

## Review

# Treatment of Syphilis

## A Systematic Review

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**IMPORTANCE** The incidence of syphilis in the United States is increasing; it is estimated that more than 55 000 new infections will occur in 2014. Treatment regimens are controversial, especially in specific populations, and assessing treatment response based on serology remains a challenge.

**OBJECTIVE** To review evidence regarding penicillin and nonpenicillin regimens, implications of the "serofast state," and treatment of specific populations including those with neurosyphilis or human immunodeficiency virus (HIV) infection and pregnant women.

**EVIDENCE REVIEW** We searched MEDLINE for English-language human treatment studies dating from January 1965 until July 2014. The American Heart Association classification system was used to rate quality of evidence.

**FINDINGS** We included 102 articles in our review, consisting of randomized trials, meta-analyses, and cohort studies. Case reports and small series were excluded unless they were the only studies providing evidence for a specific treatment strategy. We included 11 randomized trials. Evidence regarding penicillin and nonpenicillin regimens was reviewed from studies involving 11 102 patients. Data on the treatment of early syphilis support the use of a single intramuscular injection of 2.4 million U of benzathine penicillin G, with studies reporting 90% to 100% treatment success rates. The value of multiple-dose treatment of early syphilis is uncertain, especially in HIV-infected individuals. Less evidence is available regarding therapy for late and late latent syphilis. Following treatment, nontreponemal serologic titers should decline in a stable pattern, but a significant proportion of patients may remain seropositive (the "serofast state"). Serologic response to treatment should be evident by 6 months in early syphilis but is generally slower (12-24 months) for latent syphilis. Evidence defining treatment for HIV-infected persons and for pregnant women is limited, but available data support penicillin as first-line therapy.

**CONCLUSIONS AND RELEVANCE** The mainstay of syphilis treatment is parenteral penicillin G despite the relatively modest clinical trial data that support its use.

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**S**yphilis is a sexually transmitted infection caused by the spirochete *Treponema pallidum*. First described after European explorers returned from the Americas at the end of the 15th century, syphilis has been a major cause of morbidity and mortality for more than 500 years. Its clinical influence was profoundly diminished by the introduction of penicillin in the 1940s. After declining to a historic low in the year 2000, the number of syphilis cases in the United States has been increasing and now exceeds 55 000 new cases each year.<sup>1</sup> Penicillin has been the treatment of choice for more than half a century, but questions regarding the appropriate therapeutic regimen for various stages of syphilis still exist. Because *T pallidum* cannot be cultured, there is no gold standard by which to assess cure. Instead, indirect means (changes in titer of syphilis serology) must be used, contributing to inconsistencies

among studies and complicating the task of drawing evidence-based conclusions.

### Public Health Consequences

Syphilis is an important public health problem. Timely diagnosis and prompt treatment are important to limiting its clinical effects. Untreated, up to one-third of patients progress to later stages of disease.<sup>2</sup> Late syphilis can cause irreversible damage to the cardiovascular and central nervous systems, resulting in profound morbidity and even death. Without adequate screening and treatment, stillbirth, neonatal death, low birth weight, prematurity, and congenital syphilis may affect more than half of pregnancies among

women with syphilis.<sup>3,4</sup> In addition, genital ulcers due to syphilis have been linked to acquisition of human immunodeficiency virus (HIV) infection.<sup>5</sup>

## Epidemiology and At-Risk Populations

In recent years, an increasing proportion of syphilis cases in the United States have been diagnosed in men who have sex with men (MSM), often associated with high-risk sexual behavior and HIV

**ART** antiretroviral therapy

**BPG** benzathine penicillin G

**CSF** cerebrospinal fluid

**HIV** human immunodeficiency virus

**MSM** men who have sex with men

**RCT** randomized clinical trial

**VDRL** Venereal Disease Research Laboratory

coinfection.<sup>6</sup> In 2013, more than 16 000 of the total reported cases were primary and secondary syphilis, the most transmissible stages of infection, and three-quarters of these occurred in MSM.<sup>6</sup> The highest rates of primary and secondary syphilis are currently found

in younger men (aged 20-29 years), a change since 2006, when those aged 35 to 59 years were most affected. Primary and secondary syphilis disproportionately affect black men, whose infection rate (27.9 per 100 000) is more than 5-fold higher than the rate among white men (5.4 per 100 000).<sup>1</sup>

## Stages of Syphilis

Syphilis occurs in overlapping stages, classified according to symptoms and time since initial infection (Table 1). Appropriate staging is important for determining infectivity and treatment duration. A diagnosis of early syphilis (primary, secondary, and early latent syphilis) implies that *T pallidum* infection occurred within the previous year.<sup>9</sup> Late syphilis represents manifestations occurring more than 1 year and even decades after initial infection. Latent syphilis refers to *T pallidum* infection with reactive syphilis serologic findings but without clinical manifestations of disease. It includes both early latent (within 1 year of infection) and late latent (1 year or more after infection) syphilis.

## Methods

One of us (M.E.C.) searched MEDLINE for English-language human treatment studies dating from January 1965 through July 2014. The initial search was limited to clinical trials, systematic reviews, and meta-analyses consisting of syphilis treatment studies. We excluded articles involving only diagnostic testing, screening, or prevention. Reference lists of identified articles were searched for additional relevant references (eFigure in the Supplement). Case reports and series were not included unless they were the only studies providing evidence for a specific treatment strategy. The American Heart Association classification of recommendations was used to grade the quality of evidence (Table 2). Grade A indicates data from many large randomized clinical trials (RCTs); grade B, data from fewer, smaller RCTs, careful analyses of nonrandomized studies, or observational registries; and grade C, expert consensus.<sup>29</sup>

## Results

### Treatment of Syphilis

The MEDLINE search for syphilis treatment identified 418 articles, of which 40 were included in this review. After reviewing the reference lists of these articles for additional relevant studies, we identified 102 articles for inclusion in our review, including RCTs, meta-analyses, and cohort studies. In total, the review included 11 randomized trials, and the evidence regarding penicillin and nonpenicillin regimens was reviewed from studies involving 11 102 patients (Table 3 and Table 4).

