BRITISH COLUMBIA
CENTRE *for* EXCELLENCE
in HIV/AIDS

THERAPEUTIC GUIDELINES FOR OPPORTUNISTIC INFECTIONS SYPHILIS

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ABBREVIATIONS: ANS, asymptomatic neurosyphilis; ART, antiretroviral therapy; BCCDC, British Columbia Centre for Disease Control; B-STI, bacterial sexually transmitted infection; CI, confidence interval; CM, contingency management; CSF, cerebrospinal fluid; doxy-PrEP, doxycycline pre-exposure prophylaxis; doxy-PEP, doxycycline post-exposure prophylaxis; DuDHS, dual daily HIV and syphilis; EIA, enzyme immunoassay; HPV, human papilloma virus; IM, intramuscular; IV, intravenous; LGV, lymphogranuloma venereum; MSM, men who have sex with men; MRSA, methicillin resistant *Staphylococcus aureus;* PLWH, person living with HIV; PO-OD, orally one daily; RCT, randomized controlled trial; RPR, rapid plasma reagin; RR, relative risk; TP-PA, *Treponema pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory.

I. PREVALENCE

Syphilis has been steadily increasing globally over the past 20 years[1]. This has been occurring predominantly in urban areas and disproportionally affecting men who have sex with men (MSM) who are often persons living with HIV (PLWH)[1]. In British Columbia, the annual case count has more than doubled during the past few years, increasing from 909 to 1,973 new cases between 2020 and 2022, and with a projected further increase for 2023[2]. Currently, males account for 67% of cases in BC; however, there has been an 86% increase in the number of reported females in the first quarter of 2023. Heterosexual partners account for 61% of cases and 37% are MSM[2]. Recent increases have also been observed for both neurosyphilis and congenital syphilis with the 2022 case counts being 72 and 14, respectively[2].

II. CLINICAL PRESENTATION

Primary syphilis develops within 2-6 weeks of becoming infected and typically includes a painless chancre at the site of initial contact (e.g., genital, oral, perianal, rectal) and possibly regional lymphadenopathy. *Treponema pallidum* disseminates to other organs including the central nervous system within days after initial infection.

Secondary syphilis develops 1-2 months following primary syphilis and most often presents with findings which may include a rash (predominantly on the palms and soles), mucosal lesions, fever, alopecia, and generalized lymphadenopathy[1]. Laboratory studies may also reflect evidence of hepatitis (elevated alkaline phosphatase) or nephritis. Approximately 10% of patients will simultaneously manifest findings of both primary and secondary syphilis with a chancre and a rash.

Neurosyphilis may occur at any stage of syphilis. Among the 40% of individuals who have CNS invasion by *T.pallidum*, 10% may develop early neurosyphilis which is either asymptomatic or symptomatic (e.g., meningitis or meningovascular syphilis). Late neurosyphilis is much less common and may develop 2-50 years after becoming initially infected including meningovascular disease, general paresis and tabes dorsalis[1].

Ocular and otic syphilis, like neurosyphilis may develop at any stage of syphilis[1]. Sensorineural hearing loss, tinnitus, or vertigo are usual presenting symptoms for otic syphilis[3]. Ocular symptoms usually include visual disturbances related to anterior, posterior, or panuveitis, or optic neuritis[4].

Early latent syphilis is an asymptomatic phase within the first year of becoming infected. It may occur either between primary and secondary or after secondary syphilis. In the absence of treatment, approximately one quarter of patients will have a recurrent episode of secondary syphilis, usually within the first year following initial infection.

Late latent syphilis is defined as asymptomatic infection of >1 year since becoming infected. If the duration of latent syphilis cannot be determined based upon previous history and serologic test results, then for management purposes it should be

assumed to be late latent in order to avoid the possibility of undertreating late latent disease with a single dose of benzathine penicillin G.

Tertiary syphilis. Without treatment, approximately 30% of individuals with late latent syphilis will progress over 2-50 years to tertiary syphilis, which may manifest with findings of late neurosyphilis (as above), gummatous disease, cardiovascular (e.g., aortic aneurysm), ocular, or otic syphilis.

Congenital syphilis. Most infants with congenital syphilis will be asymptomatic at birth. However, depending upon the timing of infection in pregnancy, up to 40% will have symptoms[2], including generalized lymphadenopathy, hepatomegaly, jaundice, rash, nasal discharge and/or skeletal abnormalities. Symptoms of late congenital syphilis occur after age two, and are the result of scarring and persistent inflammation such as interstitial keratitis, hearing loss, gummas, cognitive deficits as well as facial, tooth, and skeletal abnormalities. Congenital syphilis can be fatal.

Atypical syphilis presentations have been reported to occur more often in PLWH including: i) a greater likelihood of presenting with secondary vs primary syphilis (53% vs 33%, respectively)[5]; ii) more often to have persistent chancres (43% vs 15%)[5]; iii) multiple chancres[6]; and iv) the rare presentation of lues maligna ("malignant syphilis")[7].

