Sexually Transmitted Infections
UPDATE for 2013

MN Reproductive and Sexual Health Update
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STIs – what are they?
- Infections which are spread from person to person via sexual contact
- Significant cause of morbidity
  - Immediate pain and suffering
  - Sequelae of infection
- Significant expenditure of resources

STD vs. STI
- Sexually transmitted disease
  - Long-standing, generally accepted term in US
  - Replaced earlier term "venereal disease" (VD)
- Sexually transmitted infection
  - Seems to be term of choice in Europe
  - Perhaps less stigmatizing
  - Implies that asymptomatic infections may not cause actual clinical "disease"

Venus, the Roman goddess of love

STI epidemiology: incidence vs. prevalence
- Incidence: # of new cases per year
  - US STI incidence = 20 million cases annually
- Prevalence: # of cases at any point in time
  - US STI prevalence = 110 million cases

THAT’S A LOT OF STIs
Let's start with....

SYPHILIS

Syphilis – clinical presentation

- Primary infection: painless genital ulcers
- Secondary infection: palmar-plantar rash
- Tertiary infection: neurological, cardiovascular, etc.

**Latent syphilis**: positive blood test but no signs or symptoms
Syphilis - diagnosis

- Darkfield microscopy
  - direct visualization of bacteria from lesions
- Serologic diagnosis
  - screen with non-treponemal test
    - RPR or VDRL
  - confirm with treponemal test
    - FTA-ABS or TP-PA

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Syphilis screening paradigm

TRADITIONAL

Non-treponemal tests
(i.e., RPR, VDRL)
- NON-SPECIFIC TO TP
- QUANTITATIVE
- REACTIVITY DECLINES WITH TIME

reflex to

Treponemal tests
(i.e., TPPA, FTA-Abs)
- SPECIFIC TO TP
- QUALITATIVE
- REACTIVITY PERSISTS OVER LIFETIME

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EMERGING / NEW...

Non-treponemal tests
(i.e., EIA, CLIA)
- SPECIFIC TO TP
- QUALITATIVE
- REACTIVITY PERSISTS OVER LIFETIME

reflex to

Treponemal tests
(i.e., RPR, VDRL)
- NON-SPECIFIC TO TP
- QUANTITATIVE
- REACTIVITY DECLINES WITH TIME
Why switch to EIA for screening?

- Automated (high throughput)
- Low cost in high volume settings
- Less lab occupational hazard (pipetting)

Be careful…

- EIA tests cannot distinguish active disease from old (treated) disease
- Lots of confusion re: management of patients with discrepant serology (e.g., positive EIA and negative RPR)

Treatment of syphilis

- Early syphilis: primary, secondary, early latent -- infection less than 1 year
  - Benzathine PCN-G 2.4 million units IM x 1
- Late syphilis: infection greater than 1 year or unknown duration (NOT neurosyphilis)
  - Benzathine PCN-G 2.4 million units IM q week x 3 doses

Tx of syphilis - penicillin allergy

- Doxycycline 100mg PO bid (or tetracycline 500mg PO qid)
  - treat for 2 weeks for early syphilis
  - treat for 4 weeks for late syphilis
- If pregnant and PCN-allergic: hospitalize and desensitize to PCN, since no other medication effectively crosses the placenta
Now let’s turn our attention to **GONORRHEA**

**Gonorrhea**
- **Bacterial agent:** *Neisseria gonorrhoeae*
  - non-motile Gram-negative diplococcus
  - often referred to as “gonococcus” (GC)
  - causes urethral inflammation in males
  - causes cervical inflammation in females

**Gonorrhea—Rates, United States, 1941–2011**

**Gonorrhea—Rates by Sex, United States, 1991–2011**

**Gonorrhea—Rates by State, United States and Outlying areas, 2011**

**Gonorrhea - diagnosis**
- Gram stain of urethral or cervical discharge
  - many PMNs
  - Gram-negative diplococci
  - provides presumptive diagnosis of infection
- Nucleic acid amplification tests (NAATs)
  - gold-standard, test of choice
  - detect small numbers of organisms
  - more sensitive, allows earlier diagnosis
  - can perform on genital, extra-genital, or urine specimens
Gonorrhea - diagnosis

