Objectives

At the completion of this unit, participants will

- Become familiar with common pathogens associated with genital ulcers in patients living in the United States.
- Discuss the pros and cons to currently available diagnostics for genital ulcer disease (GUD).
- Choose the currently recommended therapy for the specific or most likely causative STI in your patients with GUD.
- Know possible complications for untreated GUD and determine how to counsel patients regarding these complications and determine treatment strategies.

Etiology of genital ulcer disease (GUD)

- 516 GUD patients from STD Clinics in 10/11 US cities with highest syphilis rates
- Excluded patients with typical herpes
- Ulcer specimens tested using PCR for HSV, T. pallidum, H. ducreyi
  - HSV 333 (64.5%)
  - Syphilis 64 (12.4%)
  - HSV + syphilis 13 (2.5%)
  - Chancroid 16 (3.1%)
  - PCR negative 116 (22.4%)

Mertz K, et al. JID 1998; 178:1795-1798

New study using NAATS/PCR

Etiology of Genital Ulcer Disease. A Prospective Study of 278 Cases Seen in an STD Clinic in Paris
Emilie Hope-Rapp, MD,* et al. STD 2012

TABLE 2: Prevalence of GUD Etiologies by Sex

<table>
<thead>
<tr>
<th>GUD Etiology</th>
<th>Total (n = 396)</th>
<th>Women (n = 291)</th>
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<tbody>
<tr>
<td>HSV</td>
<td>333 (64.5%)</td>
<td>215 (74.6%)</td>
<td>118 (11.3%)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>64 (12.4%)</td>
<td>12 (4.1%)</td>
<td>52 (49.5%)</td>
</tr>
<tr>
<td>HSV + syphilis</td>
<td>13 (2.5%)</td>
<td>12 (4.1%)</td>
<td>1 (0.9%)</td>
</tr>
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<td>16 (3.1%)</td>
<td>8 (2.7%)</td>
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</tr>
<tr>
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<td>116 (22.4%)</td>
<td>122 (42.1%)</td>
<td>34 (32.1%)</td>
</tr>
</tbody>
</table>

TABLE 3: Prevalence of HIV Infection, by GUD Etiologies and Sex

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The Public Health Challenge

Syphilis

**Good news**
- Caused by the bacterium *Treponema pallidum*
- Curable with cheap antibiotics
- Incubation period is 9 to 90 days
- Should be able to find exposed sex contacts and treat them before they are infectious

**Bad news**
- Presents with protean manifestations and may be challenging to recognize and appropriately diagnose
- Cannot culture organism in vitro
- Diagnosis relies on imperfect serologic tests
- Stigma attached to disease, diagnosis, and treatment
- Can cause congenital disease, stillbirths

Herpes Simplex Virus (HSV)

**Good news**
- Most infections are mild
- Suppressive therapy is available but expensive
- Direct diagnosis of lesions is available

**Bad news**
- Caused by a virus, which is not curable
- Serologic tests are available, but expensive
- All infected people can shed the virus regardless of symptoms, and are thus contagious
- Most people don’t know they are infected
- Stigma attached to disease, diagnosis, and treatment
- Can cause congenital disease, stillbirths

REALLY BAD NEWS!
Both are associated with HIV acquisition and transmission

Syphilis—Reported Cases by Stage of Infection, United States, 1941–2012


Primary and Secondary Syphilis—Rates by Sex and Male-to-Female Rate Ratios, United States, 1990–2012
Primary and Secondary Syphilis—Rates by Region, United States, 2003-2012

Primary and Secondary Syphilis—Rates by State, United States and Outlying Areas, 2012

NOTE: The total rate of primary and secondary syphilis for the United States and outlying areas (Guam, Puerto Rico, and Virgin Islands) was 5.1 per 100,000 population.

Primary and Secondary Syphilis—Rates by County, United States, 2012

NOTE: In 2012, 2,123 (67.6%) of 3,142 counties in the United States reported no cases of primary and secondary syphilis.

Primary and Secondary Syphilis—Rates by Age and Sex, United States, 2012

Primary and Secondary Syphilis—Rates by Age Among Women Aged 15-44 Years, United States, 2003-2012

Primary and Secondary Syphilis—Rates by Age Among Men Aged 15-44 Years, United States, 2003-2012
Primary and Secondary Syphilis—Rates by Race/Ethnicity, United States, 2008–2012

* AI/AN = American Indians/Alaska Natives; NHOPI = Native Hawaiian and Other Pacific Islanders.


2012-Fig 38. SR, Pg 36

Primary and Secondary Syphilis—Reported Cases* by Stage, Sex, and Sexual Behavior, 2012

* Of the reported male cases of primary and secondary syphilis, 17.4% were missing sex of sex partner information.

† MSW = men who have sex with women only; MSM = men who have sex with men.

2012-Fig 39. SR, Pg 37

Primary and Secondary Syphilis—Reported Cases by Reporting Source and Sex, United States, 2003–2012

2012-Fig 41. SR, Pg 38

Primary and Secondary Syphilis—Percentage of Reported Cases* by Sex, Sexual Behavior, and Selected Reporting Sources, 2012

* Of the reported male cases of primary and secondary syphilis, 17.4% were missing sex of sex partner information, and 6.2% of reported male cases with sex of sex partner data were missing reporting source data.