III. DIAGNOSIS

The diagnosis of syphilis for both asymptomatic and symptomatic individuals mainly relies upon serological testing. Over 50% of syphilis cases diagnosed in BC are in the early latent stage of disease[2], reflecting the relatively low rate of detection of primary and secondary syphilis which are often mild and may not prompt medical attention.

a) Serology

The approach to diagnosis of syphilis has changed in recent years. Instead of using non-treponemal serology (e.g., rapid plasma reagin [RPR]) followed by a confirmatory manual treponemal test (e.g., TPPA), increasingly laboratories are moving towards an initial screening test using an automated treponemal platform test (e.g., an enzyme immunoassay [EIA]) which, if positive is followed by reflex-testing with a non-treponemal test (e.g., RPR) which provides a titre that helps to direct management. This newer approach which represents a reversal from the older paradigm is associated with improved sensitivity for both primary and late syphilis in addition to being cost effective for high volume laboratories, as outlined below.

False negative serology. Early in suspected primary syphilis, serologic tests may be negative and should be repeated 2 weeks later[1]. There are rare reports of PLWH being seronegative by RPR at presentation with secondary syphilis. Such seronegative patients suspected to have syphilis should be further investigated including a laboratory request to check for the prozone phenomenon by diluting the sample and retesting RPR in possibly swabs of a lesion sent for dark field examination or PCR (available at the British Columbia Centre for Disease Control [BCCDC]), or

dermatology evaluation with tissue biopsy including special stains for spirochete identification using either Warthin-Starry stain or immunoperoxidase[8].

Reverse sequence algorithm. The Canadian Public Health Laboratory Network considers both the reverse sequence and the traditional testing algorithms to be acceptable for the diagnosis of syphilis; however, the decision to adopt one or another method depends upon the local disease prevalence, testing volume, laboratory size, and available resources[9]. An evaluation of different testing algorithms demonstrated improved sensitivity with the reverse algorithm, with a sensitivity, specificity, and accuracy of 99.4%, 99.9%, and 99.9%, respectively[10].

The initial screening test using a treponemal EIA improves upon the suboptimal test sensitivity for the diagnosis in primary and late syphilis with rapid plasma reagin (RPR) screening in the traditional algorithm, which is 78% and 71%, respectively[11]. High volume laboratories, such as the BCCDC have tended to adopt the reverse algorithm due to the availability of automated treponemal antibody platforms (e.g. EIA) which provide improved sensitivity and facilitate high throughput testing[12].

Discordant serologic results with the reverse-sequence algorithm. When the testing results are discordant (i.e., the initial treponemal test is reactive but the subsequent non-treponemal test is negative), further testing is required with a 2nd treponemal test using antigens which are different from those in the initial treponemal test in order to clarify the discrepancy[11]. The possible explanations for discordant results include the following scenarios which need to be correlated with the clinical findings and past history of syphilis treatment in order to reach the most appropriate interpretation[1]:

Screening (EIA) treponemal test	Non-treponemal test (RPR)	Confirmatory treponemal test	Interpretation
Non-reactive			• No serologic evidence of syphilis (most likely) • Early primary syphilis • Longstanding treated syphilis
Reactive	Non-reactive	Non-reactive	• Biologic false positive
Reactive	Reactive		• Untreated or treated syphilis (most likely) • Endemic treponematoses (e.g. yaws)
Reactive	Non-reactive	Reactive	• Treated syphilis (most likely) • Longstanding untreated syphilis • Early primary syphilis • Prozone reaction

RPR (rapid plasma reagin) titre is helpful in that higher titres are suggestive of recent infection, whereas lower titres (e.g. 1:2 or 1:4) may be observed within months or a few years after curative therapy, or longer periods of time in untreated patients.

Syphilis cure is defined as the resolution of clinical findings plus a 4-fold decline in non-treponemal serological titre (e.g. RPR) within 6-12 months for early syphilis (< 1yr duration) or within 12-24 months for late syphilis (>1yr)[1]. Approximately 20% of treated patients do not have a serologic response after 6 months which drops to 11.5% by 12 months[13].

b) Neurosyphilis.

There is no single reliable diagnostic test for neurosyphilis, which depends upon an assessment of the clinical presentation, CSF results, and syphilis serologies. Although a cerebrospinal fluid (CSF) sample which is positive for either a non-treponemal test (e.g., VDRL) or *T. pallidum* PCR has high predictive value for neurosyphilis, neither test has high sensitivity[1,14]. In contrast, CSF treponemal tests are sensitive but non-specific due to transfer of treponemal antibodies across the blood brain barrier. However, preliminary results suggest that the treponemal test *Treponema pallidum* particle agglutination (TP-PA) in CSF using a cutoff titre of ≥1:640 had much improved specificity, similar to that of CSF VDRL[15]. CSF pleocytosis (>5 cell/cu mm; or >20 cells/cu mm in PLWH who are not taking antiretroviral therapy [ART]) is a sensitive but non-specific finding in neurosyphilis. Diagnostic algorithms have been developed to assist in the management of suspected neurosyphilis[16].