- Culture
  - Specialized media required with specific environmental conditions
  - More difficult, less reliable than non-culture tests (NAATs)
  - But allows antimicrobial susceptibility testing

Gonorrhea - treatment

- Ceftriaxone 250 mg IM single-dose

  PLUS

- Anti-chlamydial therapy
  - Azithromycin 1.0 gram single oral dose
  - Doxycycline 100mg twice daily for 7 days

Gonorrhea resistance

- A recurring problem over the past 80 years
- Every new antibiotic puts selective pressure on the gonococcus
  - Reduced antimicrobial effectiveness
  - Emergence of true resistance

NOT!
Historical Perspective On Gonorrhea Antimicrobial Resistance

1945
Penicillin

1939
Sulfanilamide Introduced

Late 1940s
Tetracycline

1989
Ceftriaxone Recommended; Penicillin Dropped

1993
Quinolones & Cefixime

1945-1970s
Chromosomal PCN & Tetracycline resistance – gradual increase MICs

1976
Penicillinase Producing N. gonorrhoeae

1989
Ceftriaxone Recommended; Penicillin Dropped

1991
Quinolone Resistant NG in Hawaii

1993
Quinolones & Cefixime

2007
Quinolone No Longer Recommended

Mechanisms of resistance

- Genetic mutations affect the function of
  - cell surface binding proteins
  - outer membrane protein channels
  - cellular pump repressor

International Trends in GC Cephalosporin Susceptibility, 2010 - 2011

Norway: 2 cefixime treatment failures, 2010 (Ceftriaxone MIC 0.25-0.5)

Sweden: Pharyngeal treatment failure, 2010 (Ceftriaxone MIC 0.25-0.5)

UK: 2 possible cefixime treatment failures, 2010 (Cefixime MIC 0.25)

Austria: possible cefixime treatment failure, 2011 (Cefixime MIC 1)

UK: Cefixime treatment failure, 2011 (Cefixime MIC ≥ 0.25)

China: ~30% with elevated (≥0.06) ceftriaxone MICs, 2010

The New Yorker, October 1, 2012

“Whatever freedoms were won during the sexual revolution, bacterial evolution promises soon to constrain.”

How do we monitor GC resistance in the US?

- Gonococcal Isolate Surveillance Project (GISP)
- 26-29 sentinel clinic sites throughout the country
- Urethral isolates from first 25 men from each site each month
- Susceptibility testing performed by regional labs

Location of Participating Sentinel Sites and Regional Laboratories, Gonococcal Isolate Surveillance Project (GISP), United States, 2011
Percentage of Neisseria gonorrhoeae isolates that are Ciprofloxacin-Resistant by Sex of Sex Partner, Gonococcal Isolate Surveillance Project (GISP), 1995–2011

Distribution of Minimum Inhibitory Concentrations (MICs) of Cefixime Among Neisseria gonorrhoeae Isolates, Gonococcal Isolate Surveillance Project (GISP), 2009–2011

MMWR

Update to CDC’s Sexually Transmitted Diseases Treatment Guidelines, 2010: Oral Cephalosporins No Longer a Recommended Treatment for Gonococcal Infections

GC culture recommended for test of cure

- But culture is cumbersome, time-consuming, and not widely available
- Repeat NAAT is OK if culture not available

Chlamydia

- Bacterial agent: Chlamydia trachomatis
- Obligate intracellular prokaryotic bacterium
- 3 known species
  - trachomatis: urethritis, cervicitis, conjunctivitis
  - pneumoniae: respiratory infections
  - psittaci: respiratory infections
- Antigenically complex with multiple serovars
- Genus-specific LPS antigen and species-specific antigens in major outer membrane protein

