Spotlight on Syphilis:
Clinical Update for 2017

Julie Stoltey, MD, MPH
California Department of Public Health - STD Control Branch
California Prevention Training Center
Overview:

• Screening recommendations
• Natural history
• Treatment
• Diagnostics
• Complications
  – Neurosyphilis and ocular syphilis
  – Congenital syphilis
Who Should be Screened for Syphilis?

- Pregnant women at first prenatal visit
  - And again in the third trimester and at delivery (if at high risk, or residing in area with high syphilis morbidity)
- MSM, including those on PrEP
  - Annually, or more frequently, 3-6 months if at high risk (multiple, anonymous partners, meth use)
- Correctional settings
  - Universal screening based on local area or institutional incidence
- HIV-infected individuals (at least annually)
- STD clinics / Clients with other STDs
USPSTF Syphilis Screening
Updated Recommendations in 2016

Non-Pregnant Adult/Adolescents

• USPSTF recommends screening in persons at increased risk for infection (Grade “A” recommendation)
  – Risk Assessment
    • MSM and HIV-infected individuals “highest risk for syphilis”
    • Other factors associated with increased prevalence rates include: history of incarceration or CSW, geography, race/ethnicity, male <29 yrs

• Optimal screening interval not well established
  – More frequent in MSM/HIV+ suggested by some data
    • Every 3 months enhances detection compared to annually

Syphilis Natural History

Exposure 30-50%

Primary 2-6 weeks

Secondary Possible relapse

Latent 2-20 years

Tertiary

Neurosyphilis and Ocular Syphilis can occur at any stage

Incubation Period 3-4 weeks

Possible after 3-8 weeks lesions disappear spontaneously

STD Atlas, 1997

Courtesy: Gregory Melcher, UC Davis
Susan Philip, SF DPH & UCSF
Treatment is Based on Duration of Infection

PRIMARY, SECONDARY, and EARLY LATENT (< 1 year)

Benzathine penicillin G 2.4 million units IM in a single dose

LATE LATENT or UNKNOWN DURATION

Benzathine penicillin G 2.4 million units once per week for 3 weeks

Bicillin L-A is the trade name. DO NOT USE Bicillin C-R!

Only one dose of PCN is recommended for early syphilis in HIV-infected persons, extra doses not needed.

CDC 2015 STD Treatment Guidelines www.cdc.gov/std/treatment
Serologic Response to Therapy in HIV-infected Persons with Early Syphilis

Syphilis Treatment Alternatives for Penicillin Allergic Non-Pregnant Adults

Primary, Secondary, & Early Latent
- Doxycycline 100 mg po bid x 2 weeks
- Tetracycline 500 mg po qid x 2 weeks
- Ceftriaxone 1 g IV (or IM) qd x 10-14 d
- Azithromycin 2 g po in a single dose*

Late Latent
- Doxycycline 100 mg po bid x 4 weeks
- Tetracycline 500 mg po qid x 4 weeks

In pregnancy, benzathine penicillin is the only recommended therapy. No alternatives.

* Do NOT use azithromycin in MSM or pregnant women
Speaking of Bicillin...

Bicillin (benzathine penicillin G) drug shortage update
## Penicillin G Benzathine (Bicillin L-A) Injection

**Status:** Currently in Shortage

- **Date first posted:** 04/29/2016
- **Therapeutic Categories:** Anti-Infective; Pediatric

