1) Discuss the changing epidemiology of syphilis in Iowa;
2) Explore key populations affected by syphilis, including MSM, women, and infants;
3) Review congenital syphilis;
4) Discuss screening and treatment recommendations for syphilis;
5) Explain the interpretation of various syphilis test results and how they impact diagnosis, staging, treatment, and follow up;
6) Describe newly available testing technologies and how they may be most effectively utilized.

For many years, syphilis was a relatively rare sexually transmitted infection (STI) in Iowa
* Typically had fewer than 30 cases of early syphilis and fewer than 70 for all stages
* Began to see a shift in 2012
  * Early syphilis cases more than doubled from year before
A large increase in the number of cases among men
- Of those, the majority were men who have sex with men (MSM), approx 80%
- Increases in those comorbid with HIV
- Some clusters associated with introduction from other, higher morbidity jurisdictions
- Became an epidemic among Iowa’s MSM
- Numbers increased among women also, but men represented a far greater percentage of cases (90%).
Populations affected by infectious syphilis

- MSM represent the greatest number of cases by far.
- Persons living with HIV account for 25-30% of new cases for the past 3 years.
- As syphilis increases in our state, other populations affected also.
  - In 2014, 17 cases of early syphilis among women. In 2011, 8 cases among women.
- Iowa experienced its first case of congenital syphilis in 7 years in 2014.
  - Occurred in rural Iowa

CDC screening recommendations

- Pregnant women
  - All pregnant women at the first prenatal visit
  - Retest early in the third trimester and at delivery if at high risk
- MSM
  - At least annually for sexually active MSM
  - Every 3 to 6 months if at increased risk
- Persons living with HIV
  - For sexually active individuals, screen at first HIV evaluation, and at least annually thereafter
  - More frequent screening might be appropriate depending on individual risk behaviors and the local epidemiology

Syphilis: the most complicated STI

- Syphilis is a complex STI that consists of differing stages of disease
  - Primary, secondary, and early latent are the early or infectious stages
  - Late latent is non-infectious, though can cause serious health complications for the individual
  - Neurosyphilis – not a stage but a manifestation in which bacteria reach the central nervous system; can occur at any stage
Syphilis – Stages of the Infection

**Primary**
- Characterized by painless chancres (sores) at the site of infection.
- Highly infectious.
- Resolves with or without treatment (approx. 3 weeks).

**Secondary**
- Characterized by diffuse rash and lymphadenopathy.
- Resolves with or without treatment (approx. 4 weeks).

**Early Latent**
- Resolution of signs but infection acquired <1 year ago.

**Late Latent**
- Infection >1 year ago
- Not infectious

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Signs of Primary Syphilis

![Signs of Primary Syphilis](image)

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Signs of Secondary Syphilis

![Signs of Secondary Syphilis](image)
Serological tests for syphilis

- Traditional sequence
  - Non-treponemal serological screening test
    - VDRL or RPR
    - Titer performed on reactive specimens
      - Monitor treatment
  - Reactive non-treponemal tests are confirmed by a treponemal test
    - Syphilis IgG, TPPA, or FTA
  - Biologic false positives do occur with non-treponemal tests
    - e.g., cross-reactivity in patients with autoimmune disorders

- Reverse sequence testing
  - Treponemal test performed first
    - e.g., EIA, syphilis IgG antibody
    - Reactive tests could mean: recent infection, latent infection, successfully treated syphilis, or a false positive
  - A non-treponemal test with titer is needed to determine follow up
  - Patient history is very important
Rapid syphilis testing

- There is now a CLIA-waived rapid syphilis test available in the U.S.!
- Trinity Biotech is the manufacturer
- Provides results in 10 minutes with whole blood (finger stick)
- Treponemal test
  - Useful for those with no history of syphilis. Cannot be used to screen for re-infection or determine success of treatment
- Follow the “reverse sequence”

Rapid syphilis testing

<table>
<thead>
<tr>
<th>Format</th>
<th>20 tests per kit</th>
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<td>Waived for Finger-dick whole blood only</td>
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<tr>
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Positive: Colored bands in test area AND control area
Negative: 1 colored band in control area

