

## Azithromycin versus Penicillin G Benzathine for Early Syphilis

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The demonstration in Tanzania of equivalent efficacy of azithromycin and penicillin G benzathine for treating early syphilis and presumed early latent syphilis (rapid plasma reagin titer,  $\geq 1:8$ ) represents a potentially useful advance in syphilis control. In a randomized trial reported in this issue of the *Journal*, Riedner et al.<sup>1</sup> achieved cure rates of 97.7 percent with 2 g of azithromycin given orally and 95.0 percent with 2.4 MU of penicillin G benzathine given intramuscularly. Positive or negative status with respect to human immunodeficiency virus (HIV) infection did not influence the results of treatment. Titers on rapid plasma reagin tests fell fastest in those with the highest initial titers, as shown previously by others.<sup>2</sup> Inclusion of secondary syphilis and follow-up beyond nine months would have strengthened this study. An ongoing trial in Madagascar and four U.S. cities is comparing azithromycin and penicillin G benzathine for treatment of early syphilis. A Ugandan study<sup>3</sup> followed patients with reactive serologic tests for syphilis at 10-month intervals after nonrandomized treatment with 2.4 MU of penicillin G benzathine, 1.0 g of azithromycin, or both; the three regimens yielded similar overall cure rates, although patients with initial antibody titers of 1:4 or greater (on the toluidine red unheated serum test) actually had better outcomes after azithromycin therapy than after penicillin G benzathine therapy alone.

What innovations, if any, are now warranted in the management of early syphilis? Can azithromycin be substituted for penicillin G benzathine to improve access to and acceptability of treatment in early syphilis? Would 2 g of oral azithromycin suffice for the management of bacterial genital ulcer disease in developing countries, curing chancroid as well as primary syphilis? Should azithromycin be dispensed to patients with early syphilis to deliver to their sexual partners, in a manner analogous to that of patient-delivered partner therapy for gonorrhea and chlamydial infection?<sup>4</sup>

Two important reasons for caution with such uses of azithromycin include the sustained success of penicillin G benzathine therapy for syphilis and the recent emergence of azithromycin-resistant *Treponema pallidum*. Mahoney et al. reported in 1944 that penicillin cured syphilis.<sup>5</sup> When penicillin G benzathine was introduced in 1951, the long persistence of treponemical levels of penicillin in the

blood after intramuscular injection proved ideal for single-dose treatment of early syphilis.<sup>6</sup> For 50 years, the recommended treatment for early syphilis has remained 2.4 MU of penicillin G benzathine given intramuscularly, and *T. pallidum* remains fully susceptible to penicillin. Efforts to control syphilis and to eradicate the other treponematoses (yaws, pinta, and endemic syphilis) throughout the world have relied largely on penicillin therapy. How effective have the syphilis control efforts been?

In the United States and other industrialized countries, the annual incidence rates of primary and secondary syphilis plummeted after the introduction of penicillin, from 76 per 100,000 population in 1945 to 4 per 100,000 during the period from 1955 through 1957. The incidence of syphilis approximately tripled during the 1960s and 1970s (although it never approached the levels observed during the era before penicillin). In 1982 and 1983, the HIV epidemic prompted behavior changes that curtailed the transmission of syphilis among men having sex with men. Syphilis outbreaks did continue, for example, among those affected by the crack cocaine epidemic in the United States from the mid-1980s to the early 1990s. The United States initiated an ambitious syphilis elimination program in 1999,<sup>7</sup> and there followed further declines in incidence among heterosexual populations. Unfortunately, behavioral disinhibition followed the introduction of highly active antiretroviral therapy (HAART) and, together with the nonuse of condoms with HIV-seroconcordant partners, contributed to a resurgence of syphilis among men having sex with men in the United States and parts of Europe<sup>8</sup>; the incidence of syphilis has reached levels not seen since the beginning of the HIV epidemic. In California from 1999 to 2004, the incidences of primary and secondary syphilis increased by a factor of more than 15 among men having sex with men.

Developing countries have also achieved mixed success in syphilis control. Localized reductions in the incidence of syphilis in parts of Africa,<sup>9</sup> Latin America, the Caribbean,<sup>10</sup> and Asia during the era of AIDS probably reflect both reductions in sexual-risk behaviors and application of effective biomedical interventions. However, the resurgence of syphilis among populations with or at risk for HIV infection after the introduction of HAART in industrialized countries is now also a concern in

developing countries (where HAART is finally being made more available).

