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Treatment of Syphilis
A Systematic Review

Meredith E. Clement, MD; N. Lance Okeke, MD; Charles B. Hicks, MD

Syphilis 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. 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. 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.3,4 In addition, genital ulcers due to syphilis have been linked to acquisition of human immunodeficiency virus (HIV) infection.5

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 infection.6 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.6 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).3

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 Treponema pallidum infection occurred within the previous year.9 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.29

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 reagin antigen produced by the host in response to syphilis infection.39 Nontreponemal serologic tests such as the Venereal Disease Research Laboratory (VDRL) test or the rapid plasma reagin 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 reagin 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.40 Coinfection with HIV may also contribute to therapeutic uncertainty because HIV-infected patients may experience slower serologic response rates after apparently successful treatment.41-44

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.45 Persons with low pretreatment titers are also sometimes said to be serofast when there is minimal (≤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.46 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.13,47-50 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.46

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
more than 60 years of use, there has never been a documented case of penicillin resistance. 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. 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). 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 million U of BPG are around 5%. In 1956, Smith et al 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 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, 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).

A 1997 study by Rolf et al 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
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). 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 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 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.

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. Only limited data exist regarding late latent syphilis therapy. In 2005, Kiddugavu et al 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. 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%.

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

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

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

*a* 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.

*b* Grade A due to large RCTs; however, azithromycin is used only when other options are not feasible because of macrolide resistance.
Table 3. Evidence for Penicillin Treatment of Syphilis

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Participants</th>
<th>Treatment</th>
<th>Dosing Regimens</th>
<th>Outcome Measure and Definitions</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roifs et al., 1997</td>
<td>Randomized clinical trial</td>
<td>139 patients with primary, 253 with secondary, and 149 with early latent syphilis (100 with history of syphilis)</td>
<td>276 treated with BPG and 265 with enhanced therapy</td>
<td>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</td>
<td>Treatment success: negative or ≤4-fold decrease in RPR titer</td>
<td>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</td>
<td>1-y follow-up (52% retained in study) 101/54 (19%) HIV infected</td>
</tr>
<tr>
<td>Talwar et al., 1992</td>
<td>Retrospective study</td>
<td>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)</td>
<td>1386 treated with BPG, 17 with procaine penicillin, and 139 with broad-spectrum antibiotic</td>
<td>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 doses</td>
<td>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</td>
<td>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</td>
<td>30-mo surveillance period</td>
</tr>
<tr>
<td>Fiumara, 1986</td>
<td>Retrospective study</td>
<td>88 patients with primary and 101 with secondary syphilis When combined with previous series, 588 with primary and 623 with secondary syphilis</td>
<td>All treated with BPG</td>
<td>BPG: 2.4 million U IM weekly as 2 doses</td>
<td>Patients followed up until lesions or rash healed and test results (RPR and FTA-ABS) became negative</td>
<td>88/88 with primary syphilis seronegative at 12 mo; 101/101 with secondary syphilis seronegative at 2 years</td>
<td>2-y follow-up Excluded patients with ≥4-fold increase in RPR after lesions had healed or after titer had decreased 24-fold, considered to have been reinfeeted No control group</td>
</tr>
<tr>
<td>Durst et al., 1973</td>
<td>Prospective study</td>
<td>40 patients with secondary syphilis</td>
<td>All treated with BPG</td>
<td>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)</td>
<td>Patients followed up until serologic test results became negative</td>
<td>At 12 mo: 17/40 seronegative; at 18 mo: 33/40 seronegative; at 24 mo: 40/40 seronegative</td>
<td>2-y follow-up No control group</td>
</tr>
<tr>
<td>Jefferiss and Willcox, 1963</td>
<td>Presumed retrospective study</td>
<td>211 patients with seronegative primary, 179 with seropositive primary, 196 with secondary, and 50 with early latent syphilis</td>
<td>107 treated with benzyl penicillin, 7 with benzyl penicillin plus BPG, 231 with procaine penicillin or PAM, and 291 with high-dose APPG ± PAM</td>
<td>Benzy]l penicillin: “repeated 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: &gt;10 million U PAM at varied dosing of injections</td>
<td>Patients followed up with clinical and serologic examinations monthly for 6 mo, quarterly for 1 year, and twice per year for second year</td>
<td>95% with negative VDRL test result 22 mo after treatment</td>
<td>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%)</td>
</tr>
<tr>
<td>Smith et al., 1956</td>
<td>Presumed retrospective study</td>
<td>52 patients with seronegative primary, 67 with seropositive primary, and 155 with secondary syphilis</td>
<td>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</td>
<td>BPG: 2.5 million U IM as 1 dose PAM: 4.8 million U in a single session or 2-4 sessions</td>
<td>Patients followed up according to percentage seronegative (negative or less than 4 Kahl units)</td>
<td>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 regimen</td>
<td>2-y follow-up</td>
</tr>
<tr>
<td>Sternberg and Leifer, 1947</td>
<td>Retrospective study</td>
<td>1400 patients with early syphilis: 600 (42.8%) seronegative primary, 564 (40.3%) with seropositive primary, and 236 (56.4%) with secondary syphilis</td>
<td>Sodium penicillin in aqueous solution or isotonic sodium chloride</td>
<td>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”</td>
<td>Seronegative primary syphilis: 86% followed up &gt;9 mo; satisfactory progression in 566 (94.3%) Seropositive primary syphilis: 82% followed up &gt;9 mo; satisfactory progression in 507 (89.9%) Secondary syphilis: 84% followed up &gt;9 mo; satisfactory progress at last observation in 196 (83%)</td>
<td>1-y follow-up No distinction of penicillin type; noted “patients were probably treated with penicillins of satisfactory potency” No control group</td>
<td></td>
</tr>
</tbody>
</table>