### Monitoring Syphilis Treatment Response

Both diagnosis and assessment of treatment response rely on serologic tests (Box). Treponemal tests detect antibodies to specific antigenic components of *T pallidum*, while nontreponemal tests detect antibodies to a nonspecific cardiolipin-cholesterol-lecithin reagent antigen produced by the host in response to syphilis infection.<sup>39</sup> Nontreponemal serologic tests such as the Venereal Disease Research Laboratory (VDRL) test or the rapid plasma reagent test are used to monitor treatment response because they usually correlate with disease activity. Different nontreponemal tests do not provide interchangeable measurements; for example, rapid plasma reagent titers are often higher than VDRL titers. In general, a 4-fold decline in nontreponemal titer (such as a decrease from 1:32 to 1:8) is needed to signify treatment response. There are limitations to relying on changes in serologic titers to monitor response to treatment. For example, a recent report demonstrated that 20% of patients with syphilis experienced at least a 1-dilution (2-fold) increase in nontreponemal titer within 14 days of treatment, suggesting that the actual baseline titer used to assess response is often underestimated.<sup>40</sup> Coinfection with HIV may also contribute to therapeutic uncertainty because HIV-infected patients may experience slower serologic response rates after apparently successful treatment.<sup>41-44</sup>

### The Serofast State

The serofast state refers to a situation in which nontreponemal antibodies decline (often adequately) after treatment but fail to completely revert to nonreactive.<sup>45</sup> Persons with low pretreatment titers are also sometimes said to be serofast when there is minimal ( $\leq 2$ -fold) or no change following treatment. The serofast state may represent a number of different phenomena, including persistent low-level *T pallidum* infection, variability of host antibody response to infection, or tissue injury due to nonsyphilitic inflammatory conditions.<sup>46</sup> A significant proportion of patients remain serofast after treatment (15%-41%), although rates depend on syphilis stage, pretreatment titer, and the time point at which response is assessed, all of which vary from study to study.<sup>13,47-50</sup> Available data suggest that re-treatment has a modest effect on the serofast state, with only 27% of such patients achieving serologic cure in 1 study.<sup>46</sup>

### Efficacy of Parenteral Penicillin for Early Syphilis

Treatment of syphilis is based on stage of infection and on whether there is evidence of central nervous system involvement (Figure). *Treponema pallidum* remains extremely susceptible to penicillin, an antimicrobial agent targeting bacterial cell wall synthesis. During

Table 1. Stages of Syphilis<sup>a</sup>

Syphilis Stage	Timing	Symptoms	Comment
Early syphilis (occurs within 1 year of infection)			
Primary	2-4 wk after exposure (median, 21 d)	Painless chancre, usually on the genitalia; can also occur on the perineum, anus, rectum, lips, oropharynx, or hands; may be asymptomatic.	Chancre usually clears spontaneously but widespread spirochete dissemination occurs during this stage
Secondary	2-8 wk after disappearance of chancre	Wide range of systemic symptoms including rash, fever, headache, pharyngitis, and lymphadenopathy; may be asymptomatic	Rash is usually truncal and maculopapular, frequently involving the palms and soles Condyloma lata (grayish white warty lesions) may be seen, usually on genital mucosa
Early latent	Acquisition of syphilis within the preceding year	None	Diagnosis requires (within the previous year) documented seroconversion or ≥4-fold increase in nontreponemal titer, documented seroconversion of a treponemal test, sexual exposure to a person with early syphilis, or only sexual contact was within the last 12 mo (sexual debut) <sup>9</sup>
Tertiary (late; includes neurosyphilis [see below], cardiovascular, and gummatous disease)	Occurs >1 y to decades after primary infection	Cardiovascular system involvement including dilated aorta, aortic regurgitation, or carotid ostial stenosis; gummas (granulomatous lesions) form on skin, bones, or within organs	Cardiovascular disease often as a result of vasculitis of the vasa vasorum of the ascending thoracic aorta
Latent syphilis (asymptomatic infection with normal physical examination findings in association with reactive serologic findings)			
Early latent	See above	See above	
Late latent	Diagnosis of syphilis >1 y after infection or of unknown duration	None	Cases not meeting above criteria for early latent syphilis and cases of infection at unknown time point are considered late latent syphilis
Neurosyphilis (infection of central nervous system by <i>Treponema pallidum</i> , further defined as early or late neurosyphilis)			
Early neurosyphilis	Occurs <1 y after initial infection, usually within weeks of exposure	Usually involves the meninges and vasculature: meningitis, cranial nerve defects, meningo-vascular disease, or stroke	May present simultaneously with symptoms of primary or secondary syphilis
Late neurosyphilis	Occurs >1 y after initial infection, even decades after primary infection	Usually involves the brain and spinal cord: disorders such as general paresis, dementia, or tabes dorsalis	Much less common in current period
Serofast state	Following treatment	None; patients have achieved clinical cure	Nontreponemal antibodies decline but do not completely revert to nonreactive

<sup>a</sup> Adapted from Golden et al,<sup>2</sup> Workowski et al,<sup>7</sup> and Cohen et al.<sup>8</sup>

more than 60 years of use, there has never been a documented case of penicillin resistance.<sup>51</sup> The organism's slow dividing time (30-33 hours) requires the prolonged presence of killing (treponemical) concentrations of antimicrobial agents. Depot preparations achieve this goal and have thus become the mainstay of treatment based on decades of experience.<sup>52,53</sup> Nonetheless, only limited clinical trial evidence of efficacy exists, and interpretation of data from available studies is complicated by heterogeneous definitions of syphilis stage, differences in treatment regimens, and nonstandard treatment outcome measurements (Table 3).<sup>10,30-35</sup> Despite the limitations in published studies, the predominance of evidence, including more recent high-quality studies, supports the use of parenteral penicillin, and it remains the treatment of choice. The quality of evidence for penicillin and alternate therapies, graded according to the American Heart Association classification system, is shown in Table 2.

