All Things Infectious Disease:
Clinical Topics for Primary Care

Andrew Urban MD
Professor of Medicine
Division of Infectious Diseases
University of Wisconsin School of Medicine and
Public Health

Disclosure

I have no financial interests or relationships to disclose.
All Things ID – You Pick ‘em

- Genital herpes
- *C. difficile*
- Chlamydia and Gonorrhea in 2020
- Urinary Tract Infection
- Fluoroquinolones 2020
- Recurrent cellulitis
- HIV testing
- HIV PrEP and PEP
- COVID-19 questions

COVID-19 Questions
Genital Herpes

What is the Most Common Appearance of Recurrent Genital Herpes?

- A
- B
- C
What is the Most Common Appearance of Recurrent Genital Herpes?

- A
- B

• C 45 million people have it, most do not know it
Only 10-15% of HSV-2 sero+ patients will report classic vesicles/ulcers
Often recurrent genital herpes is attributed to something else

---

TABLE 1. Patient-reported etiology of genital lesions from which HSV was isolated

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeast infection</td>
<td>Folliculitis</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>Jock itch</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>“Normal” itch</td>
</tr>
<tr>
<td>Urethral syndrome</td>
<td>Zipper burns</td>
</tr>
<tr>
<td>Menstrual complaint</td>
<td>Hemorrhoids</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>Allergy to condoms</td>
</tr>
<tr>
<td>Allergy to:</td>
<td>Irritation from:</td>
</tr>
<tr>
<td>Condoms</td>
<td>Tight jeans</td>
</tr>
<tr>
<td>Sperm</td>
<td>Sexual intercourse</td>
</tr>
<tr>
<td>Spermicide</td>
<td>Bike seat</td>
</tr>
<tr>
<td>Elastic/pantyhose</td>
<td>Insect or spider bites</td>
</tr>
<tr>
<td>Irritation or rash from:</td>
<td></td>
</tr>
<tr>
<td>Sexual intercourse</td>
<td></td>
</tr>
<tr>
<td>Bike seat</td>
<td></td>
</tr>
<tr>
<td>Shaving</td>
<td></td>
</tr>
</tbody>
</table>

RECURRENT genitourinary symptoms and signs are the clue
Asymptomatic Viral Shedding: presence of HSV on the skin or mucosa in the absence of signs of symptoms. Landmark studies using PCR have taught us a lot.

Shedding occurred an average of 28% of days

Daily acyclovir reduced shedding by 80%

Figure 2. The virologic and clinical course of HSV infection of subject 14 during placebo and acyclovir therapy. The + denotes a day in which HSV was isolated by culture; on all other days HSV cultures revealed no growth. The woman received placebo on day 1–88 of study and acyclovir 400 mg twice a day on days 89–160. Day, consecutive day of sampling.

Up to 70% of Transmission May Occur During Asymptomatic Viral Shedding

144 healthy couple serodiscordant for genital herpes. Couple were followed for a mean of 334 days, and 9.7% of partners became infected. Of these, 70% of transmissions occurred during asymptomatic shedding.
Genital Herpes is Both HSV-1 and HSV-2

- **HSV-1**
  - 70% of genital herpes in young adults
  - Recurrences less frequent (1/yr) and less severe
  - Seropositivity = cold sores or genital infection

- **HSV-2**
  - Decreasing prevalence 18% to 12.1% age 14-49
  - Causes nearly all recurrences (median 5/yr)
  - Seropositivity = genital herpes

Routine Serologic Screening for Genital Herpes in Asymptomatic Adolescents, Adults, or Pregnant is NOT RECOMMENDED by CDC or USPSTF

- **HSV-2** serologic testing
  - Low specificity
  - High false-positive rate
  - Confirmatory test not widely available

- **HSV-1** serologic testing
  - Cannot tell if the site of infection is oral or genital
# Herpes Diagnostics

<table>
<thead>
<tr>
<th>Herpes Diagnostics</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Swab for PCR** (Direct detection) | Fresh vesicle, pustule, ulcer  
Swab the base with “vigor”  
Types the virus – important for prognosis  
**BEST** test |