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Availability and Estimated Shortage Duration</th>
<th>Related Information</th>
<th>Shortage Reason (per FDASIA)</th>
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</thead>
<tbody>
<tr>
<td>Bicillin® L-A (penicillin G benzathine suspension) 600,000U Pediatric Injection Rx (NDC 60793-700-10)</td>
<td>Product on allocation. Next delivery anticipated February 2017. Supply improvement by Q1 2017. Contact Pfizer Customer Service at 800-533-4535.</td>
<td>Continuous shipments to wholesalers and distributors. Please check wholesalers and distributors for inventory. For immediate need, please contact the Pfizer Supply Continuity team at 844.804.4677 to assist in obtaining supply. Dear Customer Letter</td>
<td>Manufacturing delay</td>
</tr>
<tr>
<td>Bicillin® L-A (penicillin G benzathine suspension) 1,200,000U/2mL (NDC 60793-701-10)</td>
<td>Product on allocation. Next delivery anticipated December 2016. Supply improvement by Q1 2017. Contact Pfizer Customer Service at 800-533-4535.</td>
<td>Continuous shipments to wholesalers and distributors. Please check wholesalers and distributors for inventory. For immediate need, please contact the Pfizer Supply Continuity team at 844.804.4677 to assist in obtaining supply. Dear Customer Letter</td>
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<tr>
<td>Bicillin® L-A (penicillin G benzathine suspension) 2,400,000U/4mL (NDC 60793-702-10)</td>
<td>Product on allocation. Next delivery anticipated December 2016. Supply improvement by Q1 2017. Contact Pfizer Customer Service at 800-533-4535.</td>
<td>Continuous shipments to wholesalers and distributors. Please check wholesalers and distributors for inventory. For immediate need, please contact the Pfizer Supply Continuity team at 844.804.4677 to assist in obtaining supply. Dear Customer Letter</td>
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Message from CDC regarding the recent shortage of Penicillin G benzathine in the United States

Penicillin G benzathine is the recommended treatment for syphilis and the only recommended treatment for pregnant women infected or exposed to syphilis. Pfizer, the sole manufacturer of penicillin G benzathine (Bicillin L-A®) in the United States continues to experience a manufacturing delay of this product. CDC is working with FDA’s Drug Shortage Staff and

More information on recommended syphilis treatment and clinical management can be found in the 2015 STD Treatment Guidelines [http://www.cdc.gov/std/treatment/2015/syphilis.htm]. CDC is not recommending any changes to these treatment recommendations for patients with syphilis.

2. Adhere to the recommended dosing regimen of 2.4 million units of penicillin G benzathine IM for the treatment of primary, secondary and early latent syphilis (i.e., early syphilis) as outlined in the 2015 STD Treatment Guidelines. Additional doses to treat early syphilis do not enhance efficacy, including in patients living with HIV infection.

3. Contact your pharmacists/distributors to procure penicillin G benzathine (Bicillin L-A®), if you do not have product readily available. If product reaches a critical supply level of three weeks or less, contact Pfizer. The company contact information can be found on the FDA’s Drug Shortage Website [https://www.fda.gov/cder/shortages/]. Also, alert your state or local STD Prevention Program of any shortage of penicillin G benzathine (Bicillin L-A®) as they are informing CDC of any shortages.

4. Direct questions about syphilis clinical management to an infectious disease specialist or the on-line National Network of STD Clinical Prevention Training Centers (NNPTC) STD Clinical Consultation Network [https://www.stdccn.org/].
Summary: Bicillin L-A Shortage

- Bicillin L-A shortage appears to be ongoing; possible resolution in 1st quarter 2017
- CDPH conducted survey of a convenience sample of local health jurisdictions over the summer and identified >4000 Bicillin doses
- Recommendations:
  - Monitor Bicillin supply at your facility
  - If critical shortage and unable to purchase from your distributor:
    - Contact Pfizer Supply Continuity Team
    - Determine if other facilities in your jurisdiction have ample product that could be shared
    - Notify us at STD Control Branch ashley.williamson@cdph.ca.gov
Note: There is also a Penicillin G Procaine shortage

• Penicillin G procaine is one of the recommended treatments for congenital syphilis and an alternative treatment for neurosyphilis and ocular syphilis
• Penicillin G procaine is currently unavailable
• Pfizer estimates product may be available starting in April 2017
• Until it is available, use recommended regimens to treat these conditions that are outlined in the STD Treatment Guidelines
Point-of-Care Syphilis Tests

Rapid Immunochromatographic Assays: lateral flow immunoassays (e.g. rapid HIV-antibody tests, urine HCG)

- Syphilis Health Check (Trinity Biotech)
- Treponemal only (3rd gen EIA format, detects IgG and IgM)
- Results in 10 min
- FDA approved, CLIA waived

- DPP Syphilis Screen and Confirm (ChemBio)
- Combined treponemal and non-treponemal results
- Results in 15 min
- Not yet available in US
Syphilis Health Check