For early syphilis, studies from the 1950s onward have focused on benzathine penicillin G (BPG) and demonstrate favorable cure rates and infrequent need for re-treatment. Historical estimates for the rate of treatment failure with a single dose of 2.4 mil-

lion U of BPG are around 5%.<sup>54</sup> In 1956, Smith et al<sup>34</sup> reported BPG efficacy in early syphilis, finding that response rates with a single BPG injection were not different from multiple injections of procaine penicillin with aluminum monostearate (a long-acting formulation no longer widely available). At 2 years, 94.5% to 100% of all patients had a seronegative status, depending on stage. Similarly, Schroeter et al<sup>36</sup> showed no difference in outcomes with single-dose BPG compared with multiple-dose penicillin regimens (11.4% vs 10.7%-10.9% 2-year cumulative re-treatment rates). Some reports claim superiority with multiple doses rather than a single injection of BPG,<sup>31,32</sup> but these studies have been criticized for lack of a control group or exclusion of reinfected patients based on serological response pattern (thus overestimating success, as some of those excluded patients may actually have had treatment failure).<sup>55</sup>

A 1997 study by Rolfs et al<sup>10</sup> that included 541 patients remains the only large RCT for syphilis therapy from the 20th century. The study compared a single standard dose of 2.4 million U of intramuscular BPG with an "enhanced therapy" regimen (the addition of high-dose oral amoxicillin/probenecid to BPG) and found no difference in outcome between the 2 groups. In that study, serologic failure was

**Table 2. Evidence for Therapy for Each Syphilis Stage**

Syphilis Stage	Primary Therapy	Grade of Evidence of Primary Therapy <sup>a</sup>	Alternative Therapy	Grade of Evidence of Alternative Therapy <sup>a</sup>	Follow-up
Early syphilis (primary, secondary)	BPG, 2.4 million U intramuscularly in 1 dose	A <sup>10-12</sup>	Doxycycline, 100 mg twice daily for 14 d	B <sup>13-19</sup>	Clinical and serologic examinations at 6 and 12 mo
			Ceftriaxone, 1-2 g/d intramuscularly or intravenously for 10-14 d	B <sup>16,20-23</sup>	
			Tetracycline, 100 mg orally 4 times daily for 14 d	B <sup>13,15</sup>	
			Azithromycin, single 2-g dose, only if all other options not feasible	A <sup>11,12,24-27b</sup>	
Early latent syphilis	BPG, 2.4 million U intramuscularly in 1 dose	A <sup>10-12</sup>			Nontreponemal serologic tests at 6, 12, and 24 mo
Late latent syphilis	BPG, 2.4 million U intramuscularly in 3 weekly doses	C	Doxycycline, 100 mg orally twice daily for 28 d	C	
			Tetracycline, 500 mg orally 4 times daily for 28 d	C	
Tertiary syphilis (excluding neurosyphilis)	BPG, 2.4 million U intramuscularly in 3 weekly doses	C			
Neurosyphilis	Aqueous penicillin G, 18 million-24 million U/d intravenously (every 4 h or as continuous infusion) for 14 d	C	Procaine penicillin, 2.4 million U/d intramuscularly, plus probenecid, 500 mg orally 4 times daily, for 10-14 d		Repeat cerebrospinal fluid analysis every 6 months until cell count is normal if pleocytosis is initially present
			Ceftriaxone, 2 g/d intramuscularly or intravenously for 10-14 d		
HIV coinfection	Same as HIV uninfected	C <sup>10</sup>			Clinical and serologic examinations at 3, 6, 9, 12, and 24 mo
	BPG, 2.4 million U intramuscularly in 3 weekly doses for early syphilis	C <sup>28</sup>			

Abbreviations: BPG, benzathine penicillin G; HIV, human immunodeficiency virus.

<sup>a</sup> Grade A indicates data from many large randomized clinical trials (RCTs); grade B, data from fewer, smaller RCTs, careful analyses of non-randomized studies, or observational registries; and grade C, expert consensus.<sup>29</sup>

<sup>b</sup> Grade A due to large RCTs; however, azithromycin is used only when other options are not feasible because of macrolide resistance.

rigidly defined (requiring a 4-fold decline in nontreponemal titer by 3 months), contributing to the relatively high failure rate in each group (18% and 17%, respectively, at 6 months).<sup>10</sup> Only 1 patient, who was HIV infected, experienced clinical treatment failure (new rash) during follow-up. However, definitive conclusions are limited because of high loss to follow-up in the trial (52% at 1 year).

More recently, trials comparing penicillin with nonpenicillin regimens confirm the efficacy of a single intramuscular injection of 2.4 million U of BPG for early syphilis. In a 2005 RCT by Riedner et al<sup>11</sup> in which 328 patients were enrolled, 95% of those receiving BPG achieved serologic cure, a majority of whom had high-titer, presumptive early latent syphilis. Hook et al<sup>12</sup> published an RCT in 2010 that included 517 patients and compared oral azithromycin with BPG; 79% of BPG recipients achieved serologic cure by 6 months. Other recent retrospective studies have also demonstrated high success rates with single-dose BPG for early syphilis.<sup>14,15</sup>

### Penicillin in Late and Late Latent Syphilis

Minimal high-quality evidence exists to guide the therapy for late syphilis. It has been postulated that longer-duration

penicillin therapy may be required for late syphilis because treponemes appear to divide more slowly during later stages of infection, but the validity of this concept has not been rigorously assessed.<sup>7</sup> Only limited data exist regarding late latent syphilis therapy. In 2005, Kiddugavu et al<sup>25</sup> published a secondary analysis of an RCT studying 818 patients (86%) who had presumptive late latent syphilis. Benzathine penicillin G, 2.4 million U intramuscularly, was given as a single dose or along with oral azithromycin. Response rates were modest (cure rates of 56%-63%). Smith et al published a small randomized pilot study in 2004 in which 7 of 10 HIV-infected patients treated with procaine penicillin had an appropriate decline in titers, although 2 subsequently relapsed and 3 remained in a serofast state.<sup>37</sup> Most participants in this study were not taking effective antiretroviral therapy (ART), and the majority were presumed to have late latent syphilis. Another study of HIV-infected patients not taking suppressive ART who had late latent syphilis (some with central nervous system involvement) showed that 3 weekly injections of BPG resulted in an appropriate serologic response in only 62%.<sup>38</sup>