† HMO = health maintenance organization; MSW = men who have sex with women only; MSM = men who have sex with men.

2012-Fig 42. SR, Pg 38

Congenital Syphilis—Reported Cases Among Infants by Year of Birth and Rates of Primary and Secondary Syphilis Among Women, United States, 2003–2012

* CS = congenital syphilis; P&S = primary and secondary syphilis.

2012-Fig 43. SR, Pg 39
Syphilis: the clinical picture

Primary, Secondary, Tertiary Syphilis

Syphilis: Transmission
- Major routes: sexual and in utero from infected pregnant women to her fetus (vertical)
- Risk of infection after 1 exposure: 40%
- Index patient is most contagious to sexual partners during 1° and 2° stage, less so in early latent stage

Syphilis: Pathogenesis
- Penetration:
  - Enters via skin or mucus membranes
  - Divides every 30-33 hours
  - Smaller the inoculum, longer the incubation period (9-90 days)
- Dissemination:
  - Before clinical signs/symptoms, it travels via lymphatic system to regional lymph nodes and then through body via blood

Syphilis: Pathogenesis
- Some spirochetes lodge at entry site, proliferate, sensitize lymphocytes and activate macrophages
- Primary lesion (chancre) results at this site of inoculation about 3-6 weeks after initial infection
- Chancre heals spontaneously, usually without scar, within 3-8 weeks

Secondary syphilis
- T. pallidum can traverse the tight junctions between endothelial cells to enter the perivascular spaces, where large number of treponemes and immune cells accumulate
- It can induce production of MMP-1, which degrades collagen and may facilitate access to and egress from the bloodstream, resulting in systemic spread
- Usually within 3 months of infection, symptoms of secondary syphilis appear
Clinical Spectrum of Secondary Syphilis

Syphilis: Pathogenesis
- Eventually, the host suppresses the secondary infection enough so that no lesions are clinically apparent
- This is latency; 60-85% of patients remain asymptomatic
- Some progress to tertiary stage in 1-20 years
- Immunity is present with chronic infection but lost after treatment

Primary Syphilis
- Chancre: appears 2-3 wks after exposure (range 3-90 days)
  - local lesion at site of inoculation
  - typically painless, indurated, clean base
  - 25% have multiple lesions
  - Regional adenopathy: classically rubbery, painless, bilateral

Secondary Syphilis
- Onset 4-10 weeks following 1° and may overlap with it
- Rash:
  - macular, papular, pustular, combination;
  - usually nonpruritic
  - 60%-85% or more involve palms and soles
- Mucus patches (5-30%)
  - flat patches in mouth, pharynx, genitals

More primary syphilis...

More secondary syphilis...
- Condylomata lata (5-25%)
  - heaped, moist wart-like papules
  - in warm intertriginous areas
  - teeming with spirochetes
- Constitutional symptoms:
  - malaise, headache, slight fever, myalgia
  - liver/kidney involvement
  - patchy alopecia
More Secondary Syphilis...

Latent syphilis
- No clinical manifestations
- Only evidence is positive serology
- Early latent syphilis: <1 year duration
- Late latent syphilis: >1 year duration
- After 4 years patient is noninfectious; resistant to reinfection if not treated

Tertiary syphilis
- Late benign syphilis:
  - Gummatous lesions in skeletal, spinal and mucosal areas, eye and viscera
  - Average onset 4-12 years
- Cardiovascular syphilis:
  - Endarteritis of aortic vasovasorum
  - Present as aortic aneurysm, Aortic insufficiency
  - Average onset 15 years

More tertiary syphilis...

Syphilitic aortitis

Neurosyphilis
- CNS involvement occurs early
- Clinical manifestations may appear early or late and include:
  - Asymptomatic neurosyphilis, meningeal involvement (acute meningitis), meningovascular involvement, choreoretinitis, parenchymatous disease (paresis, tabes dorsalis, optic atrophy)
Congenital syphilis
- Vertical transmission can occur at any time during pregnancy and at any stage
- Among women with syphilis, perinatal transmission occurs in:
  - 50% with 1st and 2nd stages
  - 40% with early latent
  - 10% with late latent
  - 10% with tertiary

Adverse Fetal Outcomes among Pregnant Women with Untreated Syphilis
- 20% of children born to these mothers will be normal
- Intrauterine growth restriction
- Stillbirth (4%)
- Neonatal death
- Preterm birth
- Congenital infection and anomalies

Syphilis: Natural History
- Chronic infection that that is characterized by episodes of active disease interrupted by periods of latent infection
- Incubation period: 9-90 days

What’s recommended?
- Primary/Secondary Syphilis
  - Lesions?
    - Darkfield microscopy
    - Direct immunofluorescence
    - Polymerase chain reaction (PCR)
- Early Latent Syphilis
- Late Latent Syphilis
- Syphilis of Unknown Duration
- Late Syphilis

Diagnostic Points
- A positive darkfield or DFA of lesion exudate or tissue is a DEFINITIVE DX
- For presumptive diagnosis you need:
  - nontreponemal test (VDRL/RPR)
  - confirmatory treponemal test (FTA-ABS)
Syphilis - *Treponema pallidum* on darkfield