- Test useful only in individuals with no prior history of syphilis
- Kits are stored at room temperature, and are stable for 2 years/controls need to be refrigerated
- Public health pricing is available
### Notes from the Field: Evaluation of the Sensitivity and Specificity of a Commercially Available Rapid Syphilis Test — Escambia County, Florida, 2016

Weekly / October 28, 2016 / 65(42):1174–1175

<table>
<thead>
<tr>
<th>Syphilis Health Check result</th>
<th>Trep-Sure (EIA) result</th>
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<tbody>
<tr>
<td></td>
<td>Reactive</td>
</tr>
<tr>
<td>Reactive (26)</td>
<td>10</td>
</tr>
<tr>
<td>Nonreactive (176)</td>
<td>4</td>
</tr>
<tr>
<td>Total (202)</td>
<td>14</td>
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**Testing agreement% (95% CI)**

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<table>
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<tr>
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<tbody>
<tr>
<td>Sensitivity*</td>
<td>71.4 (41.9–95.1)</td>
</tr>
<tr>
<td>Specificity*</td>
<td>91.5 (87.5–95.5)</td>
</tr>
<tr>
<td>Overall agreement</td>
<td>90.1 (86.0–94.2)</td>
</tr>
</tbody>
</table>

Matthias et al. MMWR 2016;65:1175-5.
Summary: Rapid Syphilis Test

- Syphilis Health Check™ is FDA-approved CLIA-waived option for rapid syphilis testing in the U.S.
- SHC has potential benefits for use as screening or confirmatory testing in the right population/setting
- There are initial reports of issues with both sensitivity and specificity of the test
  - Training and technical assistance are essential when initiating use of this test
- California code adds layer of complication to roll out of SHC testing and limits use to ‘health care personnel providing patient care’
Ocular Syphilis
Ocular Syphilis Cluster

Public Health - Seattle & King County

HIV/STD Program

Web content notice

Ocular Syphilis in King County: January 21, 2015

Six cases of ocular syphilis have been diagnosed in WA state since mid-December, 2014, including four cases in King County.

- **Health care providers**: This relatively large number of cases – including two cases that have led to blindness – should prompt medical providers to be particularly vigilant.
  - [Download the full advisory](#) (PDF).

- **For the public**: Know the signs and symptoms of ocular syphilis. Get tested. Get cured.
  - [Download the Public Health alert for gay and bi men](#) (PDF).

- **En español**: Sífilis ocular en el Condado de King: 21 de enero, 2015 (PDF)

- **HIV / STD testing in Seattle & King County**
  Where, why and how to get tested for HIV / STD in Seattle and King County

- **For health care providers**
  HIV and STD resources for medical providers
Notes from the Field


Sophie Woolston, MD; Stephanie E. Cohen, MD; Robyn Neblett Fanfair, MD; Sarah C. Lewis, MD; Christina M. Marra, MD; Matthew R. Golden, MD

From December 1, 2014, to January 30, 2015, in King County, Washington, four cases of ocular syphilis, defined as clinical signs or symptoms consistent with ocular disease (e.g., uveitis or vision loss) in a person with laboratory-confirmed syphilis of any stage, were reported. All four cases occurred in men who have sex with men (MSM), two of whom were sex partners. Median age of the four patients was 39 years (range, 28–52 yrs). Three of the patients were infected with 3 HIV-infected. All treated. 2 considered legally blind after 5 months.

Dec 2014-Mar 2015: 8 cases in San Francisco
• 6 MSM
• 7 HIV-infected
• All treated
• 1 with permanent vision loss in one eye after 3 months

https://www.cdc.gov/mmwr/pdf/wk/mm6440.pdf

Slide courtesy of Drs. Torrone & Kidd, CDC
Clinical Advisory: Ocular Syphilis in the United States

Updated April 16, 2015

Since December 2014, 24 cases of ocular syphilis have been reported from California and Washington, with several other states reporting potential cases. The majority of cases have been among HIV-infected MSM; a few cases have occurred among HIV-uninfected persons including heterosexual men and women. Several of the cases have resulted in significant sequelae including blindness.