**Presents with lesions**

- HSV-2  
  - Expect more recurrences  
  - Counsel  
  - Suppression important
- HSV-1  
  - Expect few recurrences  
  - Counsel  
  - Suppression less studied

<table>
<thead>
<tr>
<th>Herpes Diagnostics</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Type-specific HSV-2 IgG** (IgG to glycoprotein G2) | Can distinguish HSV-2 from HSV-1  
Caution when Index values are low  
**GOOD** test with important LIMITATIONS |
| **Western Blot** (Univ Washington Clinical Virology Lab) | Can determine if low-positive type-specific HSV-2 IgG is true positive. Gold standard  
**CONFIRMATORY**, not screening, test |
| **Non type-specific antibodies** (Serology) | **WORTHLESS** but still orderable  
Older tests that cannot distinguish HSV-1/2 |
| **Herpes IgM tests** (Serology) | **WORTHLESS** but still orderable  
IgM gets made with recurrences |

**Presents with recurrent GU symptoms, no lesions**

- Type Specific Glycoprotein G  
  HSV-2 Ab  
  Positive, high index value – dx is genital herpes  
  Positive, low index value – repeat using a different  
  Type-specific assay or send WB to U Wash  
  Negative – repeat in 3 months if recent acquisition suspected
Situations for HSV-2 Type-Specific Serology

- Genital lesion might be herpes but PCR negative
  - Positive HSV-2 type-specific Ab would confirm

- Recurrent genital symptoms, but no lesion to swab
  - Positive HSV-2 type-specific Ab would confirm

- Someone desires screening or to know serostatus
  - Positive HSV-2 type-specific Ab would confirm

Be mindful that low-positive index values could be false-positive, and should be confirmed with a different type-specific test or the Univ of Washington Western blot

Management

- First episode genital herpes
  - All should be treated

- Recurrent genital herpes
  - Individualize your approach
Approach to Recurrent HSV
3 options

- Suppression
  - Reduces recurrences by 70-80%
  - Robust safety data
  - No practical concern for resistance
  - Reduces transmission to serodiscordant partner
- Intermittent self directed therapy
  - Give them a supply, start at prodrome
- Do nothing

---

Once-Daily Valacyclovir to Reduce the Risk of Transmission of Genital Herpes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valacyclovir (N=74)</th>
<th>Placebo (N=74)</th>
<th>Total No.</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquisition of symptomatic HSV-2 infection</td>
<td>4 (5.4)</td>
<td>16 (21.9)</td>
<td>20</td>
<td>0.29 (0.10-0.83)</td>
<td>0.034</td>
</tr>
<tr>
<td>Overall acquisition of HSV-2 infection</td>
<td>14 (1.9)</td>
<td>27 (3.6)</td>
<td>41</td>
<td>0.52 (0.27-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Acquisition of HSV-1 or HSV-2 infection</td>
<td>14 (1.9)</td>
<td>31 (4.2)</td>
<td>45</td>
<td>0.45 (0.24-0.84)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

- 1484 monogamous couples serodiscordant for HSV-2
  - Source partner randomized to valacyclovir 500 mg daily vs placebo x 8 mos
  - Susceptible partner monitored for acquisition of HSV

48% reduction in the risk of the seronegative partner acquiring HSV-2
Antivirals for HSV

- Acyclovir = Valacyclovir = Famciclovir
  - Choose on cost, dosing, preference
  - Clinical trials have been done on HSV-2, guidelines do not make a distinction between HSV-2 and genital HSV-1
  - Dose and duration vary by indication (table from CDC STD)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Acyclovir</th>
<th>Valacyclovir</th>
<th>Famciclovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Episode(^1)</td>
<td>400 mg TID x 7-10 d</td>
<td>1gm BID x 7-10 d</td>
<td>250 mg TID x 7-10 d</td>
</tr>
<tr>
<td>Suppression(^2)</td>
<td>400 mg BID</td>
<td>500-1000 mg once/d</td>
<td>250 mg BID</td>
</tr>
<tr>
<td>Episodic(^3)</td>
<td>3 regimens</td>
<td>2 regimens</td>
<td>3 regimens</td>
</tr>
</tbody>
</table>