Screening for neurosyphilis. The decline in the rates of symptomatic neurosyphilis since the beginning of the penicillin era suggested that penicillin therapy for early or late-latent syphilis (a single or 3 weekly intramuscular [IM] doses of benzathine penicillin, respectively) may be sufficient to prevent the development of late neurologic sequelae of asymptomatic neurosyphilis (ANS)[17]. However, reports of PLWH with symptomatic neurosyphilis who had previously been treated for early or late syphilis prompted recommendations that the diagnosis of ANS should be pursued in those with HIV and syphilis co-infection; in particular, those with a CD4 ≤350 cells/mL or a peripheral blood RPR titre of ≥1:32[17,18]. However, more recently, among a series of 59 PLWH who had all achieved serologic cure of early syphilis at a median of 8 months of follow-up after a single dose of benzathine penicillin, lumbar puncture identified only 1/59 with ANS[19].

There has also been some inconsistency in the literature in regard to ocular and otic syphilis being entities which are distinct from neurosyphilis[1], rather than being clinical manifestations of neurosyphilis[3,20]. In addition, previous recommendations had stated that all syphilis patients with either ocular complaints or a diagnosis of otosyphilis should undergo a lumbar puncture for CSF analysis[3,20]. Among those serologically diagnosed with syphilis in association with isolated ocular or otic symptoms and signs, CSF abnormalities may be seen in up to ~60% and ~10% of cases, respectively[21]. Despite these CSF findings, recent CDC (Atlanta, GA) guidelines do not recommend routine lumbar puncture for such patients (as outlined below) given the observation

that CSF laboratory abnormalities are common in early syphilis and are of uncertain clinical significance in the absence of neurologic signs or symptoms[22].

Recommendations regarding screening for neurosyphilis in PLWH are controversial**.**
Indications for lumbar puncture and CSF examination in adults and adolescent PLWH with reactive syphilis serology[22]:

1) Clinical signs or symptoms of neurosyphilis (e.g., meningeal symptoms such as headache, cranial nerve abnormalities, stroke), or
2) Ocular symptoms but no ocular findings on detailed ophthalmologic examination and no cranial nerve abnormalities.

Other indications for lumbar puncture in adults and adolescent PLWH with reactive syphilis serology which have been supported by some guidelines and experts[16,17,20,23]:

1) CD4 ≤350 cells/mL or a peripheral blood RPR titre of ≥1:32,
2) Ocular (e.g., visual disturbance) or otic (e.g., hearing loss, tinnitus) symptoms,
3) Failure to have a serologic response (4-fold decrease in titre) to treatment after 12 and 24 months for early and late syphilis, respectively.

Differential Diagnosis of syphilis depends upon the stage of disease but includes other genital, perianal, rectal, oral, or cutaneous lesions such as herpes simplex, chancroid, lymphogranuloma venereum (LGV), and mpox (monkeypox). Extragenital manifestations need to be differentiated from various neurologic and cardiac disorders.

IV. PREVENTION

Recommendation

a) Comprehensive education, preventative sexual health counseling (BII) and screening (AII) should be provided to all sexually-active individuals to include HIV/STI screening, vaccinations (e.g., hepatitis A/B, human papillomavirus [HPV]), expedited partner therapy, access to HIV-PrEP (pre-exposure prophylaxis) and HIV-PEP (post-exposure prophylaxis), and/or contraception where warranted.

b) Doxcycline bacterial STI (B-STI) prophylaxis should be offered to all high-risk individuals (as outlined below) using shared decision-making.

i) **Eligibility.** All of the following 3 eligibility criteria need to be met:
   1. Be a participant in one of the BC-CfE's drug treatment programs (either the HIV pre-exposure prophylaxis program [HIV-PrEP]; ***or*** the HIV Treatment Program for PLWH), ***plus***
   2. Be within one of the following groups: gay, bisexual, and other men who have sex with men ***or*** transgender woman, ***plus***

3. Be at increased risk of bacterial sexually transmitted infections (B-STI) such as gonorrhea, chlamydia, or syphilis as indicated either by having a history of B-STI within the past year ***or*** being clinically assessed as being at increased risk.

ii) **Inclusion Criteria:** Individuals who are: 1) either MSM or transgender women plus ≥1 episode of a bacterial sexually transmitted infections (B-STI) such as gonorrhea, chlamydia, or syphilis in the prior year(AI), ***or*** 2) either MSM or transgender women who do not have a history of B-STI in the past year, but are known to be at high risk for B-STI (e.g., taking antiretroviral HIV-PrEP)(BIII).