Rapid syphilis testing

- A great tool for those performing testing in the field (e.g., Disease Prevention Specialists) and in some clinic settings
- Positive results require further testing
  - RPR or VDRL should be run. If negative, another treponemal test must be done in order to determine whether the rapid was a false positive.
**Syphilis treatment**

- Easily treated and cured

- Primary, secondary or early latent syphilis:
  - 2.4 million units of long-acting benzathine penicillin G (Bicillin L-A), intramuscular injection

- Late latent syphilis:
  - Three injections, spaced 1 week apart, needed for late syphilis
  - Other penicillin derivatives used for neurosyphilis (most administered intravenously)

**Syphilis treatment – alternatives**

- Only to be used when patients have severe allergic reactions to penicillins (i.e., anaphylaxis).

- Primary, secondary or early latent syphilis:
  - 100mg doxycycline, b.i.d., for 14 days
  - 2 grams azithromycin in a single dose
    - LAST RESORT! – increasing resistance of T. pallidum to macrolides, especially in MSM populations

- Late latent syphilis:
  - 100mg doxycycline, b.i.d., for 28 days

**Syphilis treatment – alternatives**

- Treatment with any regimen other than Bicillin L-A requires very close monitoring to assure adequate treatment.

- Poor treatment adherence with doxycycline.

- Resistant bacteria with azithromycin.
Follow up

- Patients diagnosed with primary, secondary, or early latent syphilis (who are not comorbid with HIV):
  - Evaluate ASAP if signs/symptoms persist or recur – retreatment likely needed
  - Check titers 6 months after the completion of therapy.
    - Titer should decrease four-fold in 6-12 months (e.g., 1:128 at diagnosis, should drop to 1:32 or lower within 12 months).

- Patients who are comorbid with HIV:
  - Evaluate clinically and serologically at 3, 6, 9, 12, and 24 months after the completion of therapy.
  - Evaluating successful treatment after late latent diagnosis
    - May have had a non-reactive RPR at diagnosis. Follow up should include confirmation of non-reactive RPR and no signs/symptoms associated with syphilis.

Titers and history are important!

- Titers of non-treponemal tests are used to:
  - Useful for determining re-infection.
  - Treponemal tests are usually positive for life!
    - EIA, IgG, TPPA, FTA, etc. are antibody tests and often remain positive regardless of treatment.
  - Non-treponemal tests (e.g., RPR) are reactive at low levels for several decades for a subset of people.
    - “Serofast”
    - May remain at reactive at a low titer (e.g., 1:4 or less) for life.
  - Patient’s serologic and clinical history are always important when evaluating for syphilis.
Partner management

• Treating sex partners is vitally important to:
  • Prevent further spread of the infection.
  • Prevent the index patient from becoming re-infected.
  • Work with Public Health for help in locating partners and getting them in for treatment!
  • All sex partners of persons diagnosed with primary, secondary, or early latent syphilis should be presumptively treated, regardless of serological test results.

• All sex partners within 90 days should be treated, even if test results are negative.
  • Syphilis is an antibody test, may take time to seroconvert.
  • Sex partners from greater than 90 days prior to the diagnosis of early syphilis should be tested, at a minimum.
  • If any uncertainty of follow up with partner, treat presumptively.

• If the index patient’s titer is 1:64 or greater, treat all sex partners within the previous 90 days should be treated presumptively, regardless of index patient’s stage of infection.
• Late latent syphilis:
  • Long-term sex partners should be tested. Treat based on serologic and clinical findings.
**Sexual history**

- Remember to take a thorough sexual history.
- Syphilis can be transmitted via any type of sexual intercourse (e.g., vaginal, anal, or oral).
- Many have misconception that oral sex is safer.
  - There is truth to this for some STIs (e.g., HIV) but not for syphilis.
  - Primary syphilis is very contagious.

**Syphilis and pregnancy**

- Diagnosis and treatment history are very important in determining infection status.
- Pregnant women must be treated with Penicillin G
  - Those with allergy must be desensitized.
  - Women staged as late latent must have 3 doses spaced exactly 7 days apart.
- Untreated women have a high risk of passing the infection on to the fetus.
  - Risk is greater with early stages but can occur in late stages also.