Few clinics have darkfield microscopes
Few clinicians know how to use them

Syphilis - *Treponema pallidum* on DFA

Few labs offer this test; takes time to perform

Serologic Tests for Syphilis

- Two types
  - Treponemal (qualitative)
  - Nontreponemal (qualitative and quantitative)
- Need both types to make an accurate diagnosis of syphilis

Serological Tests for Syphilis

**Non-treponemal (reagin) tests**
- Complement Fixation Test
- Wasserman reaction
- Flocculation Reactions
- Rapid plasma reagin (RPR) test
- VDRL
- TRUST

**Treponemal (specific) tests**
- TPI
- FTA-ABS
- TPPA
- ELISA (EIA)
- Automated chemiluminescence platforms
- Current Chromatographic (POC) Tests

Selecting Syphilis Tests

Select and interpret lesion and serologic tests appropriately
- Lesion-based tests used only for Primary Stage
- Sensitivity and specificity of serology varies by stage
- Presence of antibody doesn’t distinguish past from present infection
- Quantitative Titers (RPR/VDRL) are used to evaluate response to therapy

Qualitative RPR Test
Quantitative RPR Test

Natural History of Titer Decay

Problem 3: Sensitivity of Serologic Tests for Syphilis

Table 1. Sensitivity and Specificity of Serologic Tests for Syphilis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity during stage of infection, % (range)</th>
<th>Specificity, % (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDRL (1:4)</td>
<td>70 (74–107)</td>
<td>100</td>
</tr>
<tr>
<td>TLOST (1:4)</td>
<td>65 (77–99)</td>
<td>100</td>
</tr>
<tr>
<td>RPR (1:4)</td>
<td>60 (77–95)</td>
<td>100</td>
</tr>
<tr>
<td>Early treponemal tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHA-TP (1:100)</td>
<td>70 (69–100)</td>
<td>100</td>
</tr>
<tr>
<td>TPPA (1:100)</td>
<td>88 (95–100)</td>
<td>100</td>
</tr>
<tr>
<td>THA (1:10)</td>
<td>60 (71–100)</td>
<td>100</td>
</tr>
<tr>
<td>FTA-ABS (1:14)</td>
<td>64 (70–100)</td>
<td>100</td>
</tr>
<tr>
<td>Nanotrap and ELISA</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>ELISA</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>IDEs</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
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**Treponemal Serologic Tests**

- **Principles**
  - Measure antibody directed against *T. pallidum* antigens
  - Qualitative (positive or negative)
  - Usually reactive for life (but may disappear in 1/3 of cases)

- **Treponemal tests include TP-PA, MHA-TP, FTA-ABS, ELISA (Cappia)**

---

**NOTE:** CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody-absorbed assay; IA, immunoglobulin A; IDEs, immunodiagnostic enzymes; MHA-TP, microhemagglutination assay for *T. pallidum*; NA, not available; TPPA, *T. pallidum* phase-1 protein assay; THA, *T. pallidum* phase-2 protein; TRUSE, tube reaction for unheated serum test.
Fluorescent Treponemal Antibody Test

Treponema pallidum Haemagglutination Assay

Interpretation of Results
Positive Control Dilution: (++)(+)(+)(+/-)(-)(-)

Treponema pallidum Passive Particle Agglutination Assay (TPPA)

Interpretation of Syphilis Tests

<table>
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<th>Non – T STS</th>
<th>T – STS</th>
<th>Possible diagnoses</th>
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<td>Reactive</td>
<td>Non-reactive</td>
<td>False positive RPR</td>
</tr>
<tr>
<td>Reactive</td>
<td>Reactive</td>
<td>False negative FTA</td>
</tr>
<tr>
<td>Reactive</td>
<td>Reactive</td>
<td>New case – needs treatment</td>
</tr>
<tr>
<td>Reactive</td>
<td>Reactive</td>
<td>Old case – adequately treated</td>
</tr>
<tr>
<td>Reactive</td>
<td>Reactive</td>
<td>Old case – inadequately treated</td>
</tr>
<tr>
<td>Reactive</td>
<td>Reactive</td>
<td>Old case – reinfected</td>
</tr>
<tr>
<td>Reactive</td>
<td>Reactive</td>
<td>Congenital, other treponemal</td>
</tr>
<tr>
<td>Non- Reactive</td>
<td>Reactive</td>
<td>Old case – treated or untreated</td>
</tr>
<tr>
<td>Non- Reactive</td>
<td>Reactive</td>
<td>Primary syphilis</td>
</tr>
<tr>
<td>Non-reactive</td>
<td>Non-reactive</td>
<td>Prozone reaction – rare</td>
</tr>
<tr>
<td>Non-reactive</td>
<td>Non-reactive</td>
<td>No syphilis</td>
</tr>
<tr>
<td>Non-reactive</td>
<td>Non-reactive</td>
<td>Incubating/early primary syphilis</td>
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Serologic Tests for Syphilis