iii) **Exclusion Criteria:**
- Allergy to tetracyclines
- Contraindicated medications: barbiturates, carbamazepine, phenytoin, warfarin or systemic retinoids (i.e., isotretinoin [Accutane®])

iv) **Intervention:** Doxycycline 200mg (2 x 100mg tablet or capsule) one single dose taken as soon as possible within 72 hours post-coital, up to a maximum of doxycycline 200mg once a day, at the discretion of the client

v) **Efficacy Monitoring:** Test at baseline and q3-months for gonorrhea and chlamydia at all relevant anatomic sites (urogenital, pharyngeal, and rectal), and for syphilis and HIV (if HIV uninfected at baseline)
- If an STI is diagnosed, treat according to standard STI treatment guidelines

vi) **Safety Monitoring:** Consider hematopoietic, renal, and hepatic laboratory monitoring as indicated

vii) **Caution:** Do not use doxycycline during pregnancy

viii) **Counsel:** Possible adverse drug events
- Gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain, diarrhea)
- Sun sensitivity, esophagitis, and rarely intracranial hypertension

Discussion. Longstanding public health approaches to syphilis prevention have included: education, counselling, screening, treatment, and contact tracing. Factors which have made prevention efforts more challenging over the past couple of decades have included increased risky sexual behavior since the availability of effective ART, HIV pre-exposure prophylaxis (PrEP), more frequent drug use during sex, internet use as a means of finding more sexual partners, and anonymous sex.

a) Counselling and education. Behavioral counselling has been assessed as being useful in reducing the likelihood of acquiring STIs with a moderate level of certainty

in those who are at increased risk, including individuals who: i) currently have an STI; ii) do not use condoms; or iii) have multiple partners[24].

b) Screening. Blood test syphilis screening (e.g., reverse sequence algorithm, see *Diagnosis*) has been recommended for MSM or PLWH at least annually, or at 3 to 6-month intervals for those remaining at highest risk. Syphilis screening has been assessed as having substantial benefit with a high level of certainty in high-risk adolescents and adults[25]. However, an evaluation of adherence to previously recommended screening guidelines among MSM PLWH showed that almost one-third had not been tested annually and that the highest risk individuals had not tested at recommended frequencies[26].

c) Vaccine. Despite ongoing research in this area, there is no expectation of an effective vaccine being available in the near future[27].

d) Antimicrobial prophylaxis. Despite the above-mentioned public health measures, bacterial sexually transmitted infections (B-STIs: gonorrhea, syphilis, and chlamydia) have been steadily increasing in gay, bisexual, and other men who have sex with men (MSM) over the past 2 decades[2]. This has prompted clinical trials to evaluate the potential efficacy of both pre- and post-exposure prophylaxis (PrEP and PEP) with doxycycline[28].

i) Doxycycline – General Considerations

Most of the recent focus regarding chemoprophylaxis of B-STIs has been on doxycycline[28]. Doxycycline is a second-generation, generally well tolerated tetracycline with a limited antibacterial spectrum. It is rapidly and almost completely absorbed orally. It was first available commercially in the 1960s. Since then, doxycycline has been used by millions for treatment of acne vulgaris with favorable safety and efficacy, despite a modest risk for the development of esophagitis or phototoxicity reactions, which can be mitigated against with behavioral means (i.e., swallow the medication with lots of water and use sun protection). Doxycycline has also been extensively used for primary prophylaxis for scrub typhus, leptospirosis, malaria, and Lyme disease[28]. Doxycycline is currently treatment of choice for chlamydia infection and alternative treatment for certain stages of syphilis in penicillin-allergic patients who are not pregnant. Doxycycline has been evaluated as chemoprophylaxis of B-STIs[28].

ii) Doxycycline post-exposure prophylaxis (PEP) of B-STIs

A recent open-label, randomized study of doxycycline PEP (Doxy-PEP) enrolled MSM and transgender women who were taking HIV PrEP (PrEP cohort) or persons living with HIV infection (PLWH cohort) and who had had *Neisseria gonorrhoeae* (gonorrhea), *Chlamydia trachomatis* (chlamydia), or syphilis in the past year[29]. Participants were randomly assigned to take 200mg of doxycycline within 72 hours after condomless sex (Doxy-PEP group) or receive standard care without doxycycline. STI testing was performed quarterly. The primary end point of the study was the incidence of at least one STI per follow-up quarter.

