STI clinic for a check-up. She had no obvious signs or symptoms of gonorrhea. However, a swab from her throat allowed technicians to detect *N. gonorrhoeae*’s genetic material. A sample from her vagina taken at the same time did not yield any STIs. Two weeks later, another throat swab revealed *N. gonorrhoeae* and she received a single 1,000-mg dose of ceftriaxone.

Two weeks later, on her third visit to the clinic, technicians found that another sample from her throat was positive and yet another high dose of ceftriaxone was prescribed. Requiring more than one dose of ceftriaxone is highly unusual for the treatment of an episode of gonorrhea. And it was not until April that swabs from her throat stopped testing negative for *N. gonorrhoeae*.

Further analysis of her initial throat sample revealed a strain of *N. gonorrhoeae* that could not only tolerate high concentrations of ceftriaxone but was resistant to penicillin G, cefixime and levofloxacin. However, this strain was susceptible to spectinomycin and somewhat susceptible to azithromycin.

**In Sweden**

In July 2010, a Swedish man in his 20s sought care at a local clinic because of a discharge from his penis, pain while urinating and a sore throat (this initial visit was termed Day 1). Four days earlier he had protected vaginal sex and unprotected oral sex with a casual female partner in Japan.

A type of NAAT called PCR (polymerase chain reaction) testing of his urine revealed *N. gonorrhoeae*. He was prescribed amoxicillin 750 mg twice daily for 10 days.

Day 12: Twelve days after the man first sought care, he went to an STI clinic. At this point his uro-genital symptoms had cleared but he still had a sore throat. Extensive laboratory testing could not find *N. gonorrhoeae* in his urine but a swab from his throat was eventually found to contain these germs.

Day 26: With the lab results in hand, doctors gave him an injection of ceftriaxone 250 mg.

Day 36: He returned for further care and doctors found that his throat was still inflamed and swabs from his throat confirmed that he still had *N. gonorrhoeae*.

Day 43: Doctors prescribed another course of ceftriaxone, this time at a dose of 500 mg.

Day 50: The patient returned to the STI clinic with his throat still inflamed and subsequent laboratory testing continued to confirm the presence of *N. gonorrhoeae*.

Day 71: This time doctors gave him 1,000 mg of ceftriaxone intravenously.

Days 88 and 92: Further check-ups did not find any gonorrhea-causing germs.

**In Norway—Case 1**

In July 2010, a Norwegian man in his 30s sought care at a university-based hospital because of a discharge from his penis and pain while urinating. Tests confirmed that he had gonorrhea and he was given a single dose of cefixime 400 mg orally.

Day 21: He returned with persistent symptoms and tests confirmed that gonorrhea was still present. Doctors prescribed ceftriaxone and gave him 500 mg via intramuscular injection.

Day 29: The man’s symptoms cleared and PCR and other tests could not detect *N. gonorrhoeae*. 
In Norway—Case 2

In August 2010, another man in his 30s sought care for similar symptoms. Treatment with a standard dose of ceftriaxone failed and a high dose (500 mg) was later necessary to cure him.

Both Norwegian men were infected with a similar strain of gonorrhoea that was not only resistant to cefixime but also to ciprofloxacin. After interviewing both men, investigators concluded that the two had been infected separately, in the Philippines (Case 1) and in Spain or Norway (Case 2).

Preparing for more resistance

Research teams in the Asia, Netherlands, United States, UK and South Africa have been pondering options for dealing with strains of gonorrhea that could be resistant to cefixime and ceftriaxone. At present there does not appear to be international consensus about the ideal treatment for multi-drug-resistant gonorrhea because alternatives are either more difficult to obtain, have more side effects or are given intramuscularly instead of orally. However, expect gonorrhea treatment guidelines in Canada, the UK and other high-income countries to change in the future as public health authorities prepare to deal with the growing challenge of managing gonorrhea resistant to cefixime or ceftriaxone.

There are several possible approaches for dealing with this hard-to-treat strain of gonorrhea and these approaches are explored next.

Higher doses of antibiotics

Some researchers have suggested that intensified doses of cefixime or ceftriaxone be administered for the treatment of gonorrhea. A similar approach was used in the 1950s and 1960s with penicillin as this infection became more difficult to treat. However, there may be less opportunity to intensify the dose with cefixime, currently prescribed in a single 400-mg oral dose. Higher doses can cause nausea, vomiting and diarrhea.