- Monitor titers to determine “cure”, “failure”, “reinfection/relapse”
- After therapy:
  - Cure = 4-fold (or 2 dilution) decrease (e.g. from 1:32 to 1:8)
  - Failure = no change or increase
  - Re-infection = documented titer response then a 4-fold increase

Problem 4: SEROLOGIC TITERS OF RPR/VDRL

<table>
<thead>
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<th>2-fold decline</th>
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<tbody>
<tr>
<td>1 : 1024</td>
<td></td>
</tr>
<tr>
<td>1 : 512</td>
<td></td>
</tr>
<tr>
<td>1 : 256</td>
<td></td>
</tr>
<tr>
<td>1 : 128</td>
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</tbody>
</table>
Changing Times in Syphilis Serology

- Prevalence of syphilis is extremely low in many industrialized countries
- Labor costs have increased
- Introduction of treponemal tests which can be fully automated

BIGGEST PROBLEM
Syphilis Serology - An Alternative Approach in Low Prevalence Settings

Screen with a Treponemal test (eg. TP-PA, EIA, Automated or POC test.)

Confirm with a Non-treponemal test (eg. an RPR, VDRL Test)

It is important that all specimens that test positive with the initial treponemal test be retested with a non-treponemal test to give a better indication of disease that requires therapy.

ELISA Test

Newer Approach to Screening

- All patients have a screening ELISA
- If ELISA positive or indeterminate, RPR and FTA are performed
- In some clinical situations, an RPR or an FTA is also ordered
  - pt with a genital ulcer
  - pt where we are following RPRs

What should we do with discordant treponemal/ non-treponemal results?

For the first time we will detect treponemal Ab-positive, non-treponemal Ab-negative specimens during screening.

This situation has resulted in considerable confusion among both laboratorians and clinicians
Problem 2: False-Positive Reactions in Serologic Tests for Syphilis

<table>
<thead>
<tr>
<th>Disease</th>
<th>RPR/VDRL</th>
<th>FTA-ABS</th>
<th>SLUSA</th>
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<tbody>
<tr>
<td>Age</td>
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<tr>
<td>Autoimmune Diseases</td>
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<td>Dermatologic Diseases</td>
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<td>Yes</td>
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<tr>
<td>Drug Abuse</td>
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<td>Hepatitis B virus</td>
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<td>Lyme Disease</td>
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<td>Malaria</td>
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<td>No</td>
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<tr>
<td>Malaria*</td>
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<tr>
<td>Pregnancy</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Recent Immunizations</td>
<td>Yes</td>
<td></td>
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</tr>
<tr>
<td>STD other than Syphilis</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*May cause increase in titer in women previously successfully treated for syphilis

Serologic Tests for Syphilis

- **Nontreponemal tests:** RPR, VDRL
  - Monitor titers to determine “cure”, “failure”, “reinfection/relapse”
  - After therapy:
    - Evidence of cure = 4-fold (or 2 dilution) decrease (e.g. from 1:32 to 1:8)
    - Failure = no change or increase
  - Reinfection = documented titer response then a 4-fold increase

- **Treponemal tests:** FTA-Abs, MAHTP
  - Confirmatory test
  - Titers not reported; may remain (+) after successful therapy

Rapid tests are coming!

Diagnosis of Neurosyphilis

- No single test can be used
- Dx can be made with any combination of:
  - abnormal CSF cell count (> 5 WBC)
  - abnormal CSF protein
  - Reactive CSF-VDRL (most specific)
- CSF-FTA yields more false positives, but is very sensitive; some believe a neg CSF-FTA excludes neurosyphilis

Syphilis: Treatment

Therapy for Syphilis

- Parenteral penicillin G is drug of choice for all stages of syphilis
- It is the ONLY therapy with documented efficacy for neurosyphilis or for syphilis during pregnancy
Primary and Secondary Syphilis: Therapy

Benzathine penicillin G, 2.4 million units IM in a single dose

Penicillin Allergic Nonpregnant Patients

Doxycycline 100 mg PO BID for 2 weeks

Follow-up

- Re-examine patients clinically and serologically at 6 months and 12 months after treatment
- Rolfs study states that 15% of patients with early syphilis will not achieve a two dilution decline in nontreponemal titer at 1 year

What are the serological criteria for treatment failure?

- Failure: recurrence, persistence or progression of symptoms or by rising titer
- The frequency of serological follow-up for 1° and 2° HIV-uninfected syphilis patients is every 3 months
- For latent syphilis, titers may decline 4-fold by 12-24 months, but data conflict
HIV-Infected Patients

- Primary and Secondary Syphilis
  - 2.4 million units IM benzathine penicillin G
  - Follow-up: 3, 6, 9, 12, and 24 months
  - Treatment failure within 6-12 months: CSF examination
  - Retreat with 7.2 million units penicillin if CSF if normal

Latent Syphilis

- Early latent Syphilis
  - Benzathine penicillin G 2.4 million units IM in a single dose
- Late Latent Syphilis or Syphilis of Unknown Duration
  - Benzathine penicillin G 7.2 million units total, given as three doses of 2.4 million units IM each at 1-week intervals

What if they miss a week?

- Pharmacology data suggest that an interval of 10-14 days between doses might be acceptable before starting over.
- If the patient is pregnant, adhere strictly to the weekly dose regimen. If she misses a week, start over.