In brief, the incidences of the three evaluated B-STIs were lower with doxycycline than with standard care; in the PrEP cohort, the relative risks were 0.45 (95% confidence interval [CO]: 0.32 to 0.65) for gonorrhea, 0.12 (95% CI: 0.05 to 0.25) for chlamydia, and 0.13 (95% CI: 0.03 to 0.59) for syphilis, and in the PLWH cohort, the relative risks were 0.43 (95% CI: 0.26 to 0.71), 0.26 (95% CI: 0.12 to 0.57), and 0.23 (95% CI: 0.04 to 1.29), respectively. Five grade 3 adverse events (diarrhea 3; headache or migraine 2) and no serious adverse events were attributed to doxycycline. Doxycycline was discontinued in 2% of participants due to adverse effects or patient preference. Among those randomized to Doxy-PEP, 89% reported that taking Doxy-PEP was acceptable or very acceptable. Of the participants with gonorrhea culture available, tetracycline-resistant gonorrhea occurred in 5 of 13 in the doxycycline groups and 2 of 16 in the standard-care groups. This study focused on those at highest risk for B-STIs and was not limited to MSM and transgender women receiving HIV PrEP, but also included PLWH who had a B-STI in the previous year. Consequently, the results of this study are also generally applicable to the higher risk population of PLWH in BC receiving ART.

ANRS 174 DoxyVac Study. This is a 2 by 2 factorial multicenter, open-label, randomized controlled trial (RCT) of doxycycline and meningococcal B vaccine, to assess the ability of each strategy to prevent B-STIs in MSM taking HIV PrEP and known to have had a B-STI in the previous 12 months[30]. This French study was unblinded by the data safety and monitoring board (DSMB) in September 2022, following the announcement of the Luetkemeyer trial results outlined above[29], and it was recommended that all participants be offered doxycycline chemoprophylaxis going forward. Doxycycline use was associated with an adjusted hazard ratio of 0.16 (95% CI: 0.08 to 0.30, p <0.0001) for the combined endpoint of first episode of chlamydia or syphilis. The lesser impact of the intervention on gonococcal infections in the study was attributed to the very high level of baseline gonococcal resistance to tetracyclines in France (estimated at over 65% in 2021), which is considerably higher than what has been reported elsewhere, including Canada[31]. The ANRS 174 protocol results[30] were entirely consistent with those of the above-mentioned Luetkemeyer doxy-PEP study[29].

iii) Doxycycline pre-exposure prophylaxis (PrEP) of B-STIs

In a non-blinded pilot study, 30 PLWH with a history of ≥2 prior episodes of syphilis were randomized to receive doxy-PrEP with doxycycline 100 mg once daily for 36 weeks or an incentive-based financial contingency management (CM)[32]. The doxycycline recipients were less likely to develop any B-STI during follow-up compared to the CM recipients (odds ratio 0.27, 95% CI: 0.09 to 0.83, p=0.02).

Similar results were reported from a recent pilot Canadian multicenter study, including BC-CfE and BCCDC investigators, the Dual Daily HIV and Syphilis (DuDHS) trial. This was a trial aimed to determine the feasibility of using emtricitabine/tenofovir orally one daily (PO-OD) for HIV-PrEP together with doxycycline 100mg PO-OD for syphilis/chlamydia prevention among high-risk MSM. Analysis was conducted following the first 24 weeks of follow-up of the 52

subjects enrolled, when the deferred treatment arm had not yet received doxycycline[33]. During the first 24 weeks, there were four B-STIs in the immediate treatment arm equating to an incidence rate of 34.9 cases per 100 person-years (95% CI: 13.1 to 93.0) and 17 B-STIs in the deferred treatment arm equating to an incidence rate of 159.7 cases per 100 person-years (95% CI: 99.3 to 257.9)[33]. There were no cases of syphilis or chlamydia in the immediate treatment arm; in the deferred treatment arm, there was one case of syphilis (8.7 per 100 person-years; 95% CI: 1.2 to 62.0) and nine cases of chlamydia (78.7 per 100 person-years; 95% CI: 40.9 to 151.2). Individuals in both treatment arms contracted gonorrhea; four in the immediate treatment arm (34.9 per 100 person-years; 95% CI: 13.1 to 93.0) and seven in the deferred treatment arm (62.0 per 100 person years; 95% CI: 29.6 to 130.1). While the study was quite small, it is noteworthy that the protective effect reported was consistent to that reported in the Luetkemeyer study[29].

iv) Doxycycline chemoprophylaxis of B-STI – Women

The role of doxycycline chemoprophylaxis for B-STIs among women remains less clear. This issue was specifically addressed in a recent trial reported at CROI 2023[34]. A total of 449 women on daily HIV-PrEP in Kenya, were randomized to receive post-coital doxycycline or standard of care, using a protocol similar to Luetkemeyer's[29]. There was no statistically significant difference in the cumulative incidence of B-STIs during the study, with a total of 50 cases on doxycycline and 59 in the standard-of-care group (relative risk [RR] 0.88, 95% CI: 0.60 to 1.29, p=0.51). More specifically, chlamydia occurred in 35 women in the doxycycline group and 50 in the standard-of-care group (RR 0.73, 95% CI: 0.47 to 1.13). Gonorrhea occurred in 19 and 12 women, respectively (RR 1.64, 95% CI: 0.78 to 3.47). There was only one case of syphilis diagnosed during the study, which does not allow for meaningful disease specific comparisons. It remains currently unclear why doxy-PEP appears to be ineffective at least with respect to preventing Chlamydia.

