Penicillin Treatment of Syphilis

Clearing Away the Shadow on the Land

SUMMARY OF THE ORIGINAL ARTICLES

Penicillin Treatment of Early Syphilis: II
J. F. Mahoney, MD; R. C. Arnold, MD; Burton L. Sterner, MD; et al

The Treatment of Early Syphilis With Penicillin
J. E. Moore, MD; J. F. Mahoney, MD; CDR W. Schwartz, MC, USN; et al

The Action of Penicillin in Late Syphilis
J. H. Stokes, MD; LTC T. H. Sternberg, MC, USA; CDR W. Schwartz, MC, USN; et al

JAMA. 1944;126(2):63-67, 67-73, 73-80.

In the follow-up to a preliminary report on the use of penicillin for early syphilis, Mahoney and colleagues presented the promising posttreatment observations of the original patients studied for periods in excess of 300 days. They also reported information on the treatment of an additional 100 patients. The accompanying papers in the same issue of *JAMA* reported on the results obtained by the National Research Council's newly formed Penicillin Panel. Those preliminary results are presented for both early and late syphilis.

See www.jama.com for full text of the original *JAMA* articles.

Commentary by John M. Douglas Jr, MD

At the time of the classic reports by Mahoney and colleagues[1-3] on the response of syphilis to treatment with penicillin, infection with *Treponema pallidum* was a major global public health problem, analogous to the burden of human immunodeficiency virus (HIV) infection today. Population prevalence of syphilis in the United States was estimated to range from 5% to 10%, with prevalence rates up to 25% in lower socioeconomic groups, and syphilis was a major cause of neurologic, cardiovascular, and perinatal morbidity and mortality.[4] The serious consequences of syphilis for the population led to its designation as the "shadow on the land" and prompted US Surgeon General Thomas Parran to launch a national syphilis control campaign in 1938 based on public education, serologic testing, treatment, and a national network of sexually transmitted disease (STD) clinics.[5] Therapy at that time relied on approaches such as prolonged injections of arsenicals or malariotherapy for neurosyphilis, and while each was likely at least partially effective, they were expensive and associated with substantial toxicity.[6]

Following these initial encouraging reports,[1-3] subsequent observations refined parameters of the therapeutic use of penicillin for syphilis (eg, dose, duration, serologic follow-up to ensure response) through case series and expert clinical experience in specialty clinics rather than large, well-controlled clinical trials.[6,7] Within years, widespread use of penicillin for treatment of all stages of syphilis (primary, secondary, tertiary, latent) resulted in dramatic decreases in the incidence of syphilis and associated mortality.

From 1944 to 1954, rates of reported cases of syphilis of any stage decreased by more than 75% (from 368/100 000 to 83/100 000) with even greater declines in primary and secondary syphilis (from 62/100 000 to 4.5/100 000), which reflect more recent acquisition.[8] By 1975, rates of overall syphilis had declined by almost 90% (from 368/100 000 to 37/100 000) and rates of congenital syphilis decreased even further (from 521/100 000 to 29/100 000 livebirths).[8] Even more dramatic was the reduction in mortality due to syphilis, which declined by more than 98% from approximately 14/100 000 in 1940 to less than 0.2/100 000 by 1975 (Figure).[9]

Notably, of the 8 most common causes of infectious disease mortality in the first half of the 20th century, the decline in syphilis mortality occurred latest, coinciding al-

See also Patient Page.

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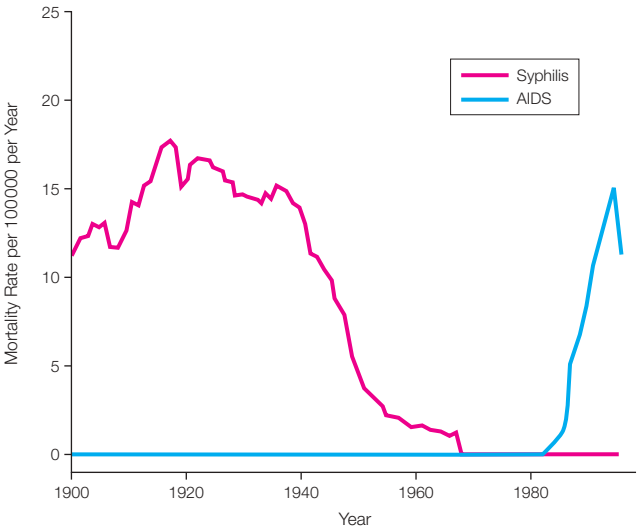
Figure. Crude Mortality Rates for Syphilis and AIDS, 1900-1996



Reprinted from Armstrong et al.[9]

most exactly with the advent of penicillin.[9] This pattern suggests that the relationship between syphilis and antimicrobial therapy is reasonably unique among major infectious diseases because no other infectious problem was reduced to this extent without a major structural intervention (eg, improved sanitation and living conditions) or vaccine. Equally notable is that levels of syphilis mortality in the prepenicillin era were as high as those due to AIDS in the early 1990s.[9] Together these trends illustrate the enormous importance of syphilis prior to the 1940s and the profound effect penicillin had on control of infection and prevention of mortality.

One somber note in the relationship between syphilis and penicillin was the infamous Tuskegee Study.[4,7] The project was initiated in the 1930s in an attempt to understand the natural history of untreated latent syphilis at a time when the primary therapeutic option was arsenicals, for which the benefit-to-toxicity ratio in latent infection was unclear. However, despite broad clinical use of penicillin therapy in the late 1940s, participants in the study were not offered treatment until the 1970s. This ethical breach prompted development of systems to protect human research participants, but also left a strong legacy of distrust of medical and public health systems among African Americans that still influences HIV and STD prevention efforts.