Table 3. Evidence for Penicillin Treatment of Syphilis

Source	Study Design	Participants	Treatment	Dosing Regimens	Outcome Measure and Definitions	Results	Comments
Rolfs et al, <sup>10</sup> 1997	Randomized clinical trial	139 patients with primary, 253 with secondary, and 149 with early latent syphilis (100 with history of syphilis)	276 treated with BPG and 265 with enhanced therapy	BPG: 2.4 million U IM as 1 dose Enhanced therapy: BPG, 2.4 million U IM in 1 dose plus 2 g amoxicillin and 500 mg probenecid orally 3 times daily for 10 d	Treatment success: negative or $\geq 4$ -fold decrease in RPR titer	Treatment failure: 18% with usual therapy and 17% with enhanced therapy at 6 mo; 15% with usual therapy and 14% with enhanced therapy at 12 mo	1-y follow-up (52% retained in study) 101/541 (19%) HIV infected
Talwar et al, <sup>30</sup> 1992	Retrospective study	1532 patients with early syphilis with 30 mo of follow-up: 1008 with primary, 429 with secondary, and 95 with latent (defined as $< 2$ y of infection)	1386 treated with BPG, 17 with procaine penicillin, and 139 with broad-spectrum antibiotics	BPG: 2.4 million U IM as 1 dose, 4.8 million U IM weekly as 2 doses Procaine penicillin: 0.6 million U/d for 10 d Broad-spectrum antibiotics at various dosages	Patients followed up for serial VDRL measurements at 2-mo intervals for first 6 mo, 3-mo intervals for the next year, and 6-mo intervals for the next year	Reactive VDRL test result in 16.5% and 6.6% (primary), 27.6% and 8.4% (secondary), and 18.9% and 11.6% (early latent) at 6 and 30 mo, respectively Results for secondary and early latent syphilis were better with 4.8 million U of BPG and procaine penicillin	30-mo surveillance period
Fiumara, <sup>31</sup> 1986	Retrospective study	88 patients with primary and 101 with secondary syphilis When combined with previous series, 588 with primary and 623 with secondary syphilis	All treated with BPG	BPG: 2.4 million U IM weekly as 2 doses	Patients followed up until lesions or rash healed and test results (RPR and FTA-ABS) became negative	88/88 with primary syphilis seronegative at 12 mo; 101/101 with secondary syphilis seronegative at 2 years	2-y follow-up Excluded patients with $\geq 4$ -fold increase in RPR after lesions had healed or after titer had decreased $\geq 4$ -fold, considered to have been reinfected No control group
Durst et al, <sup>32</sup> 1973	Prospective study	40 patients with secondary syphilis	All treated with BPG	BPG: 6.0 million U total (2.4 million U as 1 dose initially, then 2.4 million U IM as 1 dose within 5 d, then 1.2 million U IM as 1 dose within 3-5 d)	Patients followed up until serologic test results became negative	At 12 mo: 17/40 seronegative; at 18 mo: 33/40 seronegative; at 24 mo: 40/40 seronegative	2-y follow-up No control group
Jefferiss and Willcox, <sup>33</sup> 1963	Presumed retrospective study	211 patients with seronegative primary, 179 with seropositive primary, 196 with secondary, and 50 with early latent syphilis	107 treated with benzyl penicillin, 7 with benzyl penicillin plus BPG, 231 with procaine penicillin or PAM, and 291 with high-dose APPG $\pm$ PAM	Benzyl penicillin: "regular injections" of 2.5 to 5 million U BPG: unspecified dose as 1 or 2 injections Procaine penicillin: 5.1-10 million U High-dose APPG: > 10 million U PAM at varied dosing of injections	Patients followed up with clinical and serologic examinations monthly for 6 mo, quarterly for 1 year, and twice per year for second year	95% with negative VDRL test result 22 mo after treatment	Followed up for 30 mo; 238/636 (37.4%) followed up at 22-30 mo No distinction between reinfection/relapse, but low rates of both (cumulative re-treatment rate of 4.42%)
Smith et al, <sup>34</sup> 1956	Presumed retrospective study	52 patients with seronegative primary, 67 with seropositive primary, and 155 with secondary syphilis	52 with seronegative primary, 67 with seropositive primary, and 155 with secondary infection treated with BPG, 2.5 million U as single injection 166 with secondary infection treated with PAM as 1 session 415 with secondary infection treated with PAM as 2-4 sessions	BPG: 2.5 million U IM as 1 dose PAM: 4.8 million U in a single session or 2-4 sessions	Patients followed up according to percentage seronegative (negative or less than 4 Kahn units)	Seronegative at 2 y after BPG: 100% with seronegative primary, 96.0% with seropositive primary, and 94.5% with secondary syphilis Seronegative at 2 y after PAM: 91.0% with single-dose and 88.3% with divided-dose regimens	2-y follow-up
Sternberg and Leifer, <sup>35</sup> 1947	Retrospective study	1400 patients with early syphilis: 600 (42.8%) seronegative primary, 564 (40.3%) with seropositive primary, and 236 (56.4%) with secondary syphilis	Sodium penicillin in aqueous solution or isotonic sodium chloride	2.4 million U penicillin delivered over 7.5 d	"Satisfactory progress": no signs of clinical relapse and serologic test results became/ remained negative during the observation period "Unsatisfactory progress": relapse or reinfection	Seronegative primary syphilis: 86% followed up > 9 mo; satisfactory progression in 566 (94.3%) Seropositive primary syphilis: 82% followed up > 9 mo; satisfactory progression in 507 (89.9%) Secondary syphilis: 84% followed up > 9 mo; satisfactory progress at last observation in 196 (83%)	1-y follow-up No distinction of penicillin type; noted "patients were probably treated with penicillins of satisfactory potency" No control group

Abbreviations: APPG, aqueous procaine penicillin G; BPG, benzathine penicillin G; FTA-ABS, fluorescent treponemal antibody absorbed; HIV, human immunodeficiency virus; IM, intramuscularly; PAM, penicillin aluminum monostearate; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

