Introduction to Sexually Transmitted Infections

McMaster University Obstetrics & Gynecology Clinical Clerkship Lecture

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Overview

- Importance of sexually transmitted diseases:
  - High burden of disease—most common reportable infectious diseases (CT).
  - “Syndromic” approach to treatment.
  - Sequelae: infertility, cancer, chronic pain, psychiatric illness.
  - Synergistic nature (HIV and other STDs).
  - Economic issues: correlation with poverty, high cost to society.
Reportable Diseases

- Health Protection and Promotion Act:
  - “a physician...shall report thereon to the M.O.H. of the health unit (Sect.25)”
    - In practice, labs do the reporting.
    - Public health department does “contact tracing”...usually just 1st generation of contacts.

- Importance of treating contacts: syphilis, gonorrhea, chlamydia, (trichomonas).
S.T.I.’s and Public Health

FIGURE 1
STD in Canada as a Proportion of all Notifiable Diseases, 1999*

- Genital chlamydia (56%)
- Gonorrhea & Syphilis (all types) (39%)
- Other notifiable diseases (5%)

* preliminary data

Source: Division of Disease Surveillance, Health Canada, 2000
Relationship with HIV Transmission

- **Systematic review:** increase risk 2-5 fold (includes chlamydia, gonorrhea, herpes, trichomonas).
  
  (Rottingen et al., Sex Transm Dis 2001).

- **Mathematical modelling:** HIV transmission may require STD to “take off” in heterosexuals.
  
  (Boily and Anderson, Sex Transm Dis 1999).

- **Conflicting reports of effectiveness of intervention** (Rakai, Mwanza)
  
  - Confounded by herpes?
  - Stage of epidemic?
  - Mass treatment leaves “seed”?
STI and Poverty

- Strong association.
  - True association?
  - Access to care by individual, community?
**Sexually Transmissible Infections**

### Viral
- Cytomegalovirus
- Hepatitis A virus
- Hepatitis B virus
- Hepatitis C virus
- Human immunodeficiency virus
- Human papillomaviruses
- Herpes simplex viruses
- HTLV-I and HTLV-II
- Human herpesvirus 8
- Molluscum contagiosum virus

### Protozoal
- Trichomonas vaginalis
- Giardia lamblia
- Entamoeba histolytica

### Bacterial
- Chlamydia trachomatis
- Neisseria gonorrhoea
- Treponema pallidum
- Ureaplasma urealyticum
- Mycoplasma species
- Shigella, Salmonella, and Campylobacter sp.
- Calymmatobacterium granulomatis
- Hemophillus ducreyi
- Helicobacter sp.

### Ectoparasites
- Pthirus pubis (pubic lice)
- Sarcoptes scabiei (scabies)
Overview

- Agents of cervicitis, urethritis, and P.I.D.
  - Gonorrhea, chlamydia, (others).
- Herpes simplex viruses.
- Genital warts.
- Syphilis: uncommon but important.
- Trichomonas vaginalis: an emerging sexually transmitted disease.
Case 1

17 year-old girl presents to clinic with vaginal discharge. New boyfriend, “on the pill”...no condoms. On exam, cervix red and friable. Some cervical motion tenderness and left adnexal tenderness. Boyfriend seen same day: notes “a little” discharge.

Gram stain of discharge:
Gonorrhea (1)

- *Neisseria gonorrhoea*, clinical spectrum of disease:
  - Females:
    - Cervicitis (discharge, spotting).
    - Urethritis and Bartholinitis.
    - Pelvic inflammatory disease.
  - Males:
    - Urethritis, epididymo-orchitis, prostatitis.
  - Both:
    - Asymptomatic infection.
    - Pharyngitis, proctitis.
    - Disseminated infection, (arthritis, “gun-metal” lesions).
Gonorrhea (2)

Microbiology:
- Gram negative intracellular diplococcus.
- Pili a key virulence factor: attachment.
- Antigenic shift: no immunity, no vaccine.
- Diagnosis: bacteriological, now PCR-based.