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, Veneral Disease Research Laboratory.
Table 4. Evidence for Antibiotics Other Than Penicillin for Treatment of Syphilis

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Participants</th>
<th>HIV Status</th>
<th>Treatment and Dosing Regimens</th>
<th>Outcome Measures, Definitions, and Comments</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li and Zheng,13</td>
<td>Retrospective</td>
<td>641 patients with early syphilis (13.4% primary, 52.1% secondary, and 34.5% early latent)</td>
<td>Excluded HIV-infected patients</td>
<td>606 (94.5%) treated with BPG, 2.4 million U IM 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</td>
<td>Serologic response: negative or ≥4-fold decrease in VRDL or increase in RPR</td>
<td>No significant difference in serologic response rates: 91.4% of penicillin vs 82.9% of doxycycline/ tetracycline; P = .18</td>
</tr>
<tr>
<td>Psomas et al.14, 15</td>
<td>Retrospective</td>
<td>116 patients with early syphilis</td>
<td>80% HIV infected</td>
<td>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</td>
<td>Serologic response: ≥4-fold increase in VRDL or increase to &gt;1:4</td>
<td>Responses: penicillin, 39/52 (75%); ceftriaxone, 38/49 (77.6%); doxycycline, 11/15 (73.3%)</td>
</tr>
<tr>
<td>Wong et al.16, 17</td>
<td>Retrospective</td>
<td>445 primary syphilis cases</td>
<td>Excluded diagnosed HIV-infected patients but many had unknown HIV status</td>
<td>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</td>
<td>Serologic response: ≥4-fold decrease in RPR by 6 mo, ≥8-fold by 12 mo, and ≤16-fold by 24 mo, or serofast (≥1 dilution from baseline if RPR was 1:4, 1:2, or 1:1 at baseline) Failure: none of the above or 24-fold increase in RPR at 1-6 mo</td>
<td>No significant difference in serologic response rates: 409/420 (97.4%) of BPG vs 25/25 (100%) of doxycycline/ tetracycline</td>
</tr>
<tr>
<td>Ghanem et al.18, 19</td>
<td>Retrospective case-control</td>
<td>1558 patients with early syphilis</td>
<td>13.7% HIV positive in BPG vs 5.3% in doxycycline groups</td>
<td>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</td>
<td>Serologic failure: 4-fold increase in RPR 30-400 d posttreatment or lack of 4-fold decrease in RPR in 20-400 d posttreatment</td>
<td>4/73 with serologic failure in BPG group vs 0/34 in doxycycline group</td>
</tr>
<tr>
<td>Lang et al.20, 21</td>
<td>Prospective cohort</td>
<td>96 patients with syphilis; 76 returned for 1-y follow-up Syphilis stage undefined</td>
<td>15/96 had HIV infection</td>
<td>56 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</td>
<td>Serologic response: ≥4-fold decrease in RPR by 12 mo Reinflection: success then subsequent ≥4-fold increase in RPR from its lowest level or conversion to reactive Failure: no ≥4-fold decline in RPR in failure to convert a 1:4-1.2 titer to nonreactive No relapse group</td>
<td>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</td>
</tr>
<tr>
<td>Schroeter et al.22, 23</td>
<td>Prospective</td>
<td>586 patients with early syphilis</td>
<td>NA</td>
<td>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), 17 with tetracycline, 30 (3 g/d ×10 d), and 144 with erythromycin, 30 g</td>
<td>Cure: healed clinical manifestations, prompt and permanent decrease of VRDL Relapse: reappearance of lesions with dark field or significant increase in VRDL Failure: lack of significant response of VRDL after 1 y</td>
<td>Cumulative re-treatment at 24 mo: BPG, 11.4%; PAM, 10.9%; APPG, 10.7%; tetracycline, 12.7%; erythromycin, 21.3%</td>
</tr>
<tr>
<td>Psomas et al.24, 25</td>
<td>Retrospective</td>
<td>116 patients with early syphilis</td>
<td>80% HIV infected</td>
<td>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</td>
<td>Serologic response: ≥4-fold increase in VRDL or increase to &gt;1:4</td>
<td>Responses: penicillin, 39/52 (75%); ceftriaxone, 38/49 (77.6%); doxycycline, 11/15 (73.3%)</td>
</tr>
</tbody>
</table>