**Table 4. Evidence for Antibiotics Other Than Penicillin for Treatment of Syphilis**

Source	Study Design	Participants	HIV Status	Treatment and Dosing Regimens	Outcome Measures, Definitions, and Comments	Results
<b>Doxycycline/tetracycline</b>						
Li and Zheng, <sup>13</sup> 2014	Retrospective cohort	641 patients with early syphilis (13.4% primary, 52.1% secondary, and 34.5% early latent)	Excluded HIV-infected patients	606 (94.5%) treated with BPG, 2.4 million U IM weekly as 2 doses, and 35 (5.5%) with doxycycline, 100 mg twice daily for 14 d, and tetracycline, 500 mg 4 times daily for 14 d	Serologic response: negative or $\geq 4$ -fold decrease in RPR or serofast ( $\pm 1$ dilution from baseline if RPR was 1:2 or 1:1 at baseline) by 6 mo	No significant difference in serologic response rates: 91.4% of penicillin vs 82.9% of doxycycline/tetracycline; $P = .16$
Psomas et al, <sup>16</sup> 2012	Retrospective	116 patients with early syphilis	80% HIV infected	52 treated with BPG, 2.4 million U IM weekly as 1-3 doses, 49 with ceftriaxone, 1-2 g/d for 14-21 d, and 15 with doxycycline, 100 mg twice or 3 times daily for 14-21 d	Serologic response: $\leq 1:4$ VDRL titer Relapse: 4-fold increase in VDRL or increase to $> 1:4$	Responses: penicillin, 39/52 (75%); ceftriaxone, 38/49 (77.6%); doxycycline, 11/15 (73.3%) No significant difference in time to serologic response per treatment (log-rank test, $P = .90$ )
Wong et al, <sup>15</sup> 2008	Retrospective	445 primary syphilis cases	Excluded diagnosed HIV-infected patients but many had unknown HIV status	420 (94.4%) treated with BPG, 2.4 million U IM as 1 dose, and 25 (5.6%) with doxycycline/tetracycline, 100 mg twice daily for 14 d	Serologic response: $\geq 4$ -fold decrease in RPR by 6 mo, $\geq 8$ -fold by 12 mo, $\geq 16$ -fold by 24 mo, or serofast ( $\pm 1$ dilution from baseline if RPR was 1:4, 1:2, or 1:1 at baseline) Failure: none of the above or $\geq 4$ -fold increase in RPR at 1-6 mo	No significant difference in serologic response rates: 409/420 (97.4%) of BPG vs 25/25 (100%) of doxycycline/tetracycline
Ghanem et al, <sup>14</sup> 2006	Retrospective case-control	1558 patients with early syphilis	13.7% HIV positive in BPG vs 5.9% in doxycycline groups	34/87 treated with doxycycline/tetracycline, 100 mg twice daily for 14 d, met inclusion criteria and were compared with 73 randomly selected patients treated with BPG, 2.4 million U IM as 1 dose	Serologic failure: 4-fold increase in RPR 30-400 d posttreatment or lack of 4-fold decrease in RPR 20-400 d posttreatment	4/73 with serologic failure in BPG group vs 0/34 in doxycycline group
Long et al, <sup>17</sup> 2006	Prospective cohort	96 patients with syphilis; 76 returned for 1-y follow-up Syphilis stage undefined	15/96 had HIV infection	58 treated with BPG, 2.4 million U IM as 1 dose, and 18 with doxycycline, 100 mg twice daily for 14 d if penicillin allergy	Serologic response: negative or $\geq 4$ -fold decrease in RPR by 12 mo Reinfection: success then subsequent 4-fold increase in RPR from its lowest level or conversion to reactive Failure: no 4-fold decline in RPR or failure to convert a 1:4 or 1:2 titer to nonreactive No relapse group	No significant difference in serologic response rates: 94.8% of BPG vs 88.9% of doxycycline; odds ratio, 2.29; 95% CI, 0.17-21.60; $P = .59$
Schroeter et al, <sup>36</sup> 1972	Prospective	586 patients with early syphilis	NA	100 treated with BPG, 2.4 million U IM as 1 dose, 101 with PAM, 4.8 million U, 61 with APPG, 4.8 million U (0.6 million U/d for 8 d), 107 with tetracycline, 30 g (3 g/d $\times 10$ d), and 144 with erythromycin, 30 g	Cure: healed clinical manifestations, prompt and permanent decrease of VDRL Relapse: reappearance of lesions with dark field or significant increase in VDRL Failure: lack of significant response of VDRL after 1 y	Cumulative re-treatment at 24 mo: BPG, 11.4%; PAM, 10.9%; APPG, 10.7%; tetracycline, 12.7%; erythromycin, 21.3%
<b>Ceftriaxone</b>						
Psomas et al, <sup>16</sup> 2012	Retrospective	116 patients with early syphilis	80% HIV infected	52 treated with BPG, 2.4 million U IM as 1-3 doses, 49 with ceftriaxone, 1-2 g daily for 14-21 d, and 15 with doxycycline, 100 mg twice or 3 times daily for 14-21 d	Serologic response: $\leq 1:4$ VDRL titer Relapse: 4-fold increase in VDRL or increase to $> 1:4$	Responses: penicillin, 39/52 (75%); ceftriaxone, 38/49 (77.6%); doxycycline, 11/15 (73.3%) No significant difference in time to serologic response per treatment (log-rank test, $P = .90$ )

(continued)

### Efficacy of Therapies Other Than Benzathine Penicillin G for Syphilis

The evidence for nonpenicillin treatment of syphilis consists mostly of small, uncontrolled, retrospective studies, although a few larger,

randomized trials exist (Table 4).<sup>10-17,20-27,31,34-38</sup> Erythromycin is no longer recommended based on tolerability and resistance concerns,<sup>56</sup> but doxycycline, ceftriaxone, and azithromycin are still considered potential alternatives to penicillin.

Table 4. Evidence for Antibiotics Other Than Penicillin for Treatment of Syphilis (continued)