\(^1\) Sometimes need 14-21 days if healing incomplete at 10 days
\(^2\) Valacyclovir 500mg once daily not as effective when > 10 recurrences/yr
\(^3\) Acyclovir 400 mg TID x 5 days is what I recommend

C. difficile

How do the 2017 C difficile guidelines change my practice?
68 Year Old Man in Your Clinic

- Finished cephalexin for a paronychia 3 weeks ago, ever since has watery stools (3-6 per day) and cramps

- Stool C diff toxin PCR returns positive

What Would You Choose?

A. Metronidazole po x 10 days
B. Vancomycin po x 10 days
C. Vancomycin po taper/pulse
D. Fecal microbiota therapy (FMT)
Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

- Metronidazole
  - no longer recommended as first-line
  - no longer recommended for recurrent CDI
- First recurrence
  - Options depend on what was used initially
- Beyond first recurrence
  - 4 options (3 drug-based and FMT)
- No guidance on the use of monoclonal Ab
  - Bezlotoxumab

A Comparison of Vancomycin and Metronidazole for the Treatment of *Clostridium difficile*–Associated Diarrhea, Stratified by Disease Severity

**Table 2. Rate of cure of *Clostridium difficile*–associated diarrhea by disease severity and treatment.**

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>No. of patients cured/ no. of patients treated (%)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mtz group</td>
<td>Vm group</td>
</tr>
<tr>
<td>Mild</td>
<td>37/41 (90)</td>
<td>39/40 (98)</td>
</tr>
<tr>
<td>Severe</td>
<td>29/38 (76)</td>
<td>30/31 (97)</td>
</tr>
<tr>
<td>All</td>
<td>66/79 (84)</td>
<td>69/71 (97)</td>
</tr>
</tbody>
</table>

**NOTE.** Mtz, metronidazole; Vm, vancomycin.
Increasing Risk of Relapse after Treatment of *Clostridium difficile* Colitis in Quebec, Canada

Jacques Pégue, Marie-Eve Alary, Louis Valiquette, Evelyne Reiche, Joanne Ruel, Katolin Fulop, Dominique Godin, and Claude Bourassa

Department of Microbiology and Infectious Diseases, University of Sherbrooke, Sherbrooke, Quebec, Canada

- Clinical treatment failure w/ metronidazole
  - Before 2003: 10%
  - After 2003: 26%

- Probability of recurrence after metronidazole
  - Before 2003: 21%
  - After 2003: 47%

Let’s Dissect CDI Medications

- **Metronidazole**
  - Has to “drip into colon” via injured capillaries
  - Higher relapse rate, not as good in severe CDI
  - IV metronidazole is an ADJUNCT at best for severe CDI

- **Vancomycin PO** (no role for IV)
  - No GI absorption, stays in colon but has to GET INTO the colon (PO/NG/PR)
  - Taper/pulse – great pathophysiology

- **Fidaxomicin**
  - Equal efficacy, lower relapse, higher cost (vs vanco)
CDI Classification and Treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-severe</td>
<td>WBC &lt; 15 and Scr &lt; 1.5</td>
<td>Vancomycin 125 mg po QID x 10d OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fidaxomicin 200 mg po BID x 10d</td>
</tr>
<tr>
<td>Severe</td>
<td>WBC &gt; 15 or Scr &gt; 1.5</td>
<td>Vancomycin 125 mg po QID x 10d OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fidaxomicin 200 mg po BID x 10d</td>
</tr>
<tr>
<td>Fulminant</td>
<td>Hypotension, shock, ileus,</td>
<td>Vancomycin 500 mg PO/NG QID PLUS</td>
</tr>
<tr>
<td></td>
<td>megacolon</td>
<td>Metronidazole 500 mg IV q8h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IF ILEUS ADD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vancomycin 500 mg in 500 ml NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>retention enema QID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AND General Surgery and ID consults</td>
</tr>
</tbody>
</table>

Clin Infect Dis 2018;66(7):e1

Same Patient, 8 Weeks Later

- Finished a 10 day course of oral vancomycin with resolution of his diarrhea.
- However, diarrhea and cramps returned 1 week ago.
- Stool C diff PCR returns positive
What Would You Choose?