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).10,12,20-27,31,34,36-38 Erythromycin is no longer recommended based on tolerability and resistance concerns,56 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)

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
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<th>Treatment and Dosing Regimens</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spornraft-Ragaller et al   2011</td>
<td>Retrospective</td>
<td>24 patients with active syphilis (21 with primary syphilis, 3 with neurosyphilis)</td>
<td>All patients HIV infected</td>
<td>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)</td>
<td>Serologic response: negative or ≥4-fold decrease in VDRL</td>
<td>11/12 with ceftriaxone and 12/12 with penicillin had ≥4-fold decline in VDRL titers at median of 18.3 mo</td>
</tr>
<tr>
<td>Smith et al. 17 2004</td>
<td>Prospective randomized pilot</td>
<td>31 patients with asymptomatic syphilis randomized to procaine penicillin or ceftriaxone Most thought to have late latent syphilis</td>
<td>All patients HIV infected, enrolled before availability of effective antiretroviral therapy</td>
<td>10 treated with procaine penicillin, 2.4 million U IM, plus oral procobic and 14 with ceftriaxone, 1 g/d for 15 d (only 24 followed up)</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Dowell et al. 18 1992</td>
<td>Secondary</td>
<td>7 patients with neurosyphilis, 6 with latent syphilis, and 30 with presumed latent syphilis</td>
<td>All patients HIV infected</td>
<td>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</td>
<td>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</td>
<td>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 26 mo</td>
</tr>
<tr>
<td>Schöfer et al. 19 1989</td>
<td>Randomized prospective</td>
<td>28 patients with early syphilis (9 primary, 19 secondary)</td>
<td>NA</td>
<td>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</td>
<td>Serological controls were repeated 1, 2, 3, 6, and 12 mo after therapy</td>
<td>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</td>
</tr>
<tr>
<td>Hook et al. 20 1988</td>
<td>Prospective</td>
<td>11 patients with primary and 5 with secondary syphilis</td>
<td>NA</td>
<td>10 treated with ceftriaxone, 2.50 mg/d for 10 d, and 6 with ceftriaxone, 500 mg every other day as 5 doses</td>
<td>Results reported at 3 mo Daily treatment: 1/10 with VDRL persistently negative, 4/10 became seronegative, 5/10 had dilutions of ≥2 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</td>
<td></td>
</tr>
<tr>
<td>Moorthy et al. 21 1987</td>
<td>Randomized</td>
<td>18 patients with early syphilis</td>
<td>NA</td>
<td>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</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Meta-analysis</td>
<td>790 patients with early syphilis</td>
<td>NA</td>
<td>3 randomized clinical trials comparing BPG vs azithromycin in variable dosages</td>
<td>Serologic response: ≥4-fold decrease in RPR measured at 3, 6, 9, and 12 mo</td>