Epidemiology:
- Rates highest in 15-24 y.o.s, women > men.*
  - Natural clearance: importance of core group.
- Declining incidence in Canada.
  - Antibiotic resistance: PCN, tetracyclines, quinolones.
  - Current treatment (1 dose if uncomplicated): cephalosporins, quinolones, aminoglycosides.
Temporal Trends in Gonorrhea Incidence: Canada

FIGURE 7
Reported Gonorrhea Rates\(^1\) in Canada, 1980 to 1999\(^2\)

Health Canada, 2000
## Gonorrhea and Antibiotic Resistance in Canada

### Table 2

**Antimicrobial susceptibility of *N. gonorrhoeae* strains tested in Canada in 1998**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Number of strains resistant to antibiotics</th>
<th>Resistance (%) of all cultured strains in Canada n = 4,001*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>441</td>
<td>11.0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>954</td>
<td>23.8</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>381</td>
<td>9.5</td>
</tr>
<tr>
<td>Spectinomycin</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>44</td>
<td>1.1</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>25</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* 4,001 strains were tested by the Canadian *Neisseria gonorrhoeae* Antimicrobial Susceptibility Surveillance Network for 1998. The network is listed in Appendix 2.

Health Canada, 2000
Case 1 (continued)

Male partner: treated “syndromically” (azithromycin and cefixime) for urethritis.
Female partner: given cervical motion & adnexal tenderness, decision made to treat as an outpatient for P.I.D.: 2 weeks of levofloxacin and metronidazole.

Subsequent laboratory testing shows both to be infected with *Chlamydia trachomatis* as well as gonorrhea.
**Chlamydia trachomatis (1)**

- Most common reportable infectious disease in Canada.
- Assume it is present in individuals with known gonorrhea, urethritis, or cervicitis.
- Spectrum of genital disease similar to that seen with gonorrhea but:
  - **Asymptomatic** carriage much more common (~2/3)
  - Disseminated infection very rare, Fitz-Hugh-Curtis syndrome unusual.
Chlamydia (2)

- Biology: obligate intracellular pathogen.

- Culture relatively difficult:
  - Newer immunological and PCR-based tests: increased sensitivity, increased diagnosis.
  - Previously “culture negative” syndromes now known to represent chlamydial infection.
    - Easy to diagnose chlamydia via LCR on urine, genitals.
Chlamydia: Estimated Incidence

FIGURE 4
Reported Female Genital Chlamydia Rates\(^1\) in Canada by Age Group, 1997 to 1999\(^2\)

\[\text{Rate} \]
\[\begin{array}{c|c|c|c}
\text{Age Group} & \text{1997} & \text{1998} & \text{1999} \\
\hline
<1 & & & \\
1-4 & & & \\
5-9 & & & \\
10-14 & & & \\
15-19 & & & \\
20-24 & & & \\
25-29 & & & \\
30-39 & & & \\
40-59 & & & \\
60+ & & & \\
\end{array}\]

\(^1\) Rate per 100,000 population. Population estimates provided by Statistics Canada.
\(^2\) 1999 numbers are preliminary and changes are anticipated.


Health Canada, 2000
Chlamydia in Canada

Temporal Trends

Health Canada, 2000
Chlamydia (3)

- Importance of testing high-risk groups:
  - Up to 15% have silent carriage in Hamilton, Quebec City.
  - Carriage as high as 5% in pregnant women.
  - Progression to “silent” pelvic inflammatory disease.

- Chlamydia and fetal and neonatal morbidity:
  - PROM, chorioamnionitis, conjunctivitis, pneumonia.
  - Reduction in perinatal mortality from 2.4% to 0.6%. (Ryan, AJOG, 1990)

- Single-dose therapy for chlamydia now available: azithromycin 1 gram po.
  - In pregnancy? Amoxicillin x 7 days is official recommendation (for now).
Pelvic Inflammatory Disease (1)

- U.S. CDC definition (1998):
  - “spectrum of upper genital tract inflammatory disorders...includes endometritis, salpingitis, tubo-ovarian abscess, pelvic peritonitis.”
  - acute P.I.D. is infectious, “chronic P.I.D.” may be aseptic inflammation/scarring.
  - Sequelae: pelvic pain, ectopic pregnancy, infertility.
  - Strong association with prior or current gonorrhea or chlamydia.
Pelvic Inflammatory Disease (2)

- Infection commonly *polymicrobial*.
  - Gonorrhea, chlamydia or both often present, but other organisms present as well.
    - Initiation of infection by gonorrhea or chlamydia?
    - Cervicitis may allow other organisms to ascend.

- Other epidemiologic associations:
  - Contraceptive choice:
  - O.C.P. protective: why?
  - IUD: traditional association, recently challenged
    (Hubacher et al., NEJM August 2001)
Pelvic Inflammatory Disease (3)

Clinical features:

- low abdominal, adnexal, and cervical motion tenderness (minimal criteria).

  - Additional criteria: fever, discharge, gonorrhea or chlamydia isolated.

Ultrasound or laparoscopy can be useful in diagnosis.