A. Metronidazole po x 10 days
B. Vancomycin po x 10 days
C. Vancomycin po taper/pulse
D. Fecal microbiota therapy (FMT)
E. No therapy he is colonized

CDI Recurrence

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First recurrence, metronidazole used initially</td>
<td>Vancomycin x 10d</td>
<td>Do not give repeat metronidazole course</td>
</tr>
<tr>
<td>First recurrence, vancomycin used initially</td>
<td>(1) Vancomycin taper/pulse</td>
<td>125 mg PO QID x 10-14d, then</td>
</tr>
<tr>
<td></td>
<td>(2) Fidaxomicin x 10d</td>
<td>125 mg PO BID x 7d, then</td>
</tr>
<tr>
<td></td>
<td></td>
<td>125 mg PO daily x 7d, then</td>
</tr>
<tr>
<td></td>
<td></td>
<td>125 mg PO q2-3d x 2-8 weeks</td>
</tr>
<tr>
<td>Beyond first recurrence</td>
<td>(1) Vancomycin taper/pulse</td>
<td>4 options</td>
</tr>
<tr>
<td></td>
<td>(2) Vanco x 10d followed by</td>
<td>ID or GI consult</td>
</tr>
<tr>
<td></td>
<td>rifaximin x 20d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3) Fidaxomicin x 10d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4) FMT</td>
<td></td>
</tr>
</tbody>
</table>

Clin Infect Dis 2018;66(7):e1
Early Antibiotic Exposure After FMT

- 349 patients who underwent FMT
  - 12.6% overall failure rate
  - Early antibiotic use (within 8 weeks) was strongest predictor of FMT failure (OR 2.86, 1.16-7.06)
- Most pts (71%) received abx within 4 weeks of FMT
  - 36% UTI, 20% RTI, 12% SSTI
  - Cipro, cephalexin, Augmentin most common

**Flag these patients on the EHR problem list and intensive patient education**

---

**FMT in the News**

**NEJM November 21, 2019; Clinical Inf Dis November 15, 2019**

**Drug-Resistant E. coli Bacteremia Transmitted by Fecal Microbiota Transplant**

Zacharias DeFilipp, M.D., Patricia P. Bloom, M.D., Mariam Torres Soto, M.A., Michael K. Mansour, M.D., Ph.D., Mohamed R.A. Sater, Ph.D., Minam H. Huntley, Ph.D., Sarah Turbett, M.D., Raymond T. Chung, M.D., Yi-Bin Chen, M.D., and Elizabeth L. Hohmann, M.D.

Fecal microbiota transplantation (FMT) is an emerging therapy for recurrent or refractory Clostridium difficile infection and is being actively investigated for other conditions. We describe two patients in whom extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli bacteremia occurred after they had undergone FMT in two independent clinical trials; both cases were linked to the same stool donor by means of genomic sequencing. One of the patients died. Enhanced donor screening to limit the transmission of microorganisms that could lead to adverse infections events and continued vigilance to define the benefits and risks of FMT across different patient populations are warranted.