Now, what about CHLAMYDIA
Clinical presentation (C. trachomatis)

- Nongonococcal urethritis
  - may progress to epididymitis
- Mucopurulent cervicitis
  - may progress to frank salpingitis, PID
- **But: most cases of NGU and MPC are not caused by Chlamydia** (other pathogens may include Mycoplasma, Ureaplasma, Trichomonas, anaerobes)

Chlamydia - diagnosis

- Nucleic acid amplification tests (NAATs)
  - gold-standard, test of choice
  - detect small numbers of organisms
  - more sensitive, allows earlier diagnosis
  - can perform on genital, extra-genital, or urine specimens

Chlamydia - treatment

- Macrolides
  - Azithromycin is drug of choice (single-dose)
- Tetracyclines / fluoroquinolones
  - Effective, but must take multiple doses over one week (lower compliance)
  - Quinolones more expensive

Now, a few words about HPV
Human papillomavirus
- Non-enveloped DNA virus
- 200 known types
- 30-40 types are sexually transmitted
- Warts
- Cancer
- Harald zur Hausen shared the Nobel Prize in 2008 for discovering the role of HPV in cervical cancer

HPV-Associated Disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>16/18</td>
<td>70% of Cervical Cancer</td>
<td>70% of Anal Cancer</td>
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<tr>
<td></td>
<td>70% of Anal/genital Cancer</td>
<td>Transmission to women</td>
</tr>
<tr>
<td>6/11</td>
<td>90% of Genital Warts</td>
<td>90% of Genital Warts</td>
</tr>
<tr>
<td></td>
<td>90% of RRP lesions</td>
<td>90% of RRP lesions</td>
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<tr>
<td></td>
<td>Transmission to women</td>
<td></td>
</tr>
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HPV: the most common STD
- ~20 million Americans are infected with HPV
- 6 million new infections per year
- At least 50% of sexually active people get HPV at some point

HPV DNA Tests
- Qiagen Hybrid Capture II®
  - RNA probes: 13 high risk types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 & 68
- Hologic Cervista®
  - 14 high risk types (as above plus type 66)
  - Separate HPV 16/18 test
- Roche Cobas HPV®
  - 14 high risk types
  - Separate HPV 16/18 test
- GenProbe Aptima HPV®
  - 14 high risk HPV types

HPV and Anogenital Warts
- HPV 6 and 11 responsible for >90% of anogenital warts
- Infectivity >75%
- Up to 30% spontaneously regress within 4 months in women.
- Treatment can be painful and embarrassing.
- Topical and surgical therapies are available for genital warts.
- Recurrence rates vary greatly.
  - As low as 5% with podofilox or laser treatment
  - As high as 65% with other treatments

Treatment of genital warts
- Primary reason is to ameliorate symptoms
- Warts may
  - Resolve spontaneously
  - Remain unchanged
  - Increase in size or number
  - Treatment depends on wart size, number and location

Recommendations for External Genital Warts
-瞬时应用：碘伏或酒精
- 剪除1%溶液
- 变性1%溶液
- 超声波1%溶液
- 喷射
- 冷冻
- 激光
- 冷冻
- 手术
- 激光
- 烧灼
- 病理
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When should I order an HPV test?

✓ Triage of ASC-US Pap result (if age >21)
✓ Co-test with Pap in women age 30+
✓ Very selective follow up situations
✓ Triage of LSIL in post-menopausal women

When should I NOT order an HPV test?

