Troubling treatment failure against an emerging sexually transmitted infection

10 October 2013

The bacterium *Mycoplasma genitalium* (MG) is sexually transmitted and can cause inflammation of the urinary and genital tracts in men and women. This germ may also be linked to other problems, including some cases of arthritis and, in women, pelvic inflammatory disease and infertility. For background information please see the previous CATIE News story.

A note on testing for MG

Resistance testing for mycoplasmas is very complicated in comparison with other sexually transmitted infections (STIs) such as gonorrhea. Some labs use nucleic acid amplification tests (NAAT) to detect MG. But NAATs cannot be used to test for antibiotic resistance and NAAT for MG is not generally available outside of a research lab. Furthermore, techniques for assessing MG's resistance to antibiotics are not widely available.

Growing resistance to antibiotics

For the past decade the antibiotic azithromycin has been generally successful against MG infection. However, reports from several high-income countries, including Australia, Denmark, France, Japan, New Zealand and the U.S., suggest that recently MG is developing resistance to azithromycin. In some regions, azithromycin works in only about 40% of cases of MG infection. Although lab experiments with MG suggest that another antibiotic, doxycycline, can impair the growth of MG, when people are treated with doxycycline, rates of recovery from MG are generally poor.

One option has been the antibiotic moxifloxacin (Avelox). Now reports of moxifloxacin treatment failure for MG infection have appeared. Although currently small, the reports of moxifloxacin treatment failure are of concern because it is not clear what treatment options are left. Also, in some cases doctors are not sure what is the source of MG resistance, which could occur for at least any of these reasons:

- MG that carries mutations in its genes that confers protection from antibiotics
- patients not taking antibiotics exactly as directed
- the patient has been re-infected by a sexual partner(s)

In this CATIE News bulletin, we review research on moxifloxacin treatment failure and one possible future treatment option.

Study details

Researchers in Sydney, Australia, recently reviewed data and fluid samples collected between Feb 2008 and November 2011 from participants who attended sexual health clinics. The review focused on 400 participants who sought care because of symptoms associated with MG, such as urethritis. Testing revealed that none of them had chlamydia or gonorrhea.

During the review period, 53 participants were diagnosed with MG infection. Fluid samples yielding MG that could be analysed at the molecular level were available for 32 participants. Specifically, researchers were interested in searching for the genetic material of MG that had mutations in genes associated with resistance to macrolides, a
class of drugs that includes azithromycin, erythromycin and clarithromycin.

**Results**

Among the 32 participants, there were 15 (47%) who had MG with genes that conferred resistance to azithromycin and related drugs. This resistance was significantly associated with a past history of being treated with azithromycin at a single dose of 1 gram for symptoms of a urinary tract infection. Having MG with these genes was not associated with the following factors:

- contact with a sex worker
- sexual contact overseas
- male-to-male sexual contact

There were also four cases in which participants did not have a history of exposure to azithromycin but had MG that carried genes associated with azithromycin resistance. This suggests that such strains were sexually transmitted.

In cases of treatment failure with azithromycin, clinic staff provided moxifloxacin, 400 mg daily for between seven and 10 days.

Technicians detected resistance to moxifloxacin (and similar drugs such as ciprofloxacin) in 19% of participants. Yet no study participant had a history of exposure to moxifloxacin or similar drugs.

Having MG that carries genes conferring resistance to moxifloxacin and related drugs was significantly associated with the failure of moxifloxacin to treat such cases of MG. In most cases of STIs, when researchers seek to prove that a germ is resistant to an antibiotic(s), they grow (or culture) the germ in the lab with different concentrations of antibiotics. However, it is difficult to do that with MG so genetic analysis was necessary to find resistance. In contrast, participants who had MG without those drug-resistant genes were all cured with moxifloxacin treatment.

**The problem**

Researchers were dismayed to find MG with resistance to azithromycin and, to a lesser extent, moxifloxacin circulating in the Sydney community. As a possible explanation for the high rates of azithromycin resistance that they found, the researchers point to the widespread use of azithromycin in the past where a single dose of 1 gram was used to treat suspected MG infection. Furthermore, the Sydney researchers note that their study is relatively small and so cases of MG resistant to azithromycin and related antibiotics are likely greater than captured in the present study.