---

**Patient 1**
- Cirrhosis
- Clinical trial FMT for hepatic encephalopathy

**Patient 2**
- MDS
- Clinical trial FMT pre/post allogeneic stem cell txplnt

ESBL E coli bacteremia in both, linked to same stool donor

---

**FMT for recurrent CDI**

PCR screening
PCR+Microscopy--8/16 colonized
No GI sx or impact on CDI outcome

---

Andrew Urban, MD
All Things Infectious Disease
Chlamydia and Gonorrhea in 2020

Let’s Talk Epidemic
2017 data released August 2018

CDC: Sexually Transmitted Disease Rates Have Hit an All-Time High—Again

Sexually transmitted diseases surge for the 4th straight year, CDC reports

Number of babies born with syphilis in US hits 20-year high, report finds

Centers for Disease Control recorded 918 cases of syphilis in infants in 2017, a 46% increase on the previous year

Syphilis up 412%, gonorrhea 204%: Why are Orange County STD rates through the roof?
A 34 Year Old Man Presents for a Discussion on HIV PrEP

- New partner, not monogamous
- Uses condoms some of the time
- Receptive anal and oral intercourse
- HIV negative
- Rectal swab for Chlamydia is NAAT positive
What Would You Use?

A. Ceftriaxone 250 mg IM + Azithromycin 1 gm po
B. Azithromycin 1 gm po once
C. Doxycycline 100 mg po BID x 7 days
D. Levofloxacin 500 mg po x 7 days

But Dr. Urban, We Don’t See This in Our Clinics
Chlamydia is the most commonly reported STD in the United States. Chlamydia is the most common notifiable disease in the United States.

Figure 1. Chlamydia — Rates of Reported Cases by Sex, United States, 2000–2018

Ages 15-24

Figure 5. Chlamydia — Rates of Reported Cases by Age Group and Sex, United States, 2018

* Per 100,000.

cdc.gov. STD Surveillance 2018

Andrew Urban, MD
All Things Infectious Disease
Chlamydia Trachomatis
Clinical Syndromes Serotypes D-K

- Asymptomatic infection
- Conjunctivitis
- Pharyngitis
- Urethritis, epididymitis, cervicitis, Bartholinitis, PID
- Proctitis
- Reactive arthritis

- Lymphogranuloma venereum (LGV)
  - Serotypes L1-L3

2015 CDC STD Guidelines
Chlamydia Screening Recommendations

<table>
<thead>
<tr>
<th>Women</th>
<th>Pregnant Women</th>
<th>Men</th>
<th>MSM</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexually active &lt; 25</td>
<td>All &lt; 25</td>
<td>Consider screening in high prevalence clinical settings** or in populations with high burden of infection (eg MSM)</td>
<td>At least annually for sexually active MSM at sites of contact (urethra, rectum) regardless of condom use</td>
<td>For sexually active individuals, screen at first HIV evaluation, and at least annual thereafter</td>
</tr>
<tr>
<td>Sexually active &gt; 25 at increased risk**</td>
<td>If at increased risk* and &gt; 25</td>
<td>Retest during 3rd trimester for those &lt; 25 or at risk</td>
<td>Test of cure 3-4 wks after treatment and retest within 3 mos</td>
<td>More frequent based on individual risks, local epidemiology</td>
</tr>
</tbody>
</table>

NOTES
- All screening by NAAT: nucleic acid amplification tests
- BEST urogenital specimen types: (W) vaginal swab (self-collect or clinic) (M) urine
- Other options: endocervical, urethral
- Rectal and throat NAAT (2 kits) cleared by FDA in May 2019

*Increased risk: new partner, > 1 partner, partner with concurrent partners, partner w/ STD
**High prevalence clinical settings: STD clinics, adolescent clinics, correctional facilities
Extragenital Chlamydia and Gonorrhea

- Means testing rectal and pharyngeal sites when exposure at those sites has occurred

- What proportion of chlamydia and gonorrhea cases are missed by urogenital screening only?