Neurosyphilis can occur during any stage of syphilis including primary and secondary syphilis. Ocular syphilis, a clinical manifestation of neurosyphilis, can involve almost any eye structure, but posterior uveitis and panuveitis are the most common. Additional manifestations may include anterior uveitis, optic neuropathy, retinal vasculitis and interstitial keratitis. Ocular syphilis may lead to decreased visual acuity including permanent blindness. While previous research supports evidence of neuropathogenic strains of syphilis, it remains unknown if some Treponema pallidum strains have a greater likelihood of causing ocular infections.

- Clinicians should be aware of ocular syphilis and screen for visual complaints in any patient at risk for syphilis (MSM, HIV-infected persons, others with risk factors and persons with multiple or anonymous partners).
- All patients with syphilis should receive an HIV test if status is unknown or previously HIV-negative. If the test result is positive, providers should consult with a public health expert.
Morbidity and Mortality Weekly Report

Ocular Syphilis — Eight Jurisdictions, United States, 2014–2015

Sara E. Oliver, MD1,2; Mark Aubin3; Leah Atwell, MPH4; James Matthias, MPH4,5; Anna Cope, PhD5,6; Victoria Mobley, MD6; Alexandra Goode, MSc7; Sydney Minnerly, MA8; Juliet Stoltey, MD9; Heidi M. Bauer, MD9; Robin R. Hennessy, MPH5,10; Dawne DiOrio, MPA5,11; Robyn Neblett Fanfair, MD12; Thomas A. Peterman, MD5; Lauri Markowitz, MD2

Ocular syphilis, a manifestation of *Treponema pallidum* infection, can cause a variety of ocular signs and symptoms, including eye redness, blurry vision, and vision loss. Although syphilis is nationally notifiable, ocular manifestations are not reportable to CDC. Syphilis rates have increased in the United States since 2000. After ocular syphilis clusters were reported in early 2015, clusters of ocular syphilis cases were reported in Washington and California. CDC issued a clinical advisory, notifying clinical providers and health departments of a potential increase in suspected ocular syphilis cases. After this advisory, eight jurisdictions performed a review of syphilis surveillance and case investigation data to identify syphilis
Proportion of total syphilis cases with suspected ocular syphilis, 2014-2015

Case definition: Patient who met the case definition of syphilis with concurrent ocular signs or symptoms

CA: 2014 0.77 2015 0.77
FL: 2014 0.45 2015 0.17
IN*: 2014 1.1 2015 0.96
MD: 2014 0.66 2015 0.24
NYC: 2014 0.2 2015 0.2
NC: 2014 1.2 2015 1.7
TX: 2014 0.37 2015 0.19
WA: 2014 3.2 2015 3.9
Total: 2014 0.53 2015 0.65

*Indiana only reviewed cases in 2015

MMWR Nov 4 2016; 65(43):1185-88.
Slide courtesy of Drs. Torrone & Kidd, CDC
Suspected ocular syphilis, 8 jurisdictions, 2014-2015 (n=388)

- 93% male
  - 69% of males were MSM
- 56% white, 20% black, 12% Hispanic
- 51% HIV-infected
- Stage at diagnosis
  - 2% primary
  - 26% secondary
  - 20% early latent
  - 50% late or unknown duration
- 84% reported symptoms
  - 65% blurry vision
  - 33% vision loss
  - 14% pain or red eye
- 41% had eye exam
- 45% has CSF analysis with results available
  - 70% had reactive VDRL

MMWR Nov 4 2016; 65(43):1185-88.
Slide courtesy of Drs. Torrone & Kidd, CDC
What stage(s) of syphilis involves the eye? What part(s) of the eye is/are involved?

- **Every** part of the eye can be involved during **any** stage of the infection. (Semin Ophthalmol 2005; 20:161–167)
- Majority of eye manifestations associated with syphilis are also associated with many other infectious and non-infectious diseases.