Remarkably, in the years since the introduction of penicillin, and in contrast to most other bacteria for which penicillin was initially so effective (eg, *Neisseria gonorrhoeae, Streptococcus pneumoniae, Staphylococcus aureus*), there has been no apparent development of in vitro resistance to or erosion in effectiveness of penicillin for treatment of *T pallidum* infection.[6,7] Thus, in countries with reasonable health care access and public health infrastructure, syphilis has evolved from a high-morbidity pandemic to a low-level, largely concentrated endemic infection with periodic fluctuations and outbreaks. For example, in the United States, rates of primary and secondary syphilis increased in the 1960s-1970s, likely as a result of behavioral and demographic changes; increased again in the early 1980s, largely among men who have sex with men (MSM); and again increased in the late 1980s, primarily among heterosexuals, and was strongly associated with the crack cocaine epidemic.[6,7]

Subsequent declines to historically low levels in the 1990s raised hopes that domestic transmission of syphilis could be eliminated, leading to the launch of a national plan to eliminate syphilis in 1999. After several years of continued progress, rates of syphilis began to increase again in 2001, largely among MSM, apparently fueled by increased risk behavior related to optimism over improved HIV treatment, recreational drug use, and modified sexual networks related to use of the Internet for meeting partners. Similar increases in syphilis among MSM have occurred in other countries around the world, often with high rates of HIV coinfection.[7,10]

The intersection of the HIV and syphilis epidemics appears to reflect an "epidemiologic synergy" whereby each infection modifies the natural history of the other and also may mutually enhance transmission.[4,6,7] In the United States, the most important of these interactions is the effect of HIV on the course of syphilis, resulting in more severe clinical manifestations, including more numerous genital ulcers in primary and secondary syphilis and more common and rapidly developing neurologic complications. In addition to its role as an HIV-associated opportunistic infection, early syphilis infection also increases HIV viral load. Regarding transmission, syphilis appears to enhance HIV transmission 2- to 5-fold, increasing infectivity among those who are HIV-positive—due to its effect on viral load and the epithelial defects occurring in early syphilis—and also increasing susceptibility in those who are HIV-negative. Plausibly, the more numerous ulcers occurring in early syphilis in HIV-positive individuals also may enhance syphilis transmission. Although clinical trials evaluating the effect of STD control on reducing HIV incidence have yielded varying results, modeling studies indicate that in epidemiologic settings with an early, nongeneralized HIV epidemic and high levels of bacterial STD such as syphilis, STD control can enhance HIV prevention at the population level.[11]

Despite 65 years of relative success in controlling syphilis since the advent of penicillin, syphilis remains an important public health problem, with an estimated annual global incidence of 12 million.[7] Addressing this problem will require confronting several challenges. First, the serologic tests that have been the basis for syphilis diagnosis for many decades, using a sequence of tests for antibodies to nontreponemal (eg, rapid plasma reagin [RPR]) and treponemal antigens (eg, fluorescent treponemal antibody [FTA]) are not suitable for on-

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site testing, precluding same-day diagnosis and treatment, a major disadvantage in settings where follow-up cannot be ensured. Rapid tests with reasonable sensitivity are becoming available and have the potential to expedite clinical management and interruption of transmission.[12]

Second, despite continued effectiveness of injectable long-acting preparations of penicillin, there are constraints with their use, such as settings in which injections are problematic or for penicillin-allergic patients, and a single-dose oral agent could enhance control efforts. The long half-life and spectrum of activity of azithromycin make it a promising option, and several clinical trials have demonstrated efficacy comparable to penicillin.[13] Unfortunately, the identification of a resistance mutation in strains from several US cities may compromise the effectiveness of this treatment strategy.[7]

A third challenge is the inadequate use of existing prevention tools in many settings, with the global inability to control congenital syphilis a glaring example. Congenital syphilis has been dramatically reduced in the United States and other developed countries as a result of syphilis control efforts combined with maternal screening and treatment. However, congenital syphilis remains a major problem in developing countries, and globally is estimated that 0.7 million to 1.5 million cases occur annually, the majority resulting in stillbirth or perinatal death, due to lack of screening and treatment.[14] This burden rivals that of perinatal mortality from HIV infection, although it has received substantially less attention, despite estimates that prevention of congenital syphilis is substantially more cost-effective than prevention of perinatal HIV infection.[14] Prompted by the increasing availability of inexpensive rapid diagnostic tests, the World Health Organization has recently launched a strategy focused on the global elimination of congenital syphilis.[14]

Fourth, even with successful syphilis control efforts, continued vigilance is critical. A variety of circumstances, such as societal changes that modify sexual networks or reduce public health and health care services, can result in explosive epidemics, as evidenced by the resurgence of syphilis in Russia in the 1990s[15] and in China over the past 15 years.[16] In addition to morbidity related to syphilis, such reversals also create the potential for accelerating HIV epidemics.

In conclusion, the *JAMA* articles by Mahoney and colleagues[1-3] represent a landmark event in the control of a major infectious disease. Their efforts capped a 50-year era of investigation into therapeutic approaches during which time 3 scientists whose work produced new treatments for syphilis were awarded Nobel Prizes (Paul Ehrlich, Julius Wagner-Jauregg, and Alexander Fleming) and also launched the modern era of syphilis control with its many successes and setbacks. Today, syphilis is no longer such a dark shadow on the land, although its global persistence and potential for reemergence are grim reminders that there is no room for complacency in ongoing efforts to eliminate this still-important problem.

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