Syphilis and Genital Herpes: Clinical Problem Solving

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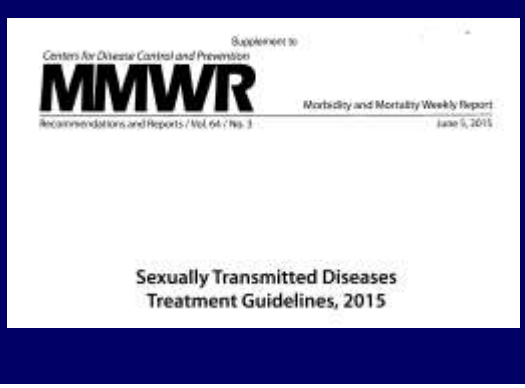
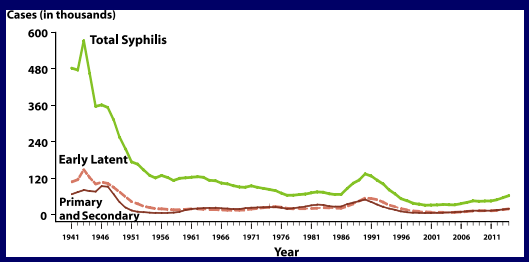
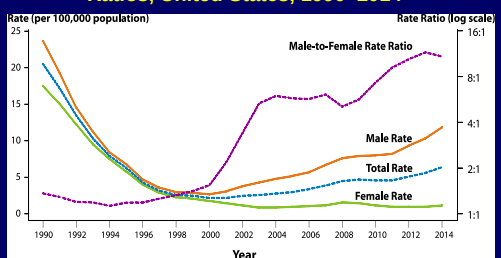


Syphilis — Reported Cases by Stage of Infection, United States, 1941–2014



Primary and Secondary Syphilis — Rates of Reported Cases by Sex and Male-to-Female Rate Ratios, United States, 1990–2014



Case 2

A 40 YO male presents following notification that his recently tested blood donation tested positive for syphilis. He is a local businessman, unmarried, states he has been involved in a monogomous relationship for the past two years. He was treated with levofloxacin for a urinary tract infection by a colleague 6 months ago.

On further history, that sex partner is a male who works as a flight attendant. To the patient's knowledge, neither has been tested for other STIs since their relationship began.

The laboratory reports the positive blood test was an EIA test for syphilis. Your next step should be:

Case 2 continued…

1. Order an TPHA test
2. Order an RPR test
3. Initiate treatment with benzathine penicillin G, 2.4 Mu
4. Request that the patient's partner present for evaluation
5. Screen for gonorrhea and chlamydia at all recent sites of sexual exposure
6. Test for HIV

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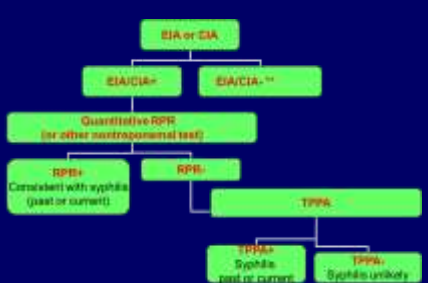
CDC-Recommended Algorithm for Reverse Sequence Syphilis Screening



CDC. MMWR 2011; 60 (5): 133-137

EIA Serologic Tests for Syphilis

EIA= Enzyme Immunoassay

Pro's
- Cloned Treponemal Antigens
- Easy to do in large numbers.
- Inexpensive

Con's
- Limited data on specificity
- Positives need quantitative test to assess response to therapy and perhaps for confirmation

Reasons For EIA+/RPR- Test Results

Past (treated) Syphilis

Chronic Untreated Syphilis

Very Early Syphilis

False Positive

Reasons for Serological Testing For Syphilis

Screening

Diagnostic Testing

Monitoring Outcomes of Therapy

Serologic Tests for Syphilis

Nontreponemal Tests (VDRL, RPR)

- Antigen - cardiolipin-lecithin-cholesterol
- Quantitative, declining over time and with treatment

Treponemal Tests (FTA-ABS, MHA-TP, TPPA, EIAs)

- Treponemal Antigens
- Qualitative with lifelong positivity

Case 2 continued…

RPR is positive at a 1:16 dilution, HIV is negative, urine and rectal specimens are positive for *C. trachomatis*. The patient is treated with 2.4 Mu of benzathine penicillin and 1.0g of azithromycin for chlamydia. As follow-up, he should:

1. Have repeat syphilis testing in three months
2. Have repeat HIV testing in three months
3. Have repeat testing for chlamydia at 3 months
4. All of the above

Case 2 continued…

Three months later the patient returns for follow-up. Gonorrhea, chlamydia, and HIV tests are negative. The RPR is positive at a 1:8 dilution. Based on his test results, the patient is:

1. A treatment failure and should now be re-treated with 2.4 Mu of benzathine penicillin G for three weeks.
2. Successfully treated and can be followed routinely
3. Serofast

Interpretation of Changing STS Titers

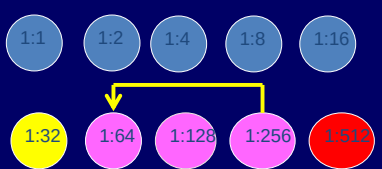
Error of RPR VDRL Tests - ± 1 dilution

Meaningful change is 2 dilution (or 4-fold) change in titer
e.g. 1:2 ➡ 1:4 or 1:1, no meaningful change
1:2 ➡ 1:8, meaningful change

Quantitative RPR or VDRL test, results are not interchangeable

Two dilution decline in titer indicates response to therapy however, failure to decline ≥ 2 dilutions does not necessarily mean patient has failed treatment

Meaningful Change in STS Titers- +/- 2 Dilutions



- Two tube or fourfold dilution decrease
- 128/4 = 32

Response To Early Syphilis Therapy at 3 Months Following Benzathine Penicillin G or Azithromycin Treatment (n=470)

Serological Cure	78.5% (369)
Serofast	20.4% (96)
Serological Failure	1.1% (5)

Hook et al, JID 2010; 201: 1729-35

TREATMENT OF EARLY SYPHILIS IN HIV-INFECTED AND UNINFECTED PERSONS

Proportion of Subjects with RPR Decline <2 Dilutions

		3 Mo.	6 Mo.	12 Mo.
Treatment Group				
	Usual	25% (175)	24% (157)	18% (137)
	Enhanced	29% (189)	19% (172)	17% (144)
HIV-Status				
	Positive	38% (76)*	28% (69)	21% (61)
	Negative	24% (287)	19% (259)	16% (219)

*P < 0.05

Rolfs et al, NEJM 1997; 44: 307-14.

Factors Associated With Serological Response To Therapy

Younger Age

Earlier Stage of Disease (1°>2°>EL)

Jarisch-Herxheimer Reaction

Higher Baseline Titer (within stage)

Not Associated – Gender, Race, Prior syphilis,

Sena et al CID 2011; 53: 1092-9

Case 3

A 54 YO woman is diagnosed with syphilis of unknown duration based on an RPR reactive at a 1:4 dilution and a reactive treponemal IgG assay. There are no signs of syphilis and no prior serological tests for syphilis in nearly 20 years. Physical examination is normal

Planned therapy with benzathine penicillin, 2.4Mu weekly for three weeks is initiated. She presents 12 days following her initial penicillin injection, stating that she was unable to keep her 1 week appointment.

What should the next course of action be?

2015 CDC STD TREATMENT GUIDELINES

Late Latent and Tertiary Syphilis

- Benzathine Penicillin G 2.4 Mu IM weekly* x 3

- Penicillin Allergy
- Doxycycline 100 mg PO, BID x 28

- Intradose interval of 10-14 days acceptable without re-starting therapy

Case 3 (Continued)

1. Restart therapy with benzathine penicillin 2.4 Mu weekly X 3, urging patient to keep future appointments
2. Change to treatment with doxycycline, 100 mg PO BID for 28 days
3. Continue planned therapy, administer 2.4 Mu benzathine penicillin G, inform the patient she needs one more injection in a week.

2015 CDC STD TREATMENT GUIDELINES

Late Latent and Tertiary Syphilis – Missed Doses

Pharmacologic considerations suggest that an interval of 10-14 days between doses of benzathine penicillin for late syphilis or latent syphilis of unknown duration might be acceptable before restarting the sequence of injections. Missed doses are not acceptable for pregnant patients receiving therapy for late latent syphilis.