Follow-up

- Repeat nontreponemal titer at 6, 12 and 24 months.
- If failure, consider LP
- Patients with a normal CSF exam, re-treat if:
  - Titers increase 4-fold
  - A high titer (>1:32) fails to decline at least 4-fold
  - Signs or symptoms attributable to syphilis develop
- Some patients remain serofast with negative CSF exam. Unclear what to do.

Jarisch-Herxheimer reaction

- Self-limited reaction to anti-treponemal therapy, seen more commonly with treatment of early stages
- Characterized by fever, malaise, nausea/vomiting, sometimes with chills and exacerbation of rash
- Occurs within 24 hours after therapy and resolves within 24 hours
- Warn patient that it is NOT ALLERGIC reaction
- Can be treated with symptomatic support
- Pregnant women should be aware that it may precipitate early labor and to notify obstetrician or go to ER if problems occur

Monitoring in HIV+

- Jarisch-Herxheimer reaction in HIV+
  - Early syphilis, high RPR, prior penicillin treatment
- Immune reconstitution inflammatory syndrome uncommon
- ART use in HIV+ with syphilis
  - Reduced risk of serologic treatment failure
  - Lower risk of neurosyphilis
  - Normalization of CSF parameters with improvement in serum RPR
**Diagnosis of Neurosyphilis**

- No single test can be used
- Dx can be made with any combination of:
  - abnormal CSF cell count (> 5 WBC)
  - abnormal CSF protein
  - Reactive CSF-VDRL with or without symptoms
- CSF-FTA yields more false positives, but is very sensitive; some believe a neg CSF-FTA excludes neurosyphilis

**Treatment**

- Aqueous crystalline penicillin G 18-24 million units a day, given as 3-4 million units IV every 4 hours or continuous infusion for 10 to 14 days
  - OR
- Procaine penicillin 2.4 million units IM a day, PLUS probenecid 500 mg orally four times a day, both for 10-14 days

**Other treatment**

- Ceftriaxone 2 grams daily IV or IM for 10-14 days
- Other regimens have not been adequately evaluated for treatment of neurosyphilis

**AND...**

- Some experts administer benzathine penicillin, 2.4 million units IM after completion of neurosyphilis treatment to provide a comparable total duration of therapy for late latent disease

**Syphilis in Pregnancy**

- All women should be screened serologically for syphilis during the early stages of pregnancy
- In pop’n where prenatal care is suboptimal, RPR-card test screening and treatment should be done at time pregnancy is diagnosed
- In high risk pop’n, screen early, at 28 weeks and at delivery
Syphilis in Pregnancy

- Any woman who delivers a stillborn after 20 weeks gestation should be tested for syphilis
- No infant should leave the hospital without the maternal serologic status having been determined at least once during pregnancy or at the time of delivers

2.4 million units benzathine penicillin G is effective therapy for 1o, 2o, and early latent antepartum syphilis
- 98% success with carefully defined congenital syphilis
- Fetal treatment failures are more frequent when moms are treated after the 20th week of gestation and with secondary syphilis

4.8 million units of benzathine penicillin G over 2 weeks is effective for antepartum syphilis BUT
- One U.S. retrospective case-control study found no improvement in prevention of CS in high-risk setting of secondary syphilis
- African retrospective study found no treatment better than a single 2.4 million unit does of benzathine penicillin in preventing preterm birth, still birth, and CS

Are there alternatives to penicillin?
- NO
- No clinical trial with other medicines
- Fetal azithromycin serum, amniotic fluid levels are low

Jarisch-Herxheimer Reaction

- Acute febrile reaction often accompanied by headaches, myalgia, and other symptoms
- Often occurs within the first 24 hours after any syphilis treatment
- More common with early syphilis
- Patients should be advised of this
- Antipyretics may be recommended but no proven methods prevent reaction

Women treated during the second half of pregnancy are at risk for premature labor and/or fetal distress if therapy precipitates the Jarisch-Herxheimer reaction
- Advise the women to seek obstetric attention if they notice any contractions or decrease in fetal movements
- Stillbirth is a rare complication of treatment and should not delay it
Syphilis in Pregnancy
Follow-up

- Serologic titers should be repeated in the third trimester and at delivery.
- Monthly checks are not necessary but may be checked in women at high risk for reinfection or in high geographic prevalence areas.
- The clinical and antibody response should be appropriate for the stage of the disease.
- Most women will deliver before their serologic response to treatment can be definitively assessed.

Genital Herpes
Herpes simplex virus type I and Herpes simplex virus type II

HSV Lesions
- Macule
- Papule
- Vesicle
- Ulcer
- Crusted Lesions
- Healed Lesion

Atypical lesion

Syphilis in Pregnancy and Congenital Syphilis

- Treponemal screening performed with reflex nontreponemal test.
- Oral step-wise penicillin dose challenge or skin testing may be helpful in identifying women at risk for acute allergy.
- Erythromycin or azithromycin does not reliably cure maternal infection or infected fetus.
- Insufficient data on ceftriaxone for treatment of maternal infection and prevention of CS.