**Congenital syphilis**

- Treponema pallidum infects the fetus or neonate.
- Transmission occurs transplacentally or while passing through the birth canal (primary syphilis).
- Spontaneous abortion or syphilitic stillbirth are possible.
- Infants that do survive to delivery often have severe health consequences.
**Congenital syphilis**

- Signs and Symptoms
  - Many are asymptomatic at birth.
  - Watery nasal discharge (becomes mucopurulent, crusting, and sanguinous) – known as “snuffles”
  - Secondary syphilis signs (e.g., rashes, lesions, condyloma lata) may develop
  - Hepatosplenomegaly, jaundice
  - Pseudoparalysis, anemia, or edema
  - Abnormalities of the long bones (seen in radiograph)

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**Serological tests for congenital syphilis**

- Mother’s past syphilis diagnoses and treatments are very important in assessing the neonate!
- Mother’s antibodies likely to cross placenta even if the bacteria do not.
- Meaning that even a mother who has been cured of syphilis may give birth to an infant with a reactive RPR, VDRL, TPPA, etc.

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**Scenario 1: Proven or highly probable congenital syphilis**

- Abnormal physical exam consistent with congenital syphilis;
  - OR
- An RPR or VDRL that is fourfold higher than the mother’s;
  - OR
- Positive darkfield test or PCR of lesions or body fluid
Scenario 1: Proven or highly probable congenital syphilis

- Recommended evaluation:
  - CSF analysis for VDRL, cell count, and protein
  - CBC with differential and platelet count
  - Others as clinically indicated
    - Long bone or chest radiographs
    - Liver-function tests
    - Neuroimaging, ophthalmologic exam, auditory brain stem response

- Recommended treatment:
  - Aqueous crystalline penicillin G 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
  OR
  - Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose for 10 days

Scenario 2: Possible Congenital Syphilis

- Neonate has normal physical exam and an RPR or VDRL titer less than fourfold higher than the mother, and:
  - Mother was not treated, inadequately treated, or has no documentation of treatment
  OR
  - Mother received recommended treatment <4 weeks before delivery
Scenario 2: Possible Congenital Syphilis

• Recommended evaluation:
  • CSF analysis for VDRL, cell count, and protein
  • CBC, differential, and platelet count
  • Long-bone radiographs

• Recommended treatment:
  • Aqueous crystalline penicillin G 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
  • OR
  • Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose for 10 days
  • OR
  • Benzathine penicillin G 50,000 units/kg/dose IM in a single dose

Scenario 3: Congenital Syphilis less likely

• Neonate has normal physical exam and an RPR or VDRL titer less than fourfold higher than the mother, and:
  • Mother adequately and appropriately treated during pregnancy.
  • Treatment was administered >4 weeks before delivery
  • Mother has no evidence of re-infection or relapse

• Recommended evaluation:
  • None

• Recommended treatment:
  • Benzathine penicillin G 50,000 units/kg/dose IM in a single dose;
  • OR
  • No treatment but close serologic follow up for infant every 2-3 months for 6 months
Scenario 4: Congenital Syphilis unlikely

- Neonate has normal physical exam and an RPR or VDRL titer less than fourfold higher than the mother, and:
  - Mother’s treatment was adequate before pregnancy
  - Mother’s titer was low and stable before and during pregnancy and at delivery (e.g. <1:4)

Recommended evaluation:
- None

Recommended treatment:
- None. Benzathine Penicillin G is an option if follow up is uncertain.

Congenital syphilis follow up

- All neonates with reactive RPR or VDRL should be examined every 2-3 months until it becomes non-reactive.
Keep Bicillin L-A on hand!

- Or know where to refer someone for treatment.
- There is no part of the state that is immune to syphilis, even rural areas.
- Isolated clusters of cases have occurred in rural Iowa.
- When patient or partner presents to clinic, may be the only chance to get them treated and stop the chain of infection.
  - Not uncommon to lose cases to follow up. May not want to be found because of stigma, shame, etc.

Syphilis - an old disease with continued relevance

- Syphilis affects a variety of populations.
  - MSM most affected in terms of numbers
  - Devastating outcomes for pregnant women
- Do not make assumptions when assessing risk or taking a sexual history.
- Syphilis is curable, but need to be diagnosed or notified of exposure!
- Combating syphilis requires increased vigilance from medicine, public health, and the general population.

References