**What is to be done?**

The Sydney researchers stated that “the current practice of treating urethritis unrelated to gonorrhea with a single 1 gram dose of azithromycin is...likely to be driving increased macrolide resistance among *M. genitalium* and causing azithromycin failure.” Researchers in Sweden conducting separate work on the response of MG to treatment have suggested that extended dosing (over five days) of azithromycin be used when treating MG.

There are few options for sexual health clinic staff when dealing with suspected cases of MG-related urinary tract infections because of at least these factors:

- MG is increasingly developing resistance to a 1-gram single dose of azithromycin.
- MG resistance testing is not widely available or routinely used.
- Using a five-day course of azithromycin therapy for MG infection has not been tested in a well-designed clinical trial to compare its effectiveness to the standard shorter 1-gram dose.
- An extended-release formulation of azithromycin, 2 grams (called Zmax SR) is available but there is no data from clinical trials about the effectiveness of this formulation against MG.
- Moxifloxacin could be prescribed instead of azithromycin but insufficient information exists about MG resistance to this antibiotic. Also, should moxifloxacin fail, there are no well-established alternatives.

Due to these factors and other factors, the Sydney team calls for more research on MG infection as well as the testing of new therapies for its treatment.
Enter solithromycin

One antibiotic that is under development could play a role in the future treatment of MG infection—if it passes phase III studies and gains regulatory approval.

The U.S.-based company Cempra Pharmaceuticals is developing a new antibiotic from the macrolide class called solithromycin (CEM-101). This drug is being primarily developed for the treatment of bacterial pneumonia. However, lab experiments suggest that it may be useful against multiple germs, including the following:

- chlamydia
- gonorrhea
- MG

Safety data so far

In a randomized, double-blind phase II study with 132 participants, researchers compared solithromycin given at a dose of 800 mg on the first day followed by 400 mg on four subsequent days, to the effect of another antibiotic, levofloxacin, given at a dose of 750 mg daily for five consecutive days. Both drugs were taken orally.

Results suggest that solithromycin is as effective as levofloxacin. However, more side effects were reported with levofloxacin (46%) than with solithromycin (30%). Most side effects were of mild-to-moderate intensity (mostly nausea and diarrhea). Several participants had to quit the study because of levofloxacin-related side effects, whereas no participants quit due to solithromycin-related side effects.

A large phase III trial comparing solithromycin against moxifloxacin for the treatment of bacterial pneumonia is underway in the U.S., Canada, Latin America and Europe.

Gonorrhea

Gonorrhea—once easily treatable with penicillin, ciprofloxacin or azithromycin—has become resistant to many drugs. The preferred treatment for gonorrhea in Canada and some high-income countries has changed over the past several years to injectable ceftriaxone (particularly in men who have sex with men and people who may have gonorrhea-causing bacteria in the throat) or higher single-dose oral cefixime (Suprax). For details about gonorrhea treatment options and resistance see this CATIE News story.

Cempra has collaborated with researchers in Toronto to conduct laboratory experiments with the bacteria that cause gonorrhea. In those lab experiments, solithromycin had anti-gonorrhea activity about four-fold greater than seen with azithromycin.

According to Cempra, a phase II clinical trial in the U.S. with 22 participants with gonorrhea found that a single dose of solithromycin was able to cure this STI.

M. genitalium

Researchers in Denmark have reported that 40% of cases of MG infection are now resistant to azithromycin treatment. In lab experiments with MG and antibiotics, researchers found that solithromycin had greater activity than any of the following antibiotics:

- azithromycin
- ciprofloxacin
- doxycycline
- moxifloxacin

However, in experiments where researchers used strains of MG that were resistant to azithromycin, about 85% of these strains were susceptible to solithromycin.

Looking to the future

The broad activity of solithromycin against different STIs may mean that it has potentially many uses, at least against
chlamydia, gonorrhea, MG and possibly even syphilis. Solithromycin must first be approved for its main intended use —bacterial pneumonia—before large clinical trials can be done with volunteers who have STIs, so that doctors can learn how to use this drug most effectively. In the meantime, the best way to prevent transmission of MG (and gonorrhea, chlamydia, HIV and many STIs) continues to be the correct and consistent use of condoms.

**Acknowledgement**

We thank Marc Steben MD, Institut national de santé publique du Québec, for his helpful discussion, research assistance and expert review.

—Sean R. Hosein

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Production of this content has been made possible through a financial contribution from the Public Health Agency of Canada.

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