Source	Study Design	Participants	HIV Status	Treatment and Dosing Regimens	Outcome Measures, Definitions, and Comments	Results
Spornraft-Ragaller et al, <sup>20</sup> 2011	Retrospective	24 patients with active syphilis (21 with primary syphilis; 3 with neurosyphilis)	All patients HIV infected	12 treated with ceftriaxone, 1-2 g intravenously for 10-21 d, and 12 with high-dose penicillin G (8 with BPG, 2.4 million U/wk as 2-3 doses, 2 with clemizole penicillin G, 1 million U/d for 14-21 d, and 2 with intravenous penicillin G, 3 × 10 million U/d for 21 d)	Serologic response: negative or ≥4-fold decrease in VDRL	11/12 with ceftriaxone and 12/12 with penicillin had >4-fold decline in VDRL titers at median of 18.3 mo
Smith et al, <sup>37</sup> 2004	Prospective randomized pilot	31 patients with asymptomatic syphilis randomized to procaine penicillin or ceftriaxone. Most thought to have late latent syphilis	All patients HIV infected; enrolled before availability of effective antiretroviral therapy	10 treated with procaine penicillin, 2.4 million U IM, plus oral probenecid and 14 with ceftriaxone, 1 g/d for 15 d (only 24 followed up)	Serologic response: ≥4-fold decrease in RPR Relapse: ≥4-fold increase in RPR, persistent titer ≥1:64, or clinical progression of disease Nonresponse: ≤2-fold change in RPR Serofast: persistent titer after treatment	Penicillin: 7/10 had response (2/10 had subsequent relapse), 3/10 were serofast Ceftriaxone: 10/14 with response (1/14 had subsequent relapse), 2/14 were serofast, 2/14 failures
Dowell et al, <sup>38</sup> 1992	Secondary	7 patients with neurosyphilis, 6 with latent syphilis, and 30 with presumed latent syphilis	All patients HIV infected	43 treated with ceftriaxone, 1-2 g/d for 10-14 d, and 13 with BPG, 2.4 million U IM as 3 weekly doses	Serologic response: ≥4-fold decrease in RPR with no subsequent increase Relapse: ≥4-fold rise in RPR after ≥4-fold decline Failure: ≥4-fold RPR increase without initial response, persistent RPR ≥1:64, or clinical progression Serofast: persistent titer after treatment with no signs of progressive disease	Ceftriaxone: 28 (65%) had response, 5 (12%) were serofast, 9 (21%) had serologic relapse, 1 (2%) progressed to neurosyphilis BPG: 8 (62%) had response, 1 (8%) was serofast, 2 (15%) had relapse, and 2 (15%) had failures All followed up for ≥6 mo
Schöfer et al, <sup>21</sup> 1989	Randomized prospective	28 patients with early syphilis (9 primary, 19 secondary)	NA	14 treated with ceftriaxone, 1 g IM 4 times daily every 2 d, and 14 with penicillin G, 1 million U/d IM for 15 d	Serological controls were repeated 1, 2, 3, 6, and 12 mo after therapy	All patients had ≥4-fold decrease in VDRL titer and resolution of clinical symptoms One adverse reaction in penicillin G group (rash); none in ceftriaxone group
Hook et al, <sup>22</sup> 1988	Prospective	11 patients with primary and 5 with secondary syphilis	NA	10 treated with ceftriaxone, 250 mg/d for 10 d, and 6 with ceftriaxone, 500 mg every other day as 5 doses	Results reported at 3 mo	Daily treatment: 1/10 with VDRL persistently negative, 4/10 became seronegative, 5/10 had dilutions of ≥3 Every-other-day treatment: 1/6 became VDRL seronegative, 5/6 had dilutions of ≥2 Of 11 patients available for follow-up at 3-23 mo, there were no cases with evidence of relapse
Moorthy et al, <sup>23</sup> 1987	Randomized	18 patients with early syphilis	NA	5 treated with ceftriaxone, 3 g as 1 dose, 5 with ceftriaxone, 2 g/d IM as 2 doses, 3 with ceftriaxone, 2 g/d IM as 5 doses, and 5 with BPG, 2.4 million U IM as 1 dose	Cure: clearance of lesions, nonreactive VDRL Sustained response: clearance of lesions, ≥4-fold decrease in VDRL by 3 mo and sustained at 12 mo Failure: clinical progression or ≥4-fold increase in VDRL	Single 3-g ceftriaxone dose: 3/5 had cure, 1/5 had sustained response, 1/5 had failure 2 g ceftriaxone in 2 daily doses: 3/5 had cure, 2/5 had sustained response 2 g ceftriaxone in 5 daily doses: 3/3 had sustained response BPG: 3/5 had cure, 1/5 had sustained response, and 1 lost to follow-up Follow-up was at 1 y
Bai et al, <sup>26</sup> 2012	Meta-analysis	790 patients with early syphilis	NA	3 randomized clinical trials comparing BPG vs azithromycin in variable dosages	Serologic response: ≥4-fold decrease in RPR measured at 3, 6, 9, and 12 mo	No statistically significant difference between azithromycin and BPG treatment in odds of cure (odds ratio, 1.04; 95% CI, 0.69-1.56) 85.7% (341/398) response rate for azithromycin and 85.0% (333/392) for BPG

(continued)

**Table 4. Evidence for Antibiotics Other Than Penicillin for Treatment of Syphilis (continued)**

Source	Study Design	Participants	HIV Status	Treatment and Dosing Regimens	Outcome Measures, Definitions, and Comments	Results
Hook et al, <sup>12</sup> 2010	Randomized clinical trial	517 patients with early syphilis: 26% primary, 46% secondary, 28% early latent primary, 46% early latent secondary, and 28% early latent	Excluded HIV-infected patients	237 treated with BPG, 2.4 million U IM as 1 dose, and 232 with azithromycin, 2.0 g orally as 1 dose	Serologic response: negative or $\geq 4$ -fold decrease in RPR by 6 mo	Serologic response in 180/232 (77.6%) with azithromycin vs 186/237 (78.5%) with BPG Increased nonserious adverse events (mostly gastrointestinal) in azithromycin group
Bai et al, <sup>27</sup> 2008	Meta-analysis	476 patients with early syphilis	NA	4 randomized clinical trials comparing BPG vs azithromycin in variable dosages	Serologic response: $\geq 4$ -fold decrease in RPR measured at 3, 6, 9, and 12 mo	95.0% (227/239) response rate for azithromycin and 84.0% (199/237) for BPG Five times more gastrointestinal adverse effects of azithromycin vs BPG, but results not significant
Kiddugavu et al, <sup>25</sup> 2005	Secondary analysis of randomized clinical trial (not randomized to therapy)	11 patients (1.1%) with primary, 122 (13%) with secondary or early latent, and 818 (86%) with presumed late latent syphilis	20.8% HIV infected	18% treated with BPG alone, 2.4 million U IM as 1 dose, 17% with azithromycin alone, 1 g orally as 1 dose, and 65% with dual therapy All treated with single dose IM regardless of presumed stage of syphilis	Serologic response: negative or $\geq 4$ -fold decrease in TRUST result by 10 mo	When initial titer $>1:4$ , higher response rate with azithromycin alone and with dual treatment vs BPG alone No difference in response rates in analysis of lower initial titers or overall (56%–63% response rates) No difference in response rates between HIV infected and uninfected
Riedner et al, <sup>11</sup> 2005	Randomized clinical trial	25 patients with primary and 303 with high-titer latent syphilis	52.1% HIV infected	163 treated with azithromycin, 2.0 g orally as 1 dose, and 165 with BPG, 2.4 million U IM as 1 dose	Serologic response: $\geq 4$ -fold decrease in RPR titer at 9 mo	97.7% response in azithromycin group vs 95.0% in BPG group
Hook et al, <sup>24</sup> 2002	Randomized pilot	60 patients with early syphilis	4% HIV infected	14 treated with BPG, 2.4 million U IM as 1 dose; 17 with single-dose azithromycin and 29 with double-dose azithromycin, 2.0 g orally as 1 dose	Serologic response: clinical resolution and negative or 4-fold decrease in RPR Serofast status: clinical resolution with no change or $\leq 2$ -fold change in RPR Failure: new lesions or $\geq 4$ -fold increase in RPR	Response rates: 12/14 (86%) of BPG, 16/17 (94%) of single-dose azithromycin, and 24/29 (83%) of double-dose azithromycin Failure in 1 with BPG and 1 with double-dose azithromycin