Infections Missed by Urethral-Only Screening for Chlamydia or Gonorrhea Detection Among Men Who Have Sex With Men

Julia L. Marcus, MPH,* Kyle T. Bernstein, PhD, ScM,† Robert P. Kohn, MPH,* Sally Liska, DrPH,* and Susan S. Philip, MD, MPH*

<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>Chlamydia, % (95% CI)</th>
<th>Gonorrhea, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethra</td>
<td>2.3 (1.8–2.9)</td>
<td>0.4 (0.2–0.6)</td>
</tr>
<tr>
<td>Rectum</td>
<td>7.8 (6.9–8.8)</td>
<td>3.6 (3.0–4.2)</td>
</tr>
<tr>
<td>Pharynx</td>
<td>1.9 (1.5–2.5)</td>
<td>5.0 (4.3–5.8)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

77% 95% cases missed by urethral screening alone
The Case for Extranetal Screening of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in the College Health Setting


**4093 college men**

Percent cases missed by urogenital screening alone

<table>
<thead>
<tr>
<th></th>
<th>Chlamydia</th>
<th>Gonorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Chlamydia</em></td>
<td>26%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Sex Trans Dis 2017;44(5):274

---

*Neisseria gonorrhoeae* and *Chlamydia trachomatis* Among Women Reporting Extranetal Exposures

Joshua D. Trebach, BS,* C. Patrick Chaulk, MD,*† Kathleen R. Page, MD,*† Susan Tuddenham, MD, MPH,* and Khalid G. Ghanem, MD, PhD*†

**4400 women**

Percent cases missed by urogenital screening alone

<table>
<thead>
<tr>
<th></th>
<th>Chlamydia</th>
<th>Gonorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Chlamydia</em></td>
<td>14%</td>
<td>30%</td>
</tr>
</tbody>
</table>

STD 2015;42(5):233

---

Andrew Urban, MD
All Things Infectious Disease
Extragenital Gonorrhea and Chlamydia Among Men and Women According to Type of Sexual Exposure

David M. Bamberger, MD,* ‡ Georgia Graham, MD,* ‡ Lesha Dennis, BA, † and Mary M. Gerkovitch, PhD‡

4093 men and women
Percent cases missed by urogenital screening alone

<table>
<thead>
<tr>
<th></th>
<th>Chlamydia</th>
<th>Gonorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSW</td>
<td>33%</td>
<td>36%</td>
</tr>
<tr>
<td>WSM</td>
<td>33%</td>
<td>28%</td>
</tr>
</tbody>
</table>

Sex Trans Dis 2019;46(5):329

CDC Who Should Be Screened for Oral/Rectal Infections and When?

- Sexually active MSM who report exposure
  - At least annually, every 3-6 mos if risks persist or sexual partners have multiple partners
  - Rectal gonorrhea and chlamydia
  - Oral gonorrhea

- Women and MSW
  - Consider in anyone reporting exposure

*cdc.gov Screening/Questions and Answers/2015 STD Treatment Guidelines
Why Isn’t More EG Testing Being Done?

- Clinician factors
  - Sexual history taking skills
  - Knowledge about STD trends and risks
- Laboratory considerations
  - Swabs (be sure to use correct one)
  - Often GC and chlamydia NAAT are run together
  - Self-collect vs clinic collect
  - Cost

Many state health departments have excellent resources available

History for All Patients: 5 Ps

- **Partners**
  - # partners last 90 days and gender

- **Practices**
  - sites of sexual contact (oral, genital, vaginal, anal), injection drug use

- **Protection**
  - frequency of condom use

- **Past History**
  - previous STDs and testing

- **Prevention of Pregnancy**
  - contraception use

Rectal Chlamydia

- Asymptomatic (most common)

- Proctocolitis
  - Rectal pain, discharge, bleeding

- LGV (Lymphogranuloma venereum)
  - Short lived painless ulcer painful inguinal adenopathy
  - Proctocolitis can be severe; mimic IBD
  - L1-L3 serovars – specific LGV testing needed
  - Longer treatment duration 21 days

- Increased risk of HIV acquisition
  - 8-fold increased risk with 2 prior CT or GC rectal infections

JAIDS. 2010;53(4):537
2015 CDC STD Guidelines
MMWR 2016;65:920

Andrew Urban, MD
All Things Infectious Disease
The efficacy of azithromycin and doxycycline for the treatment of rectal chlamydia infection: a systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Efficacy difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