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Commentary

Hope for new antibiotics for syphilis treatment

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Syphilis is a multi-stage disease caused by infection with *Treponema pallidum* subspecies *pallidum* (*T. pallidum*). Syphilis is usually transmitted by contact with an infected sexual partner or by passage from an infected pregnant woman to her fetus (congenital syphilis). Globally, an estimated six million new cases of syphilis occur each year in persons aged 15–49 years. In 2016, 661,000 cases of congenital syphilis resulted in over 200,000 fetal and neonatal deaths [1].

Because there is no vaccine to prevent syphilis, early diagnosis and treatment of infected persons and their contacts are key to syphilis control. In the pre-antibiotic era, syphilis patients were treated with arsenicals, toxic compounds that required prolonged therapy that often led to treatment failure. A major breakthrough occurred in 1943 when Mahoney and colleagues reported that penicillin could cure syphilis [2]. Although their initial studies were performed in rabbits because *T. pallidum* was not yet cultivable, it quickly became apparent that penicillin was effective for treatment of patients with early and late syphilis, pregnant women with syphilis and infants with congenital syphilis. Within a few years, widespread use of penicillin, in conjunction with sex education and improved diagnostic tests, resulted in dramatic decreases in the incidence of syphilis. However, syphilis re-emerged becoming an endemic disease with periodic fluctuations and sporadic outbreaks [2,3]. Fortunately, *T. pallidum* has remained susceptible to penicillin, which is still the preferred treatment for all stages of syphilis [4]. A single intramuscular (IM) injection of 2·4 million units (MU) of benzathine penicillin G (BPG) is recommended for early syphilis, while an IM injection of 2·4 MU of BPG given once weekly for three weeks is recommended for late syphilis. Because BPG does not achieve a sufficient concentration in cerebrospinal fluid (CSF), aqueous penicillin G (18–24 MU per day) given intravenously (IV) for 10–14 days is the recommended treatment for neurosyphilis. There are no proven alternatives to BPG for pregnant women with syphilis. Those who are penicillin-allergic must be desensitized and treated with BPG.

Despite its proven effectiveness for syphilis, the use of penicillin has some important limitations. Penicillin must be given by trained personnel and there is potential for severe allergic reactions. Shortages of BPG, as reported by 39 countries during 2014–2016, can compromise patient treatment [5]. Data for alternative antibiotics are mostly from small, retrospective studies with a few larger, randomized trials. According to U.S. CDC Sexually Transmitted Diseases Treatment Guidelines, men and non-pregnant women with early syphilis who are allergic to penicillin may be treated with doxycycline (100 mg orally, twice daily for 14 days) or ceftriaxone (1 g daily IM or IV for 10–14 days) [4]. Empirical use of azithromycin (2 g orally as a single dose) is problematic due to emergence and spread of macrolide-resistant *T. pallidum* [3].

Although there is a need for alternative antibiotics for syphilis treatment, working with *T. pallidum* is not straight forward. *In vivo* assays to examine antibiotic susceptibility of *T. pallidum*, a prerequisite to human clinical trials, must be performed in experimentally infected rabbits due to lack of a small animal model. These studies are expensive and require many days and a number of rabbits to generate meaningful data. *In vitro* assays to examine antibiotic susceptibility have been hindered by the inability to culture this bacterium. In 1988, Norris and Edmondson reported short-term *in vitro* cultivation of *T. pallidum* [6]. Recent refinement of their system now allows long-term cultivation [7]. In this issue, Haynes et al. report culture of *T. pallidum*, coupled with rabbit infection and molecular analysis, to evaluate treponemal susceptibility to three antibiotics- linezolid, moxifloxacin, and clofazimine chosen for their pharmacological properties and activity against other pathogenic spirochetes [8]. For *in vitro* studies, *T. pallidum* cells were incubated with and without antibiotics in three 96-well plates for seven days. One plate was subcultured to a new plate without antibiotics and bactericidal activity of the antibiotics was evaluated by qPCR. Treponemal growth was evaluated in the remaining plates by qPCR. For *in vivo* studies, rabbits were infected intradermally with *T. pallidum* and randomly assigned to antibiotic or control groups (penicillin or no antibiotic). Treatment commenced when injection sites contained treponemes in needle aspirates by dark-field microscopy (DFM). Primary outcome, treatment efficacy, was defined as time to lesion healing measured from treatment start date. Secondary outcome was absence of treponemes or treponemal mRNA in injection sites, absence of seroconversion and CSF abnormalities, and negative rabbit infectivity test (RIT, inability of transferred lymph nodes from infected rabbits to cause infection in naïve

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rabbits). Only linezolid (and the penicillin control) showed *in vitro* bactericidal activity against *T. pallidum*. Similar to penicillin, linezolid induced healing of early lesions in infected rabbits. DFM and qPCR analysis indicated treponemes were not present in injection sites after day three post-treatment with linezolid. Additionally, their serologic tests did not convert to positive, CSF was not abnormal, and RIT was negative. Based on these promising results, Haynes et al. propose that linezolid merits investigation as an alternative to penicillin for treatment of syphilis in humans. Linezolid has several attributes of an ideal candidate for such studies. It is low-cost, safe, generally well-tolerated when delivered as an oral, short course regimen, and has excellent bioavailability, achieving concentrations in human tissues and CSF that are predicted to be sufficient for treponemicidal activity [9,10]. A notable limitation of linezolid is the lack of adequate well-controlled studies in pregnant women, precluding its use in pregnant women with syphilis [10]. Nonetheless, Haynes et al. have demonstrated the utility of a novel approach to evaluate alternative antibiotics as potential candidates for efficacy testing in human clinical trials. Availability of new alternative antibiotics would expand therapeutic options for syphilis treatment, benefitting patients and aiding efforts to eliminate syphilis, a disease once designated as the “shadow on the land”.

Contributors

Lola Stamm conceived and wrote the commentary.

Declaration of Competing Interest

The author declares no conflict of interest.

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