Pelvic Inflammatory Disease (4)

- **Treatment:**
  - Broad-spectrum antibiotic regimen.
  - Should treat chlamydia, gonorrhea, enteric organisms and anaerobes
    - (e.g., metronidazole+levofloxacin, doxycycline+cefotetan, ampicillin+gentamicin+metronidazole).

- **Criteria for admission:**
  - Unable/unlikely to comply.
  - Pregnant.
  - Severe illness, fever, nausea, vomiting.
  - Abscess present.
Genital Herpes (1)

- Most common cause of ulcerative genital disease in North America.
  - Also common in developing world.
  - Caused by HSV-2 > HSV-1.
- Approximately 25% of U.S adults seropositive for HSV-2.
- Wide spectrum of disease severity: 50-90% of infected individuals unaware of infection.
  - “Urinary tract infection, yeast infection” (Langenberg, Ann Intern Med ‘89)
Genital herpes (2)

- Asymptomatic shedding common (~1-10% of days).
  - Infection probably commonly transmitted by shedders.
- Primary HSV syndrome may require hospitalization:
  - Urinary retention, meningitis in 5-10%.
- Relapsing ulcerative genital disease
- May manifest as itching, discharge, meningitis.
Genital Herpes
Diagnosis and Treatment

- Clinical picture not necessarily classical:
  - Viral culture, direct fluorescent antigen testing, Tzanck smear.

- Newer type-specific serological assays:
  - Appropriate application?

- Highly effective, nontoxic antiviral agents:
  - Acyclovir, valacyclovir, famcyclovir.
    - Shorten duration of primary and relapse disease.
    - Suppressive therapy: decreased symptoms and shedding
    - Decreased transmission?

- **Condoms** prevent transmission within couples!
  - (better for male→female transmission than female → male). (Wald, JAMA 2001)
Maternal-fetal transmission of HSV:

- may result in systemic or CNS disease in newborn, with death or cognitive delay.
- Increasing recognition of risk associated with new infection in 3rd trimester (Brown, NEJM 1997).

Current obstetrical practice: Caesarean section in women with visible HSV lesions at delivery.

- No established role for peripartum HSV cultures.
- No established role for antiviral drugs in pregnant women with history of genital HSV.
Genital Warts

- Caused by human papilloma virus, > 100 types!
  - Infection with HPV very common:
    - 40-70% shed HPV transiently.
  - Warts appear in a minority (types 6, 11).
  - Varied appearances.
    - Emotional distress, maternal-fetal transmission can occur.

- HPV 16, 18, 31, 45 also associated with carcinoma of the cervix, anus.
  - Presence of warts not directly related to cancer risk.
Epidemiology of HPV

- In Ontario:
  - Cross-sectional prevalence of HPV carriage 24% in women.
    - Carriage predicted by # of lifetime partners.
      (Sellors, CMAJ 2000).
  - Cohort of 1075 women with baseline normal Pap and HPV(-) followed longitudinally.
    - RR of abnormal Pap = 13.0 (95% CI 4.7-35.6).
    - Median duration of detectability of HPV 14 months.
      (Woodman et al., Lancet, 2001)
Time-Varying Hazards Related to HPV Acquisition

Derived from Woodman et al., Lancet 2001
Genital Warts: Therapy

- **MD/RN applied:**
  - liquid nitrogen.
  - TCA.
  - Podophyllin 25%.

- **Self-applied:**
  - Podophyllin 5%.
  - Immiquimod.

- Podophyllin, immiquimod not used in pregnancy.
  - Most respond, but relapses common.
  - Virus not eradicated.
    - New vaccines?
Syphilis

- *Treponema pallidum*: a spirochete.

- **Demographics are destiny!**
  - Syphilis is rare N. America, but more common in some populations (African-Americans, MSM).

- **Importance:**
  - Outbreaks in MSM in California, Seattle, Chicago, Montreal, Vancouver.
  - Influence of the Internet (Klausner et al., JAMA 2000).
  - Interaction between HIV and syphilis.

- **Immigration:**
  - From areas with high rates of syphilis.
  - Endemic treponematoses and syphilis serology.
FIGURE 12
Infectious Syphilis* in Canada – Average Annual Cases from 1997 to 1999**

Average annual cases over 3 years

- 0
- 1-50
- >50

\[ r = \text{1999 rate per 100,000 population} \]

Infectious syphilis: primary and secondary and early latent.
* 1999 numbers are preliminary.