V) Drug resistance and doxycycline prophylaxis of B-STIs

The issue of antimicrobial resistance during doxy-PEP use was further evaluated in a study targeting gonorrhea, as well as *Staphylococcus aureus* from skin isolates, and other *Neisseria* species that commonly reside in the throat[35]. When the participants who were diagnosed with gonorrhea while they were in the study were considered, tetracycline resistant gonorrhea was more prevalent among those on doxy-PEP (30% vs 11%). This suggests that doxy-PEP may be less protective against strains of gonorrhea that already have tetracycline resistance. Taking doxy-PEP affected the extent to which participants were "colonized" by *Staphylococcus aureus*, which can be associated with subsequent clinical staphylococcal infections. Doxy-PEP reduced colonization from 44% to 31%, but the cultures that were resistant to doxycycline went up from 5% to 13%, a small but statistically significant increase. There was no increase in the presence of methicillin resistant Staphylococcus aureus (MRSA) overall or with doxycycline-

resistant MRSA. Other throat-based *Neisseria* species did not appear to be affected by doxy-PEP use; doxycycline resistance was already present in about two-thirds of these bacteria, and this did not change significantly after 12 months of Doxy-PEP. The potential impact of long term-antibiotic use on microbiome, and community-level antimicrobial resistance warrant continued monitoring of this important issue.

Summary of recent Doxy-PEP and Doxy-PrEP studies. Taken together, the data available to date provides compelling evidence in support of recommending doxycycline chemoprophylaxis of B-STIs among selected MSM and transgender women, including high-risk PLWH on ART, and all HIV-PrEP recipients. Currently, this recommendation does not include cisgender women or transgender men who are either living with HIV or taking antiretroviral HIV-PrEP due to the lack of clinical trial evidence supporting the use of Doxy-PEP or Doxy-PrEP in these populations.

V. TREATMENT

Penicillin formulations which combine short- and long-acting penicillins, e.g., benzathine-procaine penicillin (Bicillin C-R) are not recommended for syphilis treatment, but sometimes have been given inadvertently instead of the standard benzathine penicillin[36].

a) Early syphilis.

Primary and secondary syphilis in adults

Recommendation: benzathine penicillin G 2.4 million units IM as a single dose(AII).

Discussion. Concerns that some PLWH have had suboptimal responses to standard therapy[37] have prompted trials of augmented antibiotic therapy for early syphilis. However, multiple studies of alternate treatment regimens have failed to demonstrate improved outcomes using either 2 or 3 once-weekly doses of benzathine penicillin[38,39] or a single dose of benzathine penicillin enhanced with the addition of a 10-day course of amoxicillin with probenecid[40]. One observational study from Taiwan[41] reported similar response rates with 1 vs 3 weekly doses of benzathine penicillin; however in follow-up, the single dose group had more patients with 4-fold RPR titre rises which were categorized as treatment failures. However, these latter cases may have been misclassified as treat failures instead of being categorized as reinfections, as discussed in the report of a similar study[38].

b) Latent syphilis

- Early latent syphilis (<1 year duration)

Recommendation: benzathine penicillin G 2.4 million units IM as a single dose(AII).

- Late latent syphilis (>1 year duration, or unknown duration)

Recommendation: benzathine penicillin G 2.4 million units IM once weekly for 3 doses (total 7.2 million units)(AII).

Discussion. The optimal management is unclear for non-pregnant people with late latent syphilis (or syphilis of unknown duration) who are not available to receive their 2nd or 3rd doses of benzathine penicillin G on time on days 7 and 14 of treatment[22,42]. However, based upon pharmacologic and in vitro studies[42] and clinical experience[22], consideration of the need to restart the series of 3 doses is related to the length of the delay in dosing as outlined in the table below[43]. For dosage intervals of 10 days, there may be suboptimal penicillin concentrations for less than 30 hours.

Interval between doses	Assessment
• 7 days	Gold standard
• 7-9 days	Acceptable (missed doses >9 days are not acceptable for **pregnant people** and require retreatment)
• 6-10 days	Acceptable
• 11-14 days	May be acceptable based on clinical experience;[22] consider retreatment
• >14 days	Inadequate; retreatment indicated

c) Tertiary syphilis

• Cardiovascular syphilis or gummas, provided there is no evidence of neurosyphilis such as signs or symptoms or cerebrospinal fluid abnormalities.

Recommendation: benzathine penicillin G 2.4 million units IM once weekly for 3 doses (total 7.2 million units)(AII).

d) Neurosyphilis, Ocular syphilis, and Otosyphilis

Recommendation: aqueous crystalline penicillin G 18-24 million units/day given as 3-4 million units IV every 4 hours or by continuous infusion for 10-14 days.