2015 CDC STD TREATMENT GUIDELINES
Late Latent Syphilis Response To Therapy

Quantitative nontreponemal serological tests should be repeated at 6, 12, and 24 months

CSF exam should be performed for 1) A 4-fold increase in titers; 2) An initial titer >1:32 fails to decline 4-fold; 3) Signs or symptoms attributable to syphilis develop

Latent Syphilis: Response To Therapy

Case 4

A 37 YO male presents for evaluation of a genital ulcer. On examination there is a solitary, painless, 1.5 cm genital ulcer with an indurated base. You treat him for primary syphilis with 2.4 Mu of benzathine penicillin. Your diagnosis is confirmed by an RPR positive a 1:8 titer and a reactive treponemal EIA test.

He refers his regular partner who is also treated.

At 4 weeks following therapy his RPR has decline to 1:2

5 weeks later he returns, stating that his syphilis "is back". He denies new exposures for himself and his regular partner

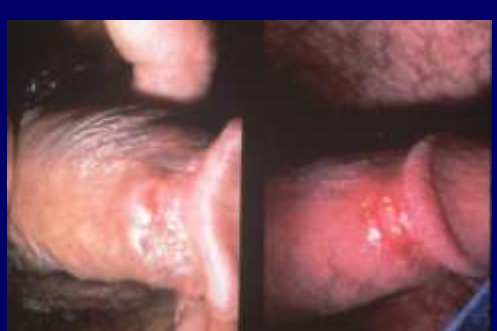
What now?

Case 4

1. Retreat with 2.4 Mu benzathine penicillin Mu
2. Retreat with 2.4 Mu Penicillin G weekly X 3
3. Repeat the RPR
4. Perform a herpes PCR test
5. Perform a type-specific herpes serological test

Case 4

1. Retreat with IM 2.4 Mu benzathine penicillin Mu
2. Retreat with IM 2.4 Mu Penicillin G weekly X 3
3. Repeat the RPR
4. Perform a herpes PCR test
5. Perform a type-specific herpes serological test



Etiology of Genital Ulcers In 516 STD Clinic Patients

515 patients recruited from STD Clinics in 10 U.S Cities With High Syphilis Rates

PCR Result	Number (%)
HSV	320 (62%)
Syphilis	51 (10%)
HSV and Syphilis	13 (3%)
Chancroid	16 (3%)
PCR Negative	116 (22%)

Mertz K et al JID 1998: 178: 1795-9

Why Herpes Is The Most Common Cause of Genital Ulcer Disease, Worldwide

Herpes prevalence > 20% in most populations, worldwide, often exceeds 40%. Recurrence of lesions is common

Classical herpes is not typical herpes

Syphilis is a relatively rare, antibiotic susceptible disease with a time-limited genital ulcer stage

Result: Clinicians are more likely to encounter an infrequent manifestation of a very common disease (HSV) than a classical presentation of one which is far less common (syphilis).

Genital Herpes Is Usually Unrecognized

Self-reported genital herpes, sexually active Americans 18-59[1]		2.1% (Women 2.9%) (Men 1.2%)
Serologic evidence of HSV-2 infection, Americans 16-74		
	1978 [2]	16.4% (Women 19.4%) (Men 13.2%)
	1990 [3]	21.7%

Laumann EO, et al. The Social Organization of Sexuality p.382-389
Johnson RE, et al. NEJM 1989. 321:7-12
Johnson RE, et al. Abstracts of the 10th ISSTDR, No. 22, Helsinki, 1993

Genital Herpes: What People Say They Have

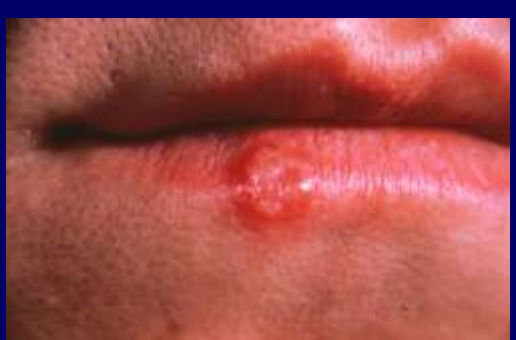
Yeast Infections
Zipper Cuts
Ingrown Hairs
Jock Itch
Folliculitis
Heat Rash
UTIs

Irritation From:
- **Tight Clothes**
- **Bike Seats**
- **Vigorous Sex**
- **Shaving**