Genital Herpes—Initial Visits to Physicians' Offices, United States, 1966-2012

Seroprevalence

- Few countries have population-based national estimates of HSV-2
  - U.S. NHANES: % prevalence in >12 year olds
  - European cross-sectional surveys 1989-2000: 4% in England and Wales to 24% in Bulgaria
  - Sub-Saharan Africa: 30-80% in women; 10-50% in men
  - South America: 20-40% in women
  - Asian countries: 10-30% in general population

HSV-1 and Genital Herpes

- Episodes cannot be distinguished clinically from HSV-2
- HSV-1 recurrence rate lower than HSV-2 (1 vs. 5 in the first year)
- HSV-1 shedding less frequent than HSV-2

Genital Herpes: Epidemiology of a Viral STI

- Chronic infection
- No cure
- Infectious for life
**HSV-2 and Number of Sexual Partners**

![Graph showing HSV-2 seroprevalence (%) vs. number of sexual partners for different races and genders.]

**Transmission of Genital HSV-2**

![Diagram illustrating the transmission dynamics of genital herpes.]

**Unrecognized HSV-2 Infection**

![Pie chart showing the distribution of unrecognized HSV-2 infection, with 20% asymptomatic, 20% recognized symptomatic, and 60% undiagnosed/unrecognized.]

**Overall**

- Genital herpes infections can be caused by herpes simplex virus type 1 or 2 (HSV-1, HSV-2).
- HSV infections cause substantial morbidity in affected individuals, particularly in neonates.
- Asymptomatic viral shedding is a common cause of transmission.
- The public health significance of genital herpes is under-estimated.

**Six major public health issues in genital herpes**

- Relationship of HSV-2 infection to HIV transmission and its prevention.
- Under-diagnosis of genital ulcer disease.
- Uses of type-specific serological testing.
  - Poor understanding of psychosocial impact.
  - Preventing sexual transmission of HSV.
  - Preventing neonatal herpes and maternal perinatal morbidity.

**Association of HSV-2 antibody with HIV seroconversion in 9 prospective cohort and nested case-control studies**

![Graph showing the association between HSV-2 antibody and HIV seroconversion odds ratio.]

(See notes)
Probability of HIV transmission in 174 monogamous couples: Rakai, Uganda

- 174 monogamous discordant couples without other known HIV risks; serial HIV testing over 2 – 3 years
  - 97 couples male HIV + partner
  - 77 couples female HIV + partner
- HSV-2 antibody in exposed HIV – partners was a stronger predictor of HIV acquisition than HIV viral load in HIV + partners, and was independent of symptomatic genital ulcer disease
- History of genital ulcers in HIV + people, but not HSV-2 antibodies, associated with HIV transmission


Genital herpes diagnosis: the bottom line

- Diagnostic tests for HSV need to be available and routinely used
  - Test all patients with genital ulcer disease
  - Determine virus type in all patients with genital herpes
- Virologic tests
  - Culture
  - Direct fluorescent antibody test (some don't type virus)
  - No role for microscopy/cytology (Tzanck test)
    - Never diagnose genital herpes based on Pap smear
- Type-specific serology
  - Diagoloy POCkit™
  - Focus Technologies
  - ELISA or immunoblot
  - Western Blot (ref labs only)
  - No other tests should be used

Type-specific HSV serology

**Definite Indications** (prior probability of genital herpes > 50%)
- Diagnosis of genital ulcer disease, recurrent symptoms, etc.
- Management of sex partners of persons with herpes

**Other Uses**
- Selected pregnant women and their partners
  - Request to test for herpes
  - Comprehensive STD evaluation?
- Widespread screening of sexually active persons?
  - Inexpensive confirmatory test would be immensely helpful
  - Influence on HSV transmission?
  - Influence on HIV transmission?

**Antibody to HSV-1 or -2 glycoprotein G (gG-1 or gG-2) tests available in the US**
- Western blot
  - The gold standard
- Diagoloy POCkit™
  - HSV-2 only
  - Sensitivity ~90%, Specificity 98-99%
  - Part of Dairy; 10-minute result
- Focus Technologies (formerly MRL) HerpeSelect™ HSV-1 and HSV-2 ELISA
  - Sensitivity for HSV-2 ~90%, Specificity ~98-99%
- Focus Technologies HerpeSelect™ HSV-1 and HSV-2 Differentiation Immunoblot
  - Same antigen as ELISA, probability similar performance


Additional assays available in some countries. Only gG-based tests are truly type-specific

[see notes]
Table 1. Commercial Type-Specific gG-Based Serology Kits

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>HSV Type</th>
</tr>
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<tbody>
<tr>
<td>FDA Approved</td>
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<tr>
<td>HerpeSelect® ELISA</td>
<td>Focus HSV-1, HSV-2</td>
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<tr>
<td>HerpeSelect® Immunoblot</td>
<td>Focus HSV-1, HSV-2</td>
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<tr>
<td>POCkit® HSV-2</td>
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<tr>
<td>Premier™ ELISA</td>
<td>Meridian</td>
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<tr>
<td>Off the market</td>
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<tr>
<td>Not FDA Approved</td>
<td></td>
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<tr>
<td>Cobas® HSV-2</td>
<td>Roche HSV-2</td>
</tr>
<tr>
<td>QuickVue® HSV-2</td>
<td>Quidel HSV-1, HSV-2</td>
</tr>
</tbody>
</table>

* The Western blot assay, which is considered the gold standard, is not commercially available. HSV indicates herpes simplex virus; FDA, Food and Drug Administration; ELISA, enzyme-linked immunosorbent assay.

