

# DRUG INFORMATION ALERT

## GON(E)orrhoea or Here to Stay: the Emergence of an Unrelenting “Clap”

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Gonorrhoea, caused by *Neisseria gonorrhoeae*, is the second most commonly reported communicable disease in the United States (U.S.), as well as the second most prevalent bacterial sexually transmitted disease in the world. More than 700,000 cases occur annually in the U.S., but infection rates have been declining since the 1970's.<sup>1</sup> Since there is currently no vaccine available for gonorrhoea prevention, timely detection and appropriate antibiotic therapy are essential to control the spread of infection and prevent complications.<sup>2</sup>

Gonorrhoea is defined as the presence of *N. gonorrhoeae* in the body, mainly at mucosal sites. Infection most commonly manifests as urethritis in men, causing painful urination and discharge from the penis.<sup>3</sup> These symptoms usually lead patients to seek treatment relatively quickly. Infection in women may manifest as vaginal discharge or a burning sensation during urination, but most women are asymptomatic. Absence of early detection and treatment may result in disease transmission and complications.<sup>1,3</sup> Gonorrhoea is associated with significant morbidity in women, such as urethritis and cervicitis, which may ultimately lead to pelvic inflammatory disease, infertility, ectopic pregnancy, and pelvic pain.<sup>1</sup>

In previous years, multiple antibiotic drug classes were available for gonorrhoea treatment, including penicillins, fluoroquinolones, macrolides, tetracyclines, and first and second generation cephalosporins. Due to the emergence of antimicrobial resistance, these agents are no longer considered first-line treatment for gonorrhoea. It is estimated that nearly one-fifth of all isolates of *N. gonorrhoeae* are resistant to tetracycline, penicillin, or both, and the prevalence of fluoroquinolone-resistant *N. gonorrhoeae* is as high as 20 percent in certain parts of the U.S.<sup>4,5</sup> Susceptibility to extended-spectrum cephalosporins has also declined worldwide. Resistance to these agents has been reported in several countries around the world, with highest prevalence occurring in Japan.<sup>6-8</sup> Treatment failures with cefixime prompted the removal of cefixime from the 2006 Japanese guidelines for gonorrhoea prevention.<sup>2</sup> The first high-level ceftriaxone-resistant gonococcal strain (H041) was recently isolated in Kyoto, Japan with a reported minimum inhibitory concentration (MIC) = 2 g/ml.<sup>9</sup> Only one other



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ceftriaxone-resistant strain has been isolated (MIC = 0.5 g/ml).<sup>9</sup> Reduced extended-spectrum cephalosporin susceptibility is most likely attributable to an alteration of the *penA* gene, which is responsible for encoding the penicillin-binding protein (PBP 2).<sup>11-13</sup> Other mutations in the repressor gene allow for over-expression of the *N. gonorrhoeae* efflux pump, resulting in decreased susceptibility.<sup>12,14</sup>

Even with the emergence of cephalosporin-resistant *N. gonorrhoeae*, resistance to third generation cephalosporins, such as ceftriaxone or cefixime, is still uncommon. A single dose of ceftriaxone 250 mg intramuscularly is recommended as the treatment of choice by the Centers for Disease Control and Prevention (CDC) guidelines due to its safety, effectiveness, and administration convenience. An alternative regimen is oral cefixime 400 mg as a single dose, although bactericidal levels are not as high and sustained with this treatment compared to those produced by ceftriaxone.<sup>1</sup> However, because cefixime has worse cure rates in pharyngeal infections, ceftriaxone remains the preferred agent.<sup>15</sup> *N. gonorrhoeae* also remains susceptible to spectinomycin, an injectable antibiotic, that is reliably effective for gonorrhea treatment. Unfortunately, this agent is not currently available in the U.S.<sup>1,16</sup> In addition, the CDC also recommends dual therapy since patients are commonly co-infected with *Chlamydia trachomatis*, which is treated either with doxycycline or azithromycin. Since *N. gonorrhoeae* is commonly susceptible to doxycycline and azithromycin, dual therapy also further impedes the development of resistance.<sup>1</sup> Ertapenem has also been proposed as an alternative treatment for gonorrhea due to availability as a single-dose regimen, but cost and the potential for inducing resistance, similar to other beta-lactams, limit its use.<sup>17</sup> Trimethoprim/sulfamethoxazole, rifampin, and chloramphenicol treatment regimens may be potential alternatives, yet efficacy of these regimens have not been well-established.<sup>9,18,19</sup>

Multi-drug resistant *N. gonorrhoeae* is increasing in prevalence throughout the world. Treatment is currently limited to extended-spectrum cephalosporins, but emerging resistance to these antibiotics may diminish their availability as treatment options in the future. Judicious utilization of antibiotics and close surveillance are imperative components of containing the spread of drug-resistant *N. gonorrhoeae* strains.

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