Herpes on the Buttock

papules → vesicles → pustules → ulcers → crusts → healed

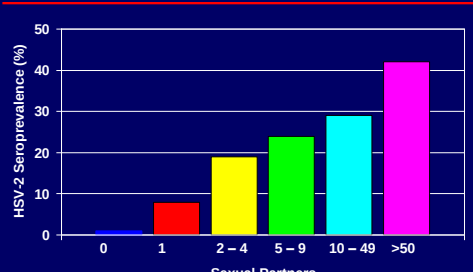
Source: Cincinnati STD/HIV Prevention Training Center



Popular Perceptions of Genital Herpes

- Genital herpes is easily recognized
- Most people with genital herpes know they are infected
- Genital herpes is usually transmitted by direct lesion contact
- The major benefit of genital herpes treatment is more rapid resolution of lesions and symptoms

HSV-2 Seroprevalence By Number Of Lifetime Sex Partners



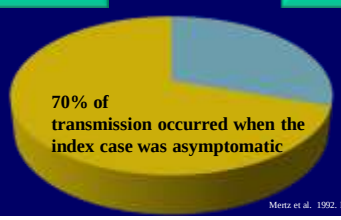
Fleming DT, et al. NEJM 1997. 337;1105-11.

Asymptomatic Viral Shedding

- No genital lesions present
  - Between clinical outbreaks
  - No history of clinical outbreaks
- Immune response present
- Common sites
  - Women: vulva and perianal region
  - Men: penile skin and perianal region
- Greatest in the first 3 months but continues
- Asymptomatic shedding is of briefer than during clinical recurrences

Genital Herpes Transmission Usually Occurs When Symptoms Are Absent

144 discordant couples followed over time → Median 334 Days → 14 of 144 partners were infected (9.7%)



Mertz et al. 1992. Herpes. Ann Intern Med. 116(3)

Genital Herpes Diagnosis

Tissue Culture

Polymerase Chain Reaction

~~Antigen Detection~~

~~Cytopathology~~

Serologic Tests

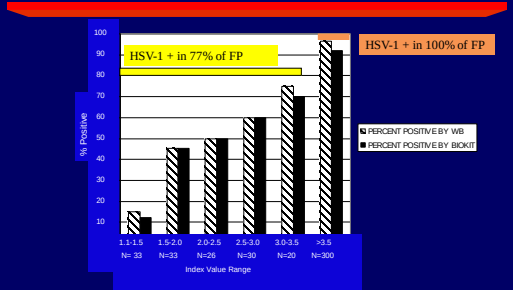
Genital Herpes Infection: Viral Shedding

	HSV-1	HSV-2
Initial	15%	85%
Recurrent	2%	98%

Type-Specific Serologic Tests

- Type-specific and nonspecific antibodies to HSV develop during the first several weeks following infection and persist indefinitely
- IgM tests are rarely useful and not recommended
- Presence of HSV-2 antibody indicates anogenital infection
- Presence of HSV-1 does not distinguish anogenital from orolabial infection.

Specificity of Focus HSV-2 ELISA



Morrow RA, Friedrich D, Meier A, Corey L. BMC Infect Dis 2005; 5:84.

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Principles of Management of Genital Herpes

Systemic antiviral chemotherapy

- Partially controls symptoms and signs of herpes episodes
- Does not eradicate latent virus
- Does not affect risk, frequency or severity of recurrences after drug is discontinued

Counseling

- Natural history
- Sexual transmission
- Perinatal transmission
- Methods to reduce transmission

Antiviral Medications

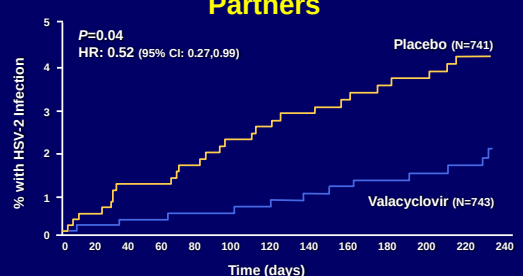
Systemic antiviral chemotherapy includes 3 oral medications:

Acyclovir Valacyclovir Famciclovir



Topical antiviral treatment has minimal clinical benefit and is not recommended.

Time to Overall Acquisition of HSV-2 Infection in Susceptible Partners



Adapted from Corey L et al. *N Engl J Med.* 2004;350:11-20.


1982
"Shhhh, Zog! ... Here come one now!"