Ceftriaxone is currently used at doses of 125 mg (in Canada) and 250 mg (in the UK) given as a single intramuscular injection. In the UK, it is likely that guidelines to be released later this year will suggest higher doses, at least 500 mg.

In Japan, ceftriaxone is administered at a dose of 1,000 mg via intravenous infusion. Given this way, doses as high as 2,000 mg have been well tolerated. So it is possible that when faced with new multi-drug-resistant strains of gonorrhea, higher doses of ceftriaxone may be useful, at least for a time.

Combination therapy

The problem with relying on azithromycin as the second antibiotic for treating gonorrhea is that this antibiotic, at a dose of 1 gram, has limited effectiveness against \textit{N. gonorrhoeae} and intensified use of this dose may amplify the development of azithromycin-resistant gonorrhea. Higher doses of azithromycin, such as two grams, can cause nausea and vomiting, particularly in thin people. Such patients may need to also take Gravol to minimize these problems. However, a sustained-release formulation containing 2 grams of azithromycin and sold as Zmax SR has become available in the past two years. This formulation is supposed to be better tolerated than the previous formulation. Note that this new formulation is expensive.

Revisiting spectinomycin

Spectinomycin is not easily available in some countries. In Canada, it can only be accessed through Health Canada’s Special Access Program (SAP). In some other countries, when spectinomycin injections were widely used for the treatment of gonorrhea, resistance was reported. Therefore, if there is resurgence in the use of spectinomycin, it is possible that resistance to this drug may become widespread. Spectinomycin’s effectiveness for the treatment of gonorrhea of the throat needs to be reassessed.

Revisiting aminoglycoside antibiotics such as gentamycin

Laboratory experiments with an old antibiotic, gentamycin, suggest that this drug has potential as a treatment for gonorrhea. However, gentamycin must be injected. Another drawback is that it belongs to the class of antibiotics
known as aminoglycosides. This class of antibiotics can cause highly unpleasant and, in some cases, dangerous side effects. In particular, gentamycin can cause a range of side effects including the following: kidney dysfunction, hearing loss and neurologic problems such as dizziness, numbness and seizures. However, the likelihood of developing these problems after a single injection is relatively low. In some countries, gentamycin may not be available but kanamycin, another aminoglycoside antibiotic, may be worth testing in clinical trials.

**Tigecycline—the need for research**

Tigecycline (Tygacil) is an antibiotic that has been available for several years and is particularly useful for treating drug-resistant bacteria. Laboratory studies suggest that tigecycline can impair gonorrhea-causing bacteria. However, there are no formal studies in people to confirm this. Moreover, tigecycline has to be administered slowly via intravenous infusion, is expensive and can cause nausea, vomiting and diarrhea. Furthermore, in some studies tigecycline is associated with more severe side effects, including painful inflammation of the pancreas gland and an increased risk of death. Taken together, all of these factors do not make tigecycline an ideal option for the treatment of gonorrhea.

**An empty cupboard**

Ideally, planning and conducting robustly designed clinical trials to explore the effectiveness of new strategies for gonorrhea treatment should be done soon, before new strains of cephalosporin-resistant gonorrhea become widespread. Such testing is important because there are no new antibiotics for gonorrhea in late-stage clinical development. In part, this problem arises because most pharmaceutical companies have withdrawn from the development of antibiotics.

Research for the development of a vaccine against gonorrhea needs to be accelerated.

**Conclusion**

As with many STIs, the best treatment for gonorrhea is still prevention. Injectable antibiotics are often more effective for rectal and pharyngeal treatment of gonorrhea. Ideally, testing for gonorrhea should be by culture (i.e., getting a swab rather than relying on urine tests that use NAAT). For men with suspected gonorrhea in the penis this can be painful but swabs can be used to grow cultures of *N. gonorrhoeae* in the lab. Cultured gonorrhea carries the advantage of being assessed for resistance to antibiotics. And, in the era of emerging resistance to cefixime and ceftriaxone, cultures of *N. gonorrhoeae* may become important and could help to refine treatment options.

**Resources**

1. **STI guidelines**
   Clear, comprehensive and easy-to-use guidelines for the diagnosis and treatment of STIs are available from the Public Health Agency of Canada at:
   

2. **Special Access Program**
   Health Canada’s SAP exists to help facilitate doctors’ access to therapies not sold in Canada. This access is limited to physicians caring for patients with serious or life-threatening conditions on a compassionate or emergency basis when conventional therapies have failed, are unsuitable or are unavailable. Physicians interested in this program can use this link to find out more:


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—Sean R. Hosein

REFERENCES:


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