Syphilis beats antibiotic—caution needed with azithromycin

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HIV is largely transmitted through unprotected anal, vaginal and, in some cases, oral sex. Syphilis is also passed on in generally the same manner. Because there has been a resurgence of unprotected sex since the turn of the century, an increase in syphilis is occurring in many parts of North America and Western Europe, including among sexually active men who have sex with men (MSM), some of whom are co-infected with HIV.

If left untreated, syphilis can damage the brain and other parts of the nervous system as well as the heart and other organs. In the time before antibiotics became available, people died from complications due to syphilis. This infection increases the risk of acquiring and transmitting HIV and possibly other sexually transmitted infections (STIs) such as LGV (lymphogranuloma venereum).

Penicillin was first used in 1944 against syphilis and since then has remained the preferred treatment for this STI. In North America today, standard therapy for the early stages of syphilis is usually a single dose of benzathine penicillin G, 2.4 million units injected into muscle.

In the setting of HIV infection, treatment of syphilis is controversial, with some experts suggesting that more intensive penicillin therapy is needed—the same dose of benzathine penicillin G repeated once weekly for three consecutive weeks. The reasons that some doctors may prefer this intensive regimen are as follows:

- Recovery from syphilis depends partly upon an effective immune response. HIV infection weakens the immune system and people who are co-infected with syphilis may not always be able to fight off this infection. Indeed, some researchers have reported that people with HIV/AIDS (PHAs) who have syphilis appear to have a more aggressive form of the infection than HIV negative people.
- The microbes that cause syphilis (called treponemes) can persist in the body despite recovery from the signs and symptoms of syphilis. Moreover, treponemes can invade many tissues, including the brain and the cerebrospinal fluid in which it floats. This can happen even during the early stages of syphilis. In one study, 25% of people with early syphilis had treponemes in their cerebrospinal fluid, whether or not they had HIV infection. Intensive therapy may prevent the development of more serious forms of syphilis such as neurosyphilis.
- There have been reports of treatment failure in PHAs after a single dose of benzathine penicillin G.

However, adherence with prolonged courses of syphilis therapy may be difficult for some people because of the need for repeated clinic visits and the unpleasantness of intramuscular injections. So it was with some excitement that health care workers greeted the arrival of the antibiotic azithromycin (Zithromax) in the early 1990s.

A new antibiotic
Azithromycin belongs to a group of antibiotics called macrolides, examples of which include clarithromycin (Biaxin) and erythromycin.

Azithromycin is taken orally, is well absorbed and penetrates many tissues, including the brain and cerebrospinal fluid. The concentration of this antibiotic in tissues remains high for many days after a single dose. This finding led to its potential for single-dose therapy.

Although azithromycin was licensed for the treatment of common bacterial infections, researchers found that it quickly blocked the growth of treponemes in lab experiments on rabbits with syphilis. In these animals, azithromycin was as effective as other antibiotics such as erythromycin and penicillin. In the mid-to-late 1990s, results from
clinical trials in people revealed that azithromycin appeared to be as effective as penicillin for the treatment of very early stages of syphilis.

Campaigns against syphilis using azithromycin were launched on the west coast of North America, particularly in Los Angeles, San Francisco and Vancouver. Initially this strategy appeared to work, reducing new cases of syphilis. However, within a year, rates of this disease began to rise again. In the February 1, 2006 issue of the journal *Clinical Infectious Diseases*, researchers in San Francisco report that up to 56% of syphilis cases in that city have treponemes that are resistant to azithromycin. This finding raises a number of issues to be discussed in this report.

**Study details**

Between January 1999 and December 2004 researchers with the San Francisco Department of Public Health began using azithromycin for the prevention and treatment of early stages of syphilis (primary and secondary). This antibiotic was usually given in a single dose of 1 or 2 grams.

During the study, 1,308 people received a diagnosis of primary or secondary syphilis. In 118 cases, researchers took samples from ulcers, sores or mucous patches caused by syphilis for analysis.

The average profile of the 118 study participants was as follows:

- 100% male
- age – 38 years
- 70% were Caucasian
- 17% were Hispanic
- 11% were Asian
- 2% were Black
- 91% were gay
- 9% were bisexual
- average number of sexual partners in the past three months – five
- 28% of participants had HIV or AIDS

**Results**

In 46 of 118 cases, researchers found treponemes that were resistant to azithromycin. Six participants who did not have fluid or tissue samples for analysis also experienced azithromycin failure by developing symptoms (ulcers, rash) or having a lab test suggestive of syphilis.

Participants who did not recover when first treated with azithromycin were re-treated with one of the following regimens:

- benzathine penicillin G — one intramuscular injection, 2.4 million units
- doxycycline — 100 mg taken orally, twice daily for two weeks

All participants who experienced treatment failure with azithromycin recovered when treated with one of the other therapies listed above.

There was no connection between any of the following characteristics and the failure of azithromycin:

- age
- ethnicity
- gender
- number of sexual partners in the past three months
- sexual orientation

Only 14% of participants reported having taken other courses of azithromycin one month before being diagnosed with syphilis. This treatment was usually for other reasons, such as Chlamydia infection.

**Trends**

Over the five years of the study, cases of azithromycin-resistant syphilis rose from an initial figure of 4% to 56%. Unfortunately, the report from San Francisco of azithromycin-resistant syphilis is not unique. Several years ago, this
problem was also reported in Baltimore, Seattle and Dublin, Ireland. What is unique to San Francisco is that researchers have a well-documented case for increasing resistance over time.

In the San Francisco study, researchers sought one specific mutation that helped treponemes resist the effects of azithromycin. There may be other mutations that have similar effects but this was not assessed in the study. As a result, it is possible that the rate of drug-resistant syphilis may be even higher than 56% in that city.

The San Francisco finding suggests that azithromycin-resistant syphilis is common, particularly among MSM. But this high rate of drug resistance is unlikely to be confined to that city. The presence of national and international sexual networks, cheap air fares and a high number of sexual partners among some MSM may all help to spread mutant treponemes to new locations. Outbreaks of syphilis are currently ongoing in some urban centres in Canada, the United States and the European Union.

The San Francisco research team recommends that intramuscular penicillin be used as the preferred therapy for primary and secondary stages of syphilis. Patients allergic to penicillin should instead be given oral doxycycline.

**Treatment guidelines for syphilis in North America**

The draft 2006 guidelines for the treatment of primary, secondary and early latent syphilis in Canada will continue to recommend an intramuscular injection of 2.4 million units of benzathine penicillin G. The Public Health Agency of Canada notes in these guidelines that people who have syphilis and who are co-infected with HIV may require longer courses of therapy. In cases of penicillin allergy, the guidelines suggest that 100 mg of doxycycline be taken twice daily for two weeks.

In “exceptional circumstances,” the Canadian guidelines suggest that alternative treatment with 1 gram/day of the antibiotic ceftriaxone (Rocephin) be given either intravenously or injected into muscle for 10 days.

The 2006 draft American guidelines are broadly similar to the Canadian guidelines. However, they continue to list a single 2-gram dose of azithromycin as a treatment option for people with a penicillin allergy. But the American guidelines do caution that “azithromycin treatment failure” is possible and close monitoring of patients is needed if this drug is prescribed for the treatment of primary and secondary syphilis.

—Sean R. Hosein

**REFERENCES:**


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