<td>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</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Participants</th>
<th>HIV Status</th>
<th>Treatment and Dosing Regimens</th>
<th>Outcome Measures, Definitions, and Comments</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hook et al., 2010</td>
<td>Randomized clinical trial</td>
<td>517 patients with early syphilis: 26% primary, 46% early latent primary, 28% early latent secondary, and 46% late latent secondary</td>
<td>Excluded HIV-infected patients</td>
<td>237 treated with BPG, 2.4 million UIM as 1 dose, and 232 with azithromycin, 2.0 g orally as 1 dose</td>
<td>Serologic response: negative or ≥4-fold decrease in RPR by 6 mo</td>
<td>Serologic response in 180/232 (77.6%) with azithromycin vs 190/237 (78.5%) with BPG Increased nonserious adverse events (mostly gastrointestinal) in azithromycin group</td>
</tr>
<tr>
<td>Bai et al., 2008</td>
<td>Meta-analysis</td>
<td>476 patients with early syphilis</td>
<td>NA</td>
<td>4 randomized clinical trials comparing BPG vs azithromycin in variable dosages</td>
<td>Serologic response: ≥4-fold decrease in RPR measured at 3, 6, 9, and 12 mo</td>
<td>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</td>
</tr>
<tr>
<td>Kiddugavu et al., 2005</td>
<td>Secondary analysis of randomized clinical trial (not randomized to therapy)</td>
<td>11 patients (1.1%) with primary, 122 (13%) with secondary or early latent, and 818 (86%) with presumed late latent syphilis</td>
<td>20.8% HIV infected</td>
<td>18% treated with BPG alone, 2.4 million UIM as 1 dose, and 17% with azithromycin alone, 1 g orally as 1 dose, and 62% with dual therapy</td>
<td>All treated with single dose IM regardless of presumed stage of syphilis</td>
<td>When initial titer &gt;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 patients</td>
</tr>
<tr>
<td>Riedner et al., 2005</td>
<td>Randomized clinical trial</td>
<td>25 patients with primary and 303 with high-titer latent syphilis</td>
<td>52.1% HIV infected</td>
<td>163 treated with azithromycin, 2.0 g orally as 1 dose, and 165 with BPG, 2.4 million UIM as 1 dose</td>
<td>Serologic response: ≥4-fold decrease in RPR titer at 9 mo</td>
<td>97.7% response in azithromycin group vs 95.0% in BPG group</td>
</tr>
<tr>
<td>Hook et al., 2002</td>
<td>Randomized pilot</td>
<td>60 patients with early syphilis</td>
<td>4% HIV infected</td>
<td>14 treated with BPG, 2.4 million UIM as 1 dose, 17 with single-dose azithromycin and 29 with double-dose azithromycin, 2.0 g orally as 1 dose</td>
<td>Serologic response: clinical resolution and negative or ≤2-fold change in RPR</td>
<td>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</td>
</tr>
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</table>

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.

Doxycline
Several studies, mostly small and retrospective, indicate that doxycline/tetracycline is effective treatment for early syphilis, with serologic response rates of 83% to 100%.13-19 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.16,17 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.