Western Blot Profiles

Focus HerpeSelect™ ELISA

POCit HSV Serology Test

Genital HSV: Treatment

General principles in management of genital herpes

- Antiviral therapy
  - The drugs are benign
  - Psychological impact is great
  - Therefore, maintain a low threshold to offer / prescribe treatment: "patient determines severity"
  - Suppressive valaciclovir ↓ transmission risk
- Counselling
  - Ameliorating psychological impact
  - Preventing transmission

Wald & Ashley-Morrow, CID 2002;355:S173-S182

(see notes)
Interventions for HSV

- Beneficial
  - Oral antiviral therapy in first episodes
  - Oral antiviral therapy at start of a recurrence
  - Daily antiviral therapy in people with high rates of recurrence
  - results in improved QoL

Recommended Regimen for First Clinical HSV Episode

- Acyclovir 400 mg PO TID
- Famciclovir 250 mg PO BID
- Valacyclovir 500 mg PO once a day

Recommended Regimen for Episodic Recurrent HSV

- Acyclovir 400 mg PO TID
- Acyclovir 800 mg PO BID
- Famciclovir 125 mg PO BID
- Valacyclovir 1 gm QD for 5 days
- Valacyclovir 500 mg PO BID for 3 days
- Famciclovir 1 gm PO BID for 1 day
- Famiciclovir 500 mg x1, 250 mg bid x2 days

Recommended Regimens for Daily Suppression of HSV

- Acyclovir 400 mg PO BID
- Famciclovir 250 mg PO BID
- Valacyclovir 500 mg PO once a day
- Valacyclovir 1.0 g QD if recurrence > 10 per year

Recommended Regimens for Daily Suppression of HSV

Does suppressive therapy decrease subclinical shedding?

  - Double-blind, placebo-controlled, crossover clinical trial comparing acyclovir 400 mg BID for 70 days, followed by a 14 days washout period, then placebo or in reverse order
  - 34 women with HSV 2 of less than 2 years’ duration
  - Daily samples of vulvar cervicovaginal and perianal areas, diary of symptoms
  - Subclinical shedding occurred on 83 or 1439 days with placebo (5.8%) vs 6 of 1611 days on acyclovir (0.37%). A 94% reduction
Comparative efficacy of famciclovir and valacyclovir for suppression of recurrent genital herpes and viral shedding

- Two randomized, double-blind, placebo-controlled studies comparing daily famciclovir 250 mg BID with valacyclovir 500 mg QD
- Study 1: randomized 320 participants and compared the clinical effect of the drugs given for 16 weeks
- Study 2 enrolled 70 HSV-2+ subjects and compared the virologic effect to the drugs given for 10 weeks

Results:
- Study 1: time to first recurrence was similar, but time to first virologically confirmed recurrence was shorter among famciclovir recipients
- Study 2: HSV was detected on 3.2% of days among famciclovir recipients and 1.3% of days among valacyclovir recipients

Conclusions: Valacyclovir appears to be somewhat better than famciclovir for suppression of genital herpes and associated shedding.

Mechanism of DNA synthesis inhibition of acyclovir and new drugs

- Helicase-primase complex unwinds HSV-DNA at the replication fork and primes both lagging and leading strands
- New drugs bind to this complex and inhibit its activity at a different site than acyclovir

So what about shedding?

- Many of these shedding episodes occur in the absence of lesions or symptoms (known as subclinical shedding).
- Mathematical models suggest that multiple, short, overlapping shedding episodes best simulate the observed shedding patterns and that a nearly constant low quantity of HSV is likely to be released from sensory DRG into the genital tract.
- Recent studies using intensive sampling (every 6 hours) of the genital and oral mucosa have produced results consistent with these models, demonstrating that most HSV detection episodes are short (median 13 hours), subclinical, and rapidly cleared.
- In addition, studies using detailed genital mapping to isolate shedding episodes have demonstrated that simultaneous, bilateral widespread genital shedding is detected frequently.
Treatment of HSV in HIV infected persons

Acyclovir Resistance

- Foscarnet, 40 mg/kg IV every 8 hours until clinical resolution
- Intravenous cidofovir 5 mg/kg once weekly might also be effective
- Topical cidofovir (1% gel) or imiquimod
- Applied to lesions once daily for 5 consecutive days

What about managing stress, diet, ‘natural’ remedies, etc?