There have been earlier efforts to strengthen syphilis control through innovative uses of azithromycin. In Vancouver, Canada, mass treatment of high-risk populations with azithromycin in 2000 to contain the spread of syphilis related to commercial sex and drug use had only a transient effect on the incidence of syphilis.<sup>11</sup> In San Francisco, patient-delivered partner therapy with azithromycin offered to male sexual partners of men with syphilis was discontinued after several azithromycin treatment failures in 2002 and 2003.

Macrolide resistance in *T. pallidum* was first documented in the United States in a man with secondary syphilis in whom a 30-day course of erythromycin failed during hospitalization. The strain of *T. pallidum* isolated from this man was later shown to have a point mutation within the 23S ribosomal RNA (rRNA) gene, at a ribosomal site targeted by macrolides.<sup>12</sup> Recently, Lukehart et al.<sup>13</sup> sought and found the same mutation in both copies of the 23S rRNA gene in *T. pallidum* from 22 percent of lesion samples from San Francisco, 11 percent from Baltimore, 13 percent from Seattle, and 88 percent from Dublin, Ireland. All but one of the strains of *T. pallidum* containing this mutation came from men who reported having sex with other men. Azithromycin proved ineffective in treating rabbits infected with *T. pallidum* containing this mutation.<sup>12</sup> Klausner et al.<sup>14</sup> recently reported that the prevalence of this mutation in *T. pallidum* among consecutively studied men in San Francisco who had sex with men and had early syphilis increased from 0 percent in 2000 to 56 percent in 2004. Similarly in Vancouver, this mutation was found in *T. pallidum* in only 1 of 47 specimens collected during the period from 2000 through 2003, as compared with 4 of 12 specimens collected from men having sex with men from 2004 and 2005 (Morshed M: personal communication). No prospective study of humans treated for early syphilis with azithromycin has yet examined the influence of the 23S rRNA mutation in *T. pallidum* on treatment outcomes. It remains unclear whether *T. pallidum* containing this mutation represents a single clone spread extensively within sexual networks in North America and Ireland or multiple strains that emerged independently. We also do not know how selective pressure from macrolide use for syphilis or other conditions may have contributed to the emergence of macrolide-resistant *T. pallidum*.

Given the sustained effectiveness of penicillin G benzathine, the lack of a sustained effect of innovative uses of azithromycin for managing outbreaks of syphilis in Vancouver and San Francisco, and the rapid emergence of macrolide-resistant *T. pallidum*, there seems little reason to change the forthcoming 2006 U.S. Sexually Transmitted Diseases [STD] Treatment Guidelines (still in draft form at the Centers for Disease Control and Prevention [CDC]), which continue to recommend 2.4 MU of penicillin G benzathine given intramuscularly for the treatment of primary, secondary, and early latent syphilis in adults. Penicillin G benzathine is now marketed in the United States as Bicillin L-A (not to be confused with Bicillin C-R, a combination of penicillin G benzathine and penicillin G procaine that is not indicated for syphilis). U.S. stockpiles of penicillin G benzathine are adequate, but distribution is problematic; the Division of STD Prevention of the CDC is developing guidance on the availability and supply of penicillin G benzathine. For those with penicillin allergy, the forthcoming U.S. guidelines list 100 mg of doxycycline given orally twice daily for 14 days, 1 g of ceftriaxone daily given intramuscularly for 8 to 10 days, or 2 g of azithromycin given as a single oral dose as possible alternatives for early syphilis, with the caution that "several cases of azithromycin treatment failure have been reported, and molecular resistance to azithromycin has been documented in several geographic areas. Because the efficacy of these alternative therapies is not well documented, close follow-up of persons receiving these therapies is essential."

Macrolide resistance in *T. pallidum* has been found everywhere it has been sought among men who have sex with men with early syphilis in North America and Dublin. Although we can hope that macrolide-resistant *T. pallidum* has not and will not spread rapidly from sexual networks of men having sex with men in North America and Ireland to sexual networks elsewhere, it will be wise to ensure close follow-up of any patients treated with azithromycin for early syphilis throughout the world. It is also essential to gather more data on the global prevalence of macrolide resistance in *T. pallidum* and its effect on treatment.

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