Given that this duration of treatment is shorter than that recommended for late latent syphilis, the addition of benzathine penicillin G 2.4 million units once weekly for 1-3 weeks can be considered upon completion of the course of intravenous penicillin(AII).

Discussion. Adjunctive systemic corticosteroid therapy has been used for ocular syphilis and otosyphilis; however, its efficacy has not been established.

e) Management of sex partners

This is usually handled by public health. Individuals who have had sexual contact with someone who has been diagnosed with primary, secondary, or early latent syphilis less than 90 days before the diagnosis was made should be treated presumptively, regardless of their serologic results(AII). However, when this time interval is >90 days and serology is not yet available and follow-up is uncertain, then treatment should be recommended presumptively(AIII). Treatment is not needed if the serology is negative[22].

f) Response to treatment

A serologic response to treatment for **primary or secondary syphilis** is a fourfold decrease in the RPR titre over 12 months, compared to the titre at the time of treatment. Clinical and serologic follow-up for PLWH should be done at 3, 6, 9, 12, and 24 months[22]. However, up to 20% of those who complete standard therapy do not have a fourfold decline in titre by 12 months. Later stage syphilis, older age, and lower initial RPR titre (<1:8) at diagnosis are less likely to achieve a fourfold titre decrease. Serologic response for **latent syphilis** is defined as a fourfold decrease in titre over 24 months which should be monitored at 6, 12, and 24 months[22]. All patients without a serologic response need further follow-up with neurological examinations, and repeat serology. The reason for persistent detectable non-treponemal antibodies (e.g., RPR test) in a given patient may or may not be due to ongoing syphilis disease activity, and includes various causes of biologic false positives, one of which is HIV disease related to antiphospholipid antibodies being produced due to B-cell dysregulation[44].

The need for further antibiotic treatment in patients who prove to be serologic non-responders is unclear and in clinical trials of such individuals additional antibiotic therapy was not associated with improved serologic responses[13,45,46]. In the absence of clinical symptoms and signs (particularly neurological) or a fourfold increase in RPR titre (suggestive of reinfection), an approach of "watchful waiting" rather than CSF examination and further doses of benzathine penicillin may be the most appropriate management plan, at least until 12 or 24 months following treatment for early or late stage syphilis, respectively[22,47].

Neurosyphilis. Immunocompetent persons and PLWH who taking effective ART and are clinically responding to treatment for neurosyphilis may not require follow-up CSF examinations since a favourable serum RPR serologic response predicts normalization of abnormal CSF results[48,49].

The Jarisch-Herxheimer reaction is an acute febrile episode associated with myalgias and headache within the first 24 hours of starting any antibiotic treatment. The reaction is usually self-limited after a few hours; however, sometimes more severe symptoms or complications develop (e.g., hypotension, myocardial injury)[50]. It occurs more often in association with early syphilis when the spirochete burden is highest. It is not an allergic reaction to the antibiotic, and patients should be warned regarding this possible complication.

Recommendations:

- Patients with persistent/recurrent symptoms compatible with primary or secondary syphilis and a fourfold increase in RPR titre are likely reinfected and should be retreated with benzathine penicillin G 2.4 million units IM once weekly for 3 doses (total 7.2 million units).
- Neurologic symptoms or signs should prompt CSF examination and treatment accordingly.

- Asymptomatic patients without a serologic response can be considered for CSF examination since this may be due to unrecognized CNS infection and should be considered for referral to a specialist.

g) Penicillin allergy

If penicillin allergy de-labeling is successful, then treatment with benzathine penicillin G should be offered. If penicillin allergy is confirmed, and there are doubts about adherence to treatment and follow-up, then penicillin desensitization and benzathine penicillin G should be considered. Otherwise, alternative antibiotic options are as follows, according to the stage of syphilis:

i) Primary and secondary syphilis in non-pregnant adults (with or without HIV infection)[22,23].

- Doxycycline 100 mg PO twice daily for 14 days(BII), ***or***
- Ceftriaxone 1 gm IV or IM daily for 10 days(BII)

Discussion. The development of widespread macrolide resistance in *Treponema pallidum* has resulted in the recommendation to no longer use azithromycin in the treatment of syphilis[51,52].

ii) Early latent syphilis (<1 year) in non-pregnant adults without HIV infection

- Doxycycline 100 mg PO twice daily for 14 days[22,23](BII)
- Ceftriaxone 1 gm IV or IM daily for 10-14 days(BII)

iii) Late latent syphilis (>1 year or unknown duration) in non-pregnant adults without HIV infection

- Doxycycline 100 mg PO twice daily for 28 days[22,23](BII)

Discussion. Another possible treatment consideration for early and late latent syphilis is ceftriaxone 1 gm IV or IM daily for 10 days[22]. Close serologic and clinical follow-up is advised for individuals receiving alternative treatments for latent syphilis given the dearth of clinical trial data. This concern applies particularly to PLWH, for whom penicillin allergy testing and desensitization is preferred. Specialist referral is recommended.

iv) Neurosyphilis, ocular syphilis, and otosyphilis.