Ceftiximone
Several small studies of intramuscular ceftixime for early syphilis have shown efficacy comparable with penicillin G.16,20-22 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.20,22

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.57 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.31,32-34 The emergence of azithromycin resistance mutations in T pallidum with resultant treatment failure has limited its usefulness in many regions of the United States.35,51-53 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.31 Azithromycin has also been associated with a 5-fold greater risk of gastrointestinal...
The Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer reaction is a significant adverse event that can occur with any antibiotic treatment for syphilis but is most common after penicillin. This reaction manifests with systemic symptoms including fever, rash, malaise, headache, and myalgias, typically occurring within 24 hours of treatment of early syphilis. It is seen in 10% to 35% of patients and is usually self-limited. The reaction is thought to result from release of lipoproteins, cytokines, and immune complexes from killed organisms.

Penicillin Allergy and Penicillin Desensitization

Given the availability of nonpenicillin options for the treatment of syphilis, the need for penicillin desensitization approaches seems limited, and it is not well studied. However, in some settings, penicillin is clearly the treatment of choice and desensitization is probably the preferred option in the following situations: (1) neurosyphilis in persons with a history of severe immediate hypersensitivity reaction to penicillin; (2) tertiary syphilis in all penicillin-allergic patients; (3) any stage of syphilis in penicillin-allergic pregnant women; and (4) congenital syphilis in penicillin-allergic infants.

Special Circumstances: Neurosyphilis, HIV-Infected Persons, and Pregnant Women

Neurosyphilis

Successful neurosyphilis treatment requires the presence of adequate, prolonged cerebrospinal fluid (CSF) concentrations of a treponemical antimicrobial (Table 5). Benzathine penicillin G should not be used because it does not reliably achieve sufficient concentrations in CSF. Intravenous administration of aqueous crystalline penicillin G achieves adequate CSF levels and is the treatment of choice for neurosyphilis. Procaine penicillin injections also achieve treponemical levels in CSF, and there is evidence of clinical impa-
proportion 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 penicillin 4 times daily.70,71

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.72,73 Risk of cross-reactivity between penicillin and ceftriaxone is negligible, but skin testing for β-lactam allergy and desensitization can be done if needed.7,57

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.75

There are few studies comparing syphilis treatment of HIV-coinfected patients with HIV-uninfected controls.76 Patients with HIV infection may be at increased risk of serologic failure following treatment, although this is controversial.41,42 Some studies comparing serologic response rates between HIV-infected and uninfected persons show no difference in treatment success rates.70,77 Other studies attribute the perceived increased risk of treatment failure to a slower decline in titer in HIV-infected individuals.42 Lower CD4 cell counts are associated with delayed treatment response and increased risk of serologic failure among HIV-infected patients.41,78 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.79-81 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).42 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.28,29 Effective ART appears to reduce the likelihood of serologic failure as well as progression to neurosyphilis.83,84

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.85-87

HIV Infection and Neurosyphilis
Reports of increased risk of neurosyphilis emerged soon after recognition of the HIV epidemic.80,81,88,89 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.81,90,91 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.37,38,92 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.93

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.94,95 Observational studies of syphilis in pregnant women suggest that standard treatment based on stage of syphilis at diagnosis is sufficient.96-99 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.100,101

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.73,103

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-

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Table 5. Parenteral Penicillin Regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Cerebrospinal Fluid Concentration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzathine penicillin G</td>
<td>Intramuscular</td>
<td>Low</td>
<td>Very low solubility leading to slow release from injection site; blood concentrations detectable up to 4 wk after injection</td>
</tr>
<tr>
<td>Aqueous procaine penicillin G</td>
<td>Intramuscular</td>
<td>High</td>
<td>Slowly dissolving; blood levels plateau at about 4 h then decrease slowly over the next 15 to 20 h</td>
</tr>
<tr>
<td>Aqueous penicillin G (benzylpenicillin)</td>
<td>Intramuscular or intravenous</td>
<td>High</td>
<td>Half-life of 42 min</td>
</tr>
</tbody>
</table>
treatment. 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 treponemical 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.7

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 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.10 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.102 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.

REFERENCES


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.

Administrative, technical, or material support: Clement.

Study supervision: Okeke, Hicks.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGaie McDermott, MD, at mmd608@northwestern.edu.


