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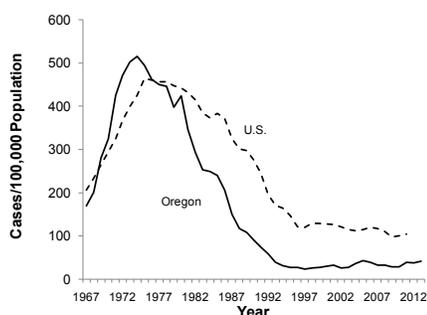
THE GONOCOCCUS ADDRESSED

Four score and four years ago, Alexander Fleming brought forth into the medical literature a new remedy, conceived in *Penicillium* and dedicated to the proposition that physicians might not merely diagnose infections, but treat them as well.<sup>1</sup>

Now we are engaged in a great microbial war, testing whether that remedy, or any remedy so conceived and so dedicated, can long remain effective. We are met on a great field of that war — the field of sexually transmitted infections (STIs). It is altogether fitting and proper that we dedicate this issue of the *CD Summary* to the gonococcus.

Although rates of gonorrhea in Oregon are well below those seen in the roaring 1960s and '70s, they have lately been creeping upwards (Figure 1). During 2012, 1,469 cases (38 per 100,000) were reported in Oregon, and during 2013, rates are up another 10% through June.

Figure 1. Gonorrhea Incidence - Oregon and the U.S., 1967–2013



GONORRHEA REFRESHER

*Neisseria gonorrhoeae* can infect the genital tract, rectum, mouth and throat. Women are more likely than men to become infected after exposure but less likely to develop symptoms: as many as 80% of women but <5% of men are asymptomatic when infected. Symptoms include sore throat, urethral, rectal, cervical or pharyngeal discharge, dysuria, menorrhagia and pelvic pain. Pelvic inflammatory disease, epididymitis, prostatitis and infertility can occur. Disseminated infections, rare in recent decades, can

cause arthritis, various skin lesions and endocarditis.<sup>2</sup>

The highest reported rates of gonorrhea occur among men and women <25 years of age. After this age, reported rates in men exceed those in women. During 2011, 35% of reported Oregon cases occurred among men who acknowledged sex with other men (MSM). African Americans have had higher reported rates (188 cases per 100,000 during 2012) than have persons of other races or Hispanics.

Although penicillin was discovered in the late 1920s, the first antimicrobial agent used to cure gonorrhea was sulfanilamide, in 1936. Resistance developed quickly, however, and by 1945, penicillin had become the drug of choice. Antimicrobial development advanced nobly, keeping ahead of the gonococcus for several decades (see Time Line,<sup>3</sup> *versus*), but by 2012, it was “time to sound the alarm. During the past 3 years, the wily gonococcus has become less susceptible to our last line of antimicrobial defense...”<sup>4</sup>

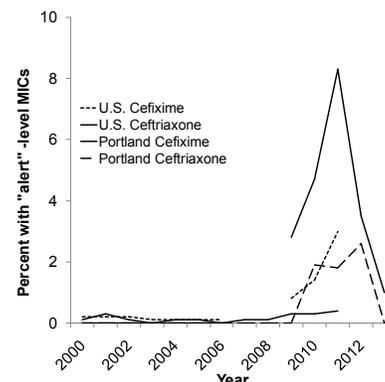
TREATMENT RECOMMENDATIONS

Since 2012, CDC’s recommended treatment for gonorrhea has been ceftriaxone, 250 mg intramuscularly, given concurrently with azithromycin, 1 gram *per os*. Though scattered cases of high-level resistance and ceftriaxone treatment failures have been reported in Europe, Asia and Australia, none have been reported to date in the U.S.; for the moment, ceftriaxone remains highly effective here.<sup>5</sup> Azithromycin also remains effective and can be used when ceftriaxone cannot be; but azithromycin resistance can emerge rapidly and has been documented in Portland,<sup>6</sup> so if used alone, the azithromycin dose should be *two* grams at once. The rationale for the recommendation of concurrent use of ceftriaxone and azithromycin is analogous to that for combination treatments for HIV and tuberculosis: if the bug gets resistant to one drug, the second drug might kill it off, preventing propagation of resistant strains.