- Ceftriaxone 2 gm IV or IM daily for 10-14 days(BII)

Discussion. PLWH should be referred for penicillin allergy testing and desensitization in order to receive optimal therapy with penicillin. There is some evidence supporting the use of ceftriaxone as an alternative treatment. A recent multicentre observational study reported from France demonstrated similar response rates for intravenous penicillin and ceftriaxone in neurosyphilis[53,54].

VI. PREGNANCY

Syphilis in pregnancy is associated with negative outcomes for both mother and child including the risk for congenital infection, prematurity, intrauterine growth restriction, fetal hydrops, low birth weight, stillbirth, and neonatal death. Maternal co-infection with syphilis enhances perinatal transmission of HIV[55], and rates of congenital syphilis are higher among pregnant women living with HIV. The most important risk factor for congenital syphilis infection is poor access to and engagement in prenatal care. All pregnant women living with HIV and/or syphilis infection should be referred to the Oak Tree Clinic at BC Women's Hospital and Health Centre for comprehensive maternal-fetal care (http://www.bcwomens.ca/health-professionals/refer-a-patient/oak-tree-clinic).

Diagnosis. Serologic testing for syphilis should happen at the first prenatal visit along with other perinatal screening[56]. Screening at delivery or after 35 weeks for those with a planned home birth is now standard of care[57]. For women living in communities with high rates of syphilis, or with ongoing risk factors for acquiring syphilis (e.g. multiple partners, drug use-related or transactional sex, late onset of prenatal care in 2nd or 3rd trimester, substance use, or unstable housing), screening should occur either monthly or at each trimester, not only for syphilis but for all STIs.

Syphilis diagnosed at any time during pregnancy requires specialized fetal assessments. In addition to treatment for syphilis, those with syphilis in pregnancy should have a detailed ultrasound looking for evidence of congenital syphilis performed at a quaternary ultrasound facility. Monitoring for adverse pregnancy events is required, and in most cases this includes ultrasounds every 4 weeks for signs of congenital syphilis, growth restriction and fetal hydrops. Pregnant women and persons should have RPR titres followed closely, ideally each trimester regardless of the timing of diagnosis to help evaluate for risk of treatment failure, re-infection and to help determine the need for neonatal treatment.

The diagnosis of congenital syphilis is complicated by transplacental transfer of maternal antibodies to the fetus which makes interpretation of reactive serologic tests for syphilis in neonates difficult. Treatment decisions are based on adequacy of maternal treatment and clinical, laboratory or radiographic evidence of syphilis in the neonate. Both Pediatric Infectious Diseases at BC Children's Hospital (http://www.bcchildrens.ca/our-services/clinics/infectious-diseases) and BCCDC (http://www.bccdc.ca/our-services/programs/sti-hiv-services) program are available for consultation. Syphilis exposed neonates should be evaluated with careful clinical exam and paired serum serologic testing with the mother to compare RPR titres. Infant RPR titres ≥4-fold the corresponding maternal titer strongly suggests congenital infection. If the mother was either not treated or treated <4 weeks prior to delivery, the baby should have a full assessment for congenital syphilis and be treated. Further details are available from the Canadian Pediatric Society (https://cps.ca/en/documents/position/congenital-syphilis)[58].

Treatment. Penicillin is the only antimicrobial with established efficacy for the treatment of congenital syphilis and prevention of congenital anomalies[59,60].

Primary, secondary, or early latent syphilis

Recommendation: benzathine penicillin G 2.4 million units IM as a single dose(AII).

Discussion. There is limited evidence supporting the use of two doses of benzathine penicillin G 2.4 million units IM one week apart for the prevention of congenital syphilis in pregnancy[61,62].

Latent or tertiary syphilis, neurosyphilis, ocular syphilis, and otosyphilis

Recommendation: all of these forms of syphilis should be treated with penicillin as for non-pregnant adults, as outlined above(AII).

Penicillin allergy. Those with a history of penicillin allergy should be evaluated for skin testing, and if allergic then desensitized and treatment with penicillin should occur with specialized support(AIII). There is inadequate experience with ceftriaxone to support its use for maternal syphilis(BIII). Doxycycline, tetracycline, and the macrolides (e.g., azithromycin and erythromycin) are not recommended because they do not treat the fetus or provide reliable maternal efficacy due to macrolide resistance(AII).

Jarisch-Herxheimer reaction may occur at anytime during pregnancy, however after fetal viability (e.g., 23+ weeks gestation age) may be associated with fetal distress or premature labour and treatment should be done in a centre with the capacity to support delivery based on the gestational age of the fetus.

Congenital syphilis.

Recommendation: Infants with possible or probable congenital syphilis infection should be treated with IV aqueous crystalline penicillin G 100,000-150,000 units/kg/day. Ongoing well baby care should be in place.

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