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**Diagram:**

- **Exposure:** 30-50%
  - **Incubation Period:** 3-4 weeks
- **1<sup>o</sup>**
  - 2-6 weeks
- **2<sup>o</sup>**
  - 25%
  - After 3-8 weeks lesions disappear spontaneously
- **Latent**
  - 2-20 years
- **Tertiary**
  - 30%

**Legend:**

- Neurosyphilis and ocular syphilis can occur at any stage.
Certain *T. pallidum* Strains Are Associated with Neurosyphilis

- Evaluated in ongoing study of neurosyphilis in Seattle
  - 50% (n=22) of patients with strain type 14d/f had neurosyphilis, compared to
  - 23% (n=9) of patients with other strain types had neurosyphilis

- Rabbit studies
  - Animals infected with 14a/a strain and 14d/f strain had greatest degree of neuroinvasion

Marra et al. JID 2010
Tantalo et al. JID 2005
Molecular Typing of *Treponema pallidum* in Ocular Syphilis

Sara Oliver, MD, MSPH,* Sharon K. Sahi, BS,† Lauren C. Tantalo, BS,† Charmie Godornes, BS,♭
Robyn Neblett Fanfair, MD, MPH,* Lauri E. Markowitz, MD,*
Sheila A. Lukehart, PhD,♭ and Christina M. Marra, MD†

- Samples from 18 patients with ocular syphilis and from 45 patients with syphilis (but without ocular symptoms) in 2015 were typed
  - At least 5 distinct strain types of *T. pallidum* were identified in ocular syphilis patients
  - 9 types identified in Seattle nonocular patients
  - 14d/g was most common type in both groups
  - Small sample size but no clear evidence of a predominant oculotropic strain causing ocular syphilis currently; limited data though

Ocular Syphilis: What do clinicians need to know?

- Clinicians should be on the alert for ocular syphilis => delays in diagnosis have been associated with visual loss*
  
  - Order syphilis serology test in patients with:
    - Visual complaints and risk factors for syphilis, or
    - Ophthalmologic findings compatible with syphilis, and
    - Order both treponemal and nontreponemal tests as prozone effect has been noted in patients with ocular syphilis

- Ask patients with syphilis about changes in their vision and conduct neurologic exam

- Patients with positive syphilis serology and visual complaints should receive immediate ophthalmologic evaluation

*Moradi Am J Ophthal 2015
Patients with suspected ocular syphilis should receive:

- Lumbar puncture with CSF examination
  - Note: a negative LP does not rule out ocular syphilis
- Treatment for neurosyphilis
- HIV test

Report cases of syphilis to the health department within 1 day

Save and store **pre-antibiotic** clinical samples at **-80°C** for molecular typing (coordinated through CDC)
Ocular Syphilis/Neurosyphilis Treatment

- **Recommended regimen:**
  - Aqueous crystalline penicillin G 18-24 million units IV daily administered as 3-4 million units IV q 4 hr for 10-14 days

  Consider: BIC 2.4 million units IM once per week up to 3 weeks after completion of 10-14 day course for late syphilis

CDC 2015 STD Treatment Guidelines
Otosyphilis

- **Diagnostic criteria**: cochleovestibular dysfunction (e.g., tinnitus, vertigo) and syphilis infection without an alternate diagnosis; ~50% bilateral
  - Diagnosis is presumptive; CSF examination is normal in 90% of cases
- **Therapy**: IV penicillin + corticosteroids

Laryngoscope 1973; 83:865-70
Laryngoscope 1977; 87:1765-1769
Laryngoscope 1984; 94:753-57

Laryngoscope 1983; 93:154

Slide courtesy Dr. Khalil Ghanem, Johns Hopkins
Summary: Ocular Syphilis

- Efforts are underway to characterize how commonly ocular syphilis occurs
- Clinicians and health department staff should remain vigilant for ocular syphilis and ensure appropriate treatment
Syphilis in Pregnancy and Congenital Syphilis
Early Congenital Syphilis (<age 2)

Common Presentations

- Asymptomatic presentations are common
  - ~2/3 infants born with CS are asymptomatic at birth – if untreated will develop symptoms
- Bone abnormalities
- Enlargement of liver +/- jaundice
  - Hepatomegaly present in almost all infants with CS
- Skin rash
- Nasal discharge (“snuffles”)
- Blood abnormalities
- Neurologic abnormalities
- Others
Early Congenital Syphilis

Asymptomatic presentations are common
Late Congenital Syphilis (>age 2)