- No clear biological basis
- Attempts to reduce stress usually are fruitless (How good are you at reducing stress in your life?)
- Unsuccessful attempts to prevent recurrences ‘naturally’ may increase psychological impact (‘If I was a better person, my herpes wouldn’t be a problem’)
- Advise patients to avoid ‘obvious’ triggers that are easily identified and avoided, but don’t go looking for them (No diaries!)
- Rely on antiviral therapy

Personal strategies: abstention during herpes outbreaks

- Requires awareness of infection and recognition of symptoms
- Partially effective
- Used successfully by many couples for several years
- Studied primarily for overt recurrent herpes in ongoing partnerships
- No data in serologically diagnosed persons counselled to recognize symptoms

Protection against HSV-2 by condoms

- 528 monogamous HSV-2-discordant couples
  - 261 HSV-2 – men, 267 HSV-2 – women
  - 18 month follow-up
- Relative transmission risk (hazard ratio) among couples with ≥ 25% condom use vs < 25% use
  - Male to female 0.085 (CI95 0.01 – 0.67)
  - Female to male 2.02 (CI95 0.32 – 12.5)

Wald et al. JAMA 2001;285:3100-3106

Protection against HSV-2 by condoms

- 1852 HSV 2 – heterosexual men and women
  - At risk of STD (>4 partners or history of STD in past year)
  - 18-month follow-up
- Relative HSV 2 infection risk (hazard ratio) among persons with ≥ 65% condom use vs < 65% use
  - Men 0.58 (CI95 0.37 – 0.92)
  - Women 0.66 (CI95 0.30 – 1.46)

Project respect data

- Project Respect: 50% decrease of acquisition among those who used condoms more than 50% of time with "occasional" partners
- Valacyclovir study, Chiron vaccine study and Project Respect: condom use protected both men and women
- Condoms are effective in decreasing the rate of HSV-2 transmission and acquisition. As the new data show effectiveness for both genders, the caveat about protection for women only can be omitted.

Does suppressive therapy prevent sexual transmission?

- Substantial but incomplete suppression of subclinical shedding
- Reduced inoculum probably results in reduced transmission risk, but cannot quantitate without prospective data
- Double-blind, multicentre, placebo-controlled clinical trial

Reduction in Transmission Risk: Valacyclovir 500 mg Once Daily

- Immunocompetent, heterosexual partners, age ≥ 18 years, in a stable monogamous relationship
- Source partner suitable for suppressive therapy, history of 9 or fewer episodes/year
- Source partners randomized to valacyclovir 500 mg once daily or placebo for 8 months
- Susceptible partner monitored for acquisition of HSV

Proportion of Susceptible Partners With Symptomatic Genital Herpes

- Placebo: 2.2% (16/741)
- Valacyclovir: 0.5% (4/743)
- 75% Reduction With Valacyclovir
  
  $P = 0.01; \text{RR} = 0.25$ (95% CI: 0.08, 0.74)

Proportion of Susceptible Partners With Overall Acquisition of HSV-2 Infection

- Placebo: 3.6% (27/741)
- Valacyclovir: 1.9% (14/743)
- 45% Reduction With Valacyclovir
  
  $P = 0.01; \text{RR} = 0.52$ (95% CI: 0.27, 0.87)

Neonatal HSV
Neonatal HSV morbidity and mortality at 1 year

Kimberlin et al. 2001

Transmission of neonatal herpes

Pregnant women with asymptomatic HSV shedding at term (n = 116)

<table>
<thead>
<tr>
<th>Type</th>
<th>Recurrent (seropositive)</th>
<th>First episode (seronegative)</th>
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<tbody>
<tr>
<td>HSV-2</td>
<td>n = 96</td>
<td>n = 20</td>
</tr>
<tr>
<td>HSV-1</td>
<td>n = 7</td>
<td>n = 3</td>
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<tr>
<td>HSV-1              1º HSV-1</td>
<td>n = 3</td>
<td>1º HSV-2</td>
</tr>
<tr>
<td>HSV-2              Non-1º</td>
<td>n = 14</td>
<td>HSV-2</td>
</tr>
</tbody>
</table>

Neonatal herpes

0 1 (14%) 3 (100%) 1 (33%) 4 (29%)

Transmission of neonatal herpes

Uses of type-specific HSV serological tests in pregnancy

- Husband/partner suspected to have genital herpes
  - If she is HSV-2-positive, reassure her (and keep a lookout for HSV lesions at term)
  - If she is HSV-2-negative, test partner; if he is positive (or if not tested), assertively counsel to avoid sex in last trimester
- Husband/partner with past STD or at risk
- Diagnostic testing: all pregnant women with apparent initial genital herpes (culture and serology)
- All pregnant women and their partners?

The Public Health Challenge

Syphilis

Good news
- Caused by the bacterium Treponema pallidum
- Curable with cheap antibiotics
- Incubation period is 9 to 90 days
- Should be able to find exposed sex contacts and treat them before they are infectious

Bad news
- Presents with protean manifestations and may be challenging to recognize and appropriately diagnose
- Cannot culture organism in vitro
- Diagnosis relies on imperfect serologic tests
- Stigma attached to disease, diagnosis, and treatment
- Can cause congenital disease, stillbirths

Herpes Simplex Virus (HSV)

Good news
- Most infections are mild
- Suppressive therapy is available but expensive
- Direct diagnosis of lesions is available

Bad news
- Caused by a virus, which is not curable
- Serologic tests are available, but expensive
- All infected people can shed the virus regardless of symptoms, and are thus contagious
- Most people don’t know they are infected
- Stigma attached to disease, diagnosis, and treatment
- Can cause congenital disease, stillbirths