Source: Health Canada, Division of STD Prevention and Control, 2000
FIGURE 1. Counties with rates above the national health objective for 2000 of 4.0 per 100,000 population — United States, 1999
FIGURE 1. Number of primary and secondary (P&S) syphilis cases overall and among men who have sex with men (MSM), by month and year — Southern California, January 1999–July 2000
Endemic Treponematoses
Syphilis: Clinical

- Usually divided into “stages”:
  - Primary: chancre.
  - Secondary: rash (back, palms, soles).
  - Latent: early latent vs. late latent.
  - Tertiary syphilis: destructive lesions of bone, eye (iris), cardiac disease, central nervous system disease.
Syphilis
Syphilis: Diagnosis

- Primary, secondary disease:
  - Can’t be cultured in vitro.
  - Darkfield microscopy.

- Serological diagnosis:
  - Nontreponemal tests (e.g., VDRL): screening.
  - Treponemal tests (e.g., MHA-TP): definitive serological diagnosis.

- Lumbar puncture with CSF VDRL:
  - For diagnosis of neurosyphilis (different treatment).
# Serologic Tests of Syphilis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sero-conversion</th>
<th>Test Characteristics</th>
<th>Cost</th>
<th>Persistence</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDRL, RPR</td>
<td>Weeks-Months</td>
<td>Good, but lots of false positives</td>
<td>Cheap</td>
<td>Non-persistent</td>
</tr>
<tr>
<td>MHA-TP, FTA, WB</td>
<td>Weeks</td>
<td>Excellent</td>
<td>Expensive</td>
<td>Life-long</td>
</tr>
</tbody>
</table>

Hook and Marra, NEJM 1992
### False Positive Serologic Tests

<table>
<thead>
<tr>
<th>Bacterial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-treponemal</strong></td>
</tr>
<tr>
<td>Pneumococcal dz.</td>
</tr>
<tr>
<td>Mycobacteria (TB, M. leprae)</td>
</tr>
<tr>
<td>Spirochetes (relapsing fever, lepto)</td>
</tr>
<tr>
<td>Malaria</td>
</tr>
<tr>
<td>Endocarditis</td>
</tr>
<tr>
<td>Rickettsial dz</td>
</tr>
<tr>
<td><strong>Treponemal</strong></td>
</tr>
<tr>
<td>Lyme dz.</td>
</tr>
<tr>
<td>Leptospirosis &amp; relapsing fever</td>
</tr>
<tr>
<td>Malaria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Viral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinia</td>
</tr>
<tr>
<td>Varicella</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Measles</td>
</tr>
<tr>
<td>Viral hep.</td>
</tr>
<tr>
<td>EBV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver disease</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Transfusion</td>
</tr>
<tr>
<td>Advanced age</td>
</tr>
<tr>
<td>Connective tissue dz.</td>
</tr>
</tbody>
</table>

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Hook and Marra, NEJM 1992

Serologic test results do not permit distinction between *T. pallidum* infection and “endemic treponematoses”: assume *T. pallidum*.
Prozone

- False negative reaction, reverts to positive with dilution of serum

No prozone

Prozone

dilute
Syphilis Treatment

- Benzathine penicillin: mainstay of therapy.
  - 1 dose (2.4 million units) adequate for early syphilis (1°, 2°, early latent).
  - 3 doses (1 per week x 3) for late latent or tertiary syphilis.
    - Neurosyphilis (includes eye disease): IV penicillin G x 10-14 days.
  - Alternative to penicillin: doxycycline.
- Follow VDRL after treatment: titre should decrease.
Pregnancy and Syphilis

- First trimester screening mandatory.

- Fetal infection:
  - Probably trans-placental.
  - Risk increases with fetal age.
  - Greatest risk with 2° and early latent dz.

- Clinical manifestations:
  - osteitis, hepatitis, “snuffles”, stillbirth

- Treatment of pregnant woman is as for non-pregnant but **only PCN** used → indication for desensitization.
Trichomoniasis (1)

- *T. vaginalis*
  - Common cause of vaginitis (along with candida and bacterial vaginosis).
  - Complaints of itching, discharge, odor.
- Diagnosis: traditionally via “wet mount”.
  - Culture available, seldom used.
  - Newer antibody-based techniques.
- Recognition as an S.T.I. relatively recent.
  - Urethritis, “itchy urethra” in male partners.
  - Reinfection if male partner is not treated.
Trichomoniasis (2)

- Treatment with metronidazole.
- Association with prematurity:
  - Screening and treatment in 2nd trimester advocated previously.
  - RCT of screening/treatment: trend towards greater prematurity in treatment arm. (Klebanoff NEJM 2001)
- Increasing recognition of importance of T. vaginalis as a cofactor in HIV transmission in U.S. (Sorvillo, Emerg Infect Dis 2001)