Common Presentations

- Hearing loss (puberty – adulthood).
  - Can develop suddenly
- Interstitial keratitis (5 years old – adulthood)
  - Inflammation of tissue of cornea, can lead to vision loss
- Bone or tooth abnormalities
- Neurologic abnormalities
- Gummas (granulomatous inflammatory response to spirochetes) in the skin or mucous membranes
- Others
Late Congenital Syphilis
Screening Recommendations – CDC

• All pregnant women should be screened for syphilis at the first prenatal visit

• Women who are at high risk for syphilis, live in areas of high syphilis morbidity, or are previously untested should be screened again both:
  – Early in the third trimester (approx 28 weeks GA)
  – At delivery

Penicillin treatment of pregnant women with syphilis is highly effective at preventing CS
Screening Recommendations – CDC

• No infant should leave the hospital without the maternal serologic status having been determined at least once during pregnancy, and again at delivery if at risk

• Any woman who delivers a stillborn infant should be tested for syphilis
Risk of Fetal Infection by Stage

• Risk of fetal infection or congenital syphilis at delivery is related to stage of syphilis during pregnancy and *T. pallidum* bacteremia
  – Highest risk during primary and secondary syphilis stages
  – Risk of fetal infection still significant in pregnant women with late latent syphilis and low titers
Treatment of Syphilis in Pregnancy

• The only treatment of syphilis in pregnancy is penicillin. There are no alternatives.
• Pregnant women should be treated with the penicillin regimen appropriate for their stage of infection.
  – Some experts recommend a 2nd dose of benzathine penicillin G be given a week after the initial dose in early syphilis
• Pregnant women with penicillin allergy should be desensitized and treated with penicillin.

All patients with syphilis should be tested for HIV.
Syphilis in Pregnancy:
Time Between Doses for Latent Syphilis

Adherence to 7 day interval between doses in pregnancy is necessary

- 40% of pregnant women are below treponemidal levels after 9 days
- Restart entire series (3 weekly doses) if dose missed (interval >7 days)

CDC 2015 STD Treatment Guidelines
Syphilis in Pregnancy: Management

- During second half of pregnancy, management should include an obstetric ultrasound
  - Case should be managed with obstetric specialist
- Women treated during second half of pregnancy are at risk for premature labor and/or fetal distress as part of Jarisch-Herxheimer reaction
  - Counsel to seek medical attention if symptoms
  - Concern for this complication should not delay treatment
Evaluation of Infants Born to Mothers with Syphilis

- CDC Guidelines have detailed guidance on treatment → too complex to cover today
- Treatment decisions based on:
  - Identification of syphilis in the mother
  - Adequate maternal treatment
  - Clinical, lab, x-ray evidence of syphilis in neonate
  - Comparison of maternal (at delivery) and neonatal non-treponemal titers (same test-preferably same lab)
  - Do not use umbilical cord blood
  - Treponemal tests are not recommended

Maternal non-trep and trep IgG antibodies can transfer via placenta thus complicating interpretation of neonate serologies
Summary: Syphilis in Pregnancy and Congenital Syphilis

- Screen all pregnant women for syphilis; screen women at risk again in 3\textsuperscript{rd} trimester and at delivery
  - Some CA counties have established 3\textsuperscript{rd} trimester/delivery screening guidance for all pregnant women
- The only treatment of syphilis in pregnancy is penicillin
- Congenital syphilis is preventable with treatment
- Management of congenital syphilis cases can be complicated – seek clinical consultation if questions
Take Home Points: Syphilis

• As syphilis increases, we need to be vigilant in our efforts to reduce morbidity associated with the disease, including ocular syphilis and congenital syphilis

• Clinician education about syphilis, including local morbidity, screening guidance and associated complications, is important

• Clinical consultation is available to healthcare providers and health department staff

• Prioritize screening, diagnosis, and treatment of pregnant women => congenital syphilis is preventable!
Acknowledgments

• Sharon Adler
• Heidi Bauer
• Stephanie Cohen
• Khalil Ghanem
• Sarah Kidd
• Ina Park
• Lizzi Torrone
Clinical Guidelines and Consultation

STD Clinical Consult Line
510-620-3400
Enter your consult online: stdccn.org

CDC STD Treatment Guidelines App
Available now, free
Search for “STD TX”

juliet.stoltey@cdph.ca.gov

Thanks!