MONITORING RESISTANCE

The Multnomah County Health Department’s STI clinic is one of almost 30 in the U.S. where gonococcal isolates are collected from the first 25 men to be seen with urethral gonorrhea each month so that minimum inhibitory concentrations (MICs) of various antibiotics can be measured and tracked.\* Although MICs at which treatment failures occur have not been defined, experts have set “alert” thresholds at 0.250 µg/mL for the oral third-generation cephalosporin cefixime and at 0.125 µg/mL for ceftriaxone. Through 2011, the percentage of isolates with MICs exceeding “alert” thresholds had increased, and the recommended dose of ceftriaxone was doubled to 250 mg. However, during the past 20 months in Portland, only one isolate has met the alert level for cefixime, and none met the threshold for ceftriaxone (Figure 2). Similar remissions have been observed in the rest of the U.S. and in Europe.

Figure 2. ‘Alert’ level cefixime and ceftriaxone MICs among *Neisseria gonorrhoeae* isolates—Portland and the U.S., 2000–2013\*



\*Cefixime MICs not tested during 2007 and 2008; (U.S. trends not available after 2011)

UNFINISHED WORK

Perhaps emergence of cephalosporin resistance can be forestalled for a time through use of antimicrobial combinations. Recent trials have demonstrated effectiveness of single-dose regimens of gentamicin plus azithromycin, and

\* [www.cdc.gov/std/gisp/](http://www.cdc.gov/std/gisp/)



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of gemifloxacin plus azithromycin.<sup>7</sup> Phase II results for solithromycin, a fourth-generation macrolide, have also been encouraging.<sup>8</sup>

Nucleic acid amplification tests have now largely superseded culture; laboratories' capacity for culture and antimicrobial sensitivity testing will have to be rebuilt to guide treatment after initial failure.

#### INCREASED DEVOTION NEEDED

The gonococcus seems unlikely to perish from the earth any time soon, so let us be here dedicated to the great task remaining before us:

- To screen at least annually
  - o all sexually active women <25 years old, including pregnant women, who have a history of previous gonorrhea or other STI, new or multiple sexual partners, inconsistent condom use, sex work, or drug use;
  - o others at high risk; for example, Multnomah County recommends screening African American women <age 30 years and all MSM;
- To treat all gonococcal infections with intramuscular ceftriaxone (250 mg) plus oral azithromycin (1 gram); and, when this is infeasible, to consult updated treatment guidelines<sup>5</sup>;
- To encourage patients with gonorrhea to talk to all sex partners from the previous 60 days and to recommend that they seek treatment and testing;
- To offer to help patients to notify partners;
- To contact your local health department to report the infection and to get help notifying partners of patients

who don't<sup>†</sup>; and

- If you suspect treatment failure, to contact the local health department or the Oregon STD Control Program<sup>‡</sup> within 24 hours. Patients with symptoms of gonorrhea after treatment should be cultured and any isolate tested for sensitivity.

The Oregon State Public Health

#### Time Line: Antibiotics for Gonorrhea

- 1936: Sulfanilamide introduced
- 1945: Penicillin becomes drug of choice
- 1945 – 1976: Recommended dose of penicillin increases from 50,000 units to 4.8 million units due to chromosomally mediated resistance
- 1976: Penicillinase-producing *Neisseria gonorrhoeae* introduced in U.S.
- 1985: Tetracycline resistance widespread
- 1989: Penicillin no longer recommended; ceftriaxone becomes primary regimen, ciprofloxacin as alternative
- 1991: Quinolone-resistant *Neisseria gonorrhoeae* identified in Hawai'i
- 1993: Quinolones or cefixime recommended as oral regimens
- 1998: Marked increase in quinolone-resistant *Neisseria gonorrhoeae* in Hawai'i
- 2000: Fluoroquinolones no longer recommended in Hawai'i
- 2004: Fluoroquinolones no longer recommended among MSM
- 2007: Fluoroquinolones no longer recommended in the U.S.

<sup>†</sup> As resources permit, Oregon local health departments interview patients with reported gonorrhea and offer assistance with partner notification, testing and treatment; statewide, attempts are made to contact about two-thirds of cases.

<sup>‡</sup> 971-673-0153

Laboratory has made arrangements for collecting and transferring isolates to the Gonorrhea Isolates Surveillance Program laboratory in Washington.

Reinfection is common, and most infections identified after treatment represent reinfection rather than treatment failure. All patients with gonorrhea should be tested for reinfection three months after treatment or at the first opportunity within the following 12 months, regardless of symptoms or history of partner treatment.

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