Abbreviations: APPG, aqueous procaine penicillin G; BPG, benzathine penicillin G; HIV, human immunodeficiency virus; IM, intramuscularly; NA, not available (study conducted prior to HIV era or did not address HIV status); PAM, penicillin

aluminum monostearate; RPR, rapid plasma reagin; TRUST, toluidine red unheated serum test; VDRL, Venereal Disease Research Laboratory.

### Doxycycline

Several studies, mostly small and retrospective, indicate that doxycycline/tetracycline is effective treatment for early syphilis, with serologic response rates of 83% to 100%.<sup>13–19</sup> Most studies used oral doxycycline, 100 mg twice daily for 14 days, a regimen that has been shown to have 73% to 89% response rates in HIV-infected patients.<sup>16,17</sup> Doxycycline is advantageous in that it has simultaneous activity against other sexually transmitted infections. However, the requirement for multiple days of treatment when using doxycycline introduces adherence concerns compared with the preferred single observed dosing with intramuscular BPG. As a result, doxycycline is considered an alternative to BPG in the treatment of syphilis.

### Ceftriaxone

Several small studies of intramuscular ceftriaxone for early syphilis have shown efficacy comparable with penicillin G.<sup>16,20–23</sup> Most of these trials used parenteral once-daily doses of 1 to 2 g for 10 to 15 days with serologic response rates of 65% to 100%. The lowest response rates were seen in HIV-infected patients, particularly among

patients with incomplete HIV suppression. Treatment failure was most often noted in HIV-infected patients with latent syphilis.<sup>37,38</sup> Ceftriaxone treatment of syphilis requires multiple daily parenteral doses and is both more cumbersome and more expensive than single-dose BPG but has the advantage of treating other coexisting sexually transmitted infections and may be useful in patients with penicillin allergy.<sup>57</sup> Use of cephalosporins in patients with penicillin allergy is discussed below.

### Azithromycin

Randomized clinical trials have shown that oral azithromycin (as a single 1- to 2-g dose) is effective in the treatment of early syphilis, with much of the data derived from studies done in Africa.<sup>11,12,24</sup> The emergence of azithromycin resistance mutations in *T pallidum* with resultant treatment failure has limited its usefulness in many regions of the United States.<sup>56,58–62</sup> In a study of 141 *T pallidum* samples collected from 11 US clinics between 2007 and 2009, the 23s rRNA A2058G point mutation (associated with macrolide resistance/treatment failure) was found in 53% of specimens.<sup>61</sup> Azithromycin has also been associated with a 5-fold greater risk of gastrointesti-



**Table 5. Parenteral Penicillin Regimens**

Drug	Route	Cerebrospinal Fluid Concentration	Comments
Benzathine penicillin G <sup>66</sup>	Intramuscular	Low	Very low solubility leading to slow release from injection site; blood concentrations detectable up to 4 wk after injection
Aqueous procaine penicillin G <sup>67</sup>	Intramuscular	High	Slowly dissolving; blood levels plateau at about 4 h then decrease slowly over the next 15 to 20 h
Aqueous penicillin G (benzylpenicillin) <sup>68</sup>	Intramuscular or intravenous	High	Half-life of 42 min

provement in some studies, but the regimen is often difficult to complete because of the need for multiple intramuscular injections that can be painful and the requirement for adherence to oral probenecid 4 times daily.<sup>70,71</sup>

Treatment of neurosyphilis in patients with significant penicillin allergy is challenging, and penicillin desensitization is probably the best option. Ceftriaxone (2 g/d intramuscularly or intravenously for 10-14 days) is an alternative, but evidence of its efficacy is limited.<sup>72-74</sup> Risk of cross-reactivity between penicillin and ceftriaxone is negligible, but skin testing for  $\beta$ -lactam allergy and desensitization can be done if needed.<sup>75</sup>

#### HIV Coinfection

Syphilis and HIV infection are strongly linked with one another. Most of the recent increase in syphilis cases in the United States has occurred in MSM, and rates of HIV coinfection as high as 50% to 70% have been reported among MSM diagnosed as having primary and secondary syphilis.<sup>75</sup>

There are few studies comparing syphilis treatment of HIV-coinfected patients with HIV-uninfected controls.<sup>76</sup> Patients with HIV infection may be at increased risk of serologic failure following treatment, although this is controversial.<sup>41,43</sup> Some studies comparing serologic response rates between HIV-infected and uninfected persons show no difference in treatment success rates.<sup>10,77</sup> Other studies attribute the perceived increased risk of treatment failure to a slower decline in titer in HIV-infected individuals.<sup>42</sup> Lower CD4 cell counts are associated with delayed treatment response and increased risk of serologic failure among HIV-infected patients.<sup>41,78</sup> Data from the pre-ART era suggest a shorter latency period before progression to neurosyphilis and an increased risk of progression to neurosyphilis despite adequate treatment for early syphilis.<sup>79-81</sup> Based on these observations, some authorities recommend a longer duration of penicillin for early syphilis in HIV-infected persons (7.2 million U of BPG given as 3 weekly 2.4 million-U doses).<sup>82</sup> A recent retrospective study of patients with primary and secondary syphilis found a nonsignificant increase in serologic response rates in HIV-infected patients who received 3 weekly doses of penicillin compared with those treated with a single dose of BPG (serologic cure in 88% with a single dose vs 97% with 3 doses;  $P = .18$ ); however, another study from 2013 demonstrated no difference in BPG treatment outcome between single-dose treatment and multiple-dose (3 weekly injections) treatment in HIV-infected patients with early syphilis.<sup>28,78</sup> Effective ART appears to reduce the likelihood of serologic failure as well as progression to neurosyphilis.<sup>83,84</sup>