✗ Screening in women under 30
✗ Any use in women under 21
✗ Diagnosis of genital warts
✗ Testing in males
✗ ASC-H, HSIL or LSIL in pre-menopausal women
✗ Before vaccination
✗ STD screening

HPV Vaccine Efficacy*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16/18-related CIN2/3 or AIS</td>
<td>100</td>
</tr>
<tr>
<td>HPV 6/11/16/18 related CIN</td>
<td>95</td>
</tr>
<tr>
<td>HPV 6/11/16/18 related genital warts</td>
<td>99</td>
</tr>
</tbody>
</table>

*Among 16-26 year old females. CIN – cervical intraepithelial neoplasia; AIS – adenocarcinoma in situ

HPV Vaccines

Merck Gardasil®
- Types 6, 11, 16, 18
- Prevent warts, cervical cancer, anal cancer
- 3-dose series

GlaxoSmithKline Cervarix®
- Types 16, 18
- Prevents cervical cancer
- 3-dose series

Routine HPV Vaccination Recommendations

- ACIP recommends routine vaccination of males and females 11-12 years of age
- In females, the vaccination series can be started as young as 9 years of age at the clinician’s discretion
- "Catch-up" vaccination recommended for males and females 13 through 26 years of age

MMWR 2007;56(RR-2):1-24

On the horizon

- Nonavalent (9 strain) HPV vaccine from Merck (V503)
  - Covers high-risk, intermediate-risk, and wart-causing viral types
    - Types 6, 11, 16, 18, 31, 33, 45, 52, and 58
  - Phase III clinical trials currently under way

That’s great, but what about VAGINITIS
Trichomoniasis Treatment

Recommended regimen:
- Metronidazole 2 g PO x 1
- Tinidazole 2 g po x 1

Alternative regimen:
- Metronidazole 500 mg PO BID x 7d

Recommended regimen in pregnancy:
- Metronidazole 2 g PO x 1

Note: Vaginal therapy is ineffective
Tinidazole is a Category C drug in pregnancy

Trichomonas

- Incidence estimates:
  1 million new infections
- Prevalence: 3% nationwide,
  10% African American women,
  20-30% among incarcerated women
- Annual screening recommended for HIV+ women
  - new or multiple partners, history of STDs

Bacterial Vaginosis

- Recommended regimens
  - Metronidazole 500mg po bid x 7d OR
  - Metronidazole gel 0.75% intravag. qday x 5 d OR
  - Clindamycin cream 2% intravag. qhs x 7 d
- Alternative regimens
  - Tinidazole 2 gm po daily x 2 days
  - Tinidazole 1 gm po daily x 5 days
  - Clindamycin 300mg po bid x 7 d OR
  - Clindamycin ovules 100gm intravag. qhs x 3 d

Bacterial Vaginosis

- Screening: No changes to recs for screening in pregnancy (still not routinely recommended)
- Treatment of non-pregnant women: no changes

Finally, let’s turn our attention to

- Innovative approaches to STD prevention
  - Expedited partner therapy (EPT)
  - STD home testing for chlamydia

First we’ll discuss

EPT
EPT = “expedited partner therapy”
- Provision of medication to sex partners of persons with STDs
- Empiric therapy without examination
- Prevents complications in the partner
- Prevents re-infection of the source case

Types of EPT
- Patient-delivered partner therapy
  - Index case delivers single-dose therapy to partners
- Pharmacy-based partner therapy
  - Names of partners are provided to local pharmacy chain, and partner stops by to pick up medication

EPT reduces re-infection of original patient

But…. EPT is not legal in all 50 states

GREEN STATES: EPT is permissible (N=27)
YELLOW STATES: EPT is potentially allowable (N=15)
RED STATES: EPT is prohibited (N=8)

Now, let’s discuss
STI home testing

STI home testing

www.iwantthekit.org
Chlamydia - internet-based home testing

- Subject registers on site to request test kit
- Supplies sent to subject
- Specimen collects specimen, mails back to laboratory
- Results delivered by telephone using code and password
- Positive patients referred for treatment

Results (2004-08)

- 3,774 kits were requested
- 1,223 (32.4%) were returned
- Median age 23
- Chlamydia prevalence 9.1%
- Self-collected swabs acceptable
- Program expanded to males, additional sites

Iwantthekit.org

- Now available to residents of:
  - Alaska
  - Maryland
  - West Virginia
  - Philadelphia, PA
  - Denver, CO
  - selected counties in IL

THANK YOU!