While HIV infection appears to affect syphilis outcomes, syphilis also appears to affect the course of HIV infection. Increased HIV replication and reduced CD4 cell counts have been reported among

HIV-infected patients with syphilis, highlighting the importance of appropriate treatment for both infections.<sup>85-87</sup>

#### HIV Infection and Neurosyphilis

Reports of increased risk of neurosyphilis emerged soon after recognition of the HIV epidemic.<sup>80,81,88,89</sup> As with all patients, successful treatment of neurosyphilis in HIV-infected persons requires sustained treponemal CSF penicillin concentrations. Some studies suggest that as many as 60% of HIV-infected patients may have failure of currently recommended neurosyphilis therapy with intravenous penicillin G.<sup>81,90,91</sup> Although penicillin is the preferred treatment for neurosyphilis, ceftriaxone, 1 to 2 g/d intravenously for 10 days, is thought to be an effective alternative in HIV-infected patients with neurosyphilis based on data from small observational studies.<sup>37,38,92</sup> One prospective study demonstrated that HIV-infected patients with low CD4 cell counts (<200/mL) were less likely to clear CSF-VDRL titers after treatment, illustrating the need for immune recovery facilitated by effective ART as part of optimal management.<sup>93</sup>

#### Pregnant Women

Most cases of congenital syphilis result from transmission of *T pallidum* to the fetus during early syphilis, while most adverse pregnancy outcomes occur in women treated for syphilis in the third trimester, demonstrating the importance of timely syphilis screening and treatment in pregnancy.<sup>94,95</sup> Observational studies of syphilis in pregnant women suggest that standard treatment based on stage of syphilis at diagnosis is sufficient.<sup>96-99</sup> A Cochrane review published in 2010 found no syphilis treatment studies that met predetermined criteria for treatment group comparisons nor any that used randomly allocated groups of pregnant women.<sup>100,101</sup>

Risks associated with the Jarisch-Herxheimer reaction in pregnant women may be significant, including induction of early labor or fetal distress. Pregnant women should be warned about this potential outcome prior to treatment, but therapy should not be delayed or withheld. Alternatives to penicillin are not recommended because of potential fetal toxicity (doxycycline) or failure of treatment to cross the placenta (azithromycin). There is limited evidence suggesting that parenteral ceftriaxone is effective, but no controlled trials have been performed.<sup>7,101</sup>

#### Discussion

Based on this review of the available literature, the preferred regimen for early syphilis, including primary, secondary, and early latent infection, is 2.4 million U of BPG in a single intramuscular injec-

tion. Late and late latent infection should be treated with 3 weekly injections of 2.4 million U of BPG, totaling 7.2 million U. Treatment response should be assessed by repeat measurements of nontreponemal serologic titers at 6 and 12 months following treatment of primary and secondary syphilis and at 6, 12, and 24 months for late and latent syphilis. Patients who are in a serofast state do not appear to benefit substantially from re-treatment. Doxycycline and ceftriaxone are also effective treatments for early syphilis when penicillin cannot be used, and reasonable evidence exists to support the use of either as alternatives to penicillin. Because of the potential for resistance, azithromycin should not be used to treat patients in the United States except when other agents are not available. Careful follow-up is essential.

Treatment of neurosyphilis should be aqueous crystalline penicillin G, 18 million to 24 million U/d via continuous infusion or divided into 6 daily doses for 10 to 14 days. Unfortunately, the data supporting this treatment regimen are modest and largely based on achievement of adequate treponemal CSF concentrations rather than demonstrated clinical efficacy. Individuals with HIV infection should be treated similarly to uninfected patients based on the available evidence and because the preponderance of data on syphilis treatment in HIV-infected persons were compiled in the era prior to the widespread availability of effective ART (which likely improves syphilis treatment responses). Although evidence is limited in pregnant women, the preferred treatment is penicillin, and pregnant women known to have penicillin allergy should be desensitized.<sup>7</sup>

Our recommendations align with those of the Centers for Diseases Control and Prevention (CDC). Although a few large RCTs support the current CDC recommendations, they are primarily based on results from early, uncontrolled studies and on decades of clinical experience. The best data exist for early syphilis because it encompasses the majority of diagnosed cases. In contrast, evidence in support of treatment recommendations for late and late latent syphilis is quite limited, as is also true for neurosyphilis, for

HIV-infected persons, and for pregnant women. The CDC's guidelines for treating syphilis in the setting of HIV infection are largely based on data from a 1997 RCT (done before the era of effective ART) that showed that HIV-infected patients respond comparably with HIV-uninfected persons.<sup>10</sup> However, only 69 HIV-infected persons in this study completed 6 months of follow-up and the only clinical failure occurred in an HIV-infected patient. Given the increasing rate of syphilis in the MSM population, there is a need for additional high-quality studies.

## Conclusions

After declining to historic lows at the turn of the 21st century, the incidence of syphilis has progressively increased in the United States, particularly in MSM. Penicillin remains the treatment of choice for all stages of syphilis, with different regimens suggested based on stage. Rigorous data from clinical trials to support the recommended regimens are generally lacking, and most existing data are limited by the lack of a gold standard to assess cure. Furthermore, the absence of homogeneous diagnostic definitions and outcome measurements among the available studies limits comparisons.<sup>102</sup> Larger, high-quality studies would be beneficial, especially in the disproportionately affected HIV-infected population, but seem unlikely to be carried out. Current recommendations are largely driven by clinical experience and expert opinion because available data are limited and sometimes conflicting. The accumulated clinical experience suggests that the current guidelines are largely successful. With the preponderance of available clinical data supporting penicillin as the preferred treatment option, the use of benzathine penicillin G offers a convenient, directly observed regimen that combines ease of administration with demonstrated antitreponemal activity. Penicillin will likely remain the cornerstone of syphilis treatment for years to come.

## ARTICLE INFORMATION

**Author Contributions:** Dr Clement had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** All authors.

**Acquisition, analysis, or interpretation of data:** Clement, Hicks.

**Drafting of the manuscript:** Clement, Hicks.

**Critical revision of the manuscript for important intellectual content:** Okeke, Hicks.

**Statistical analysis:** Clement, Hicks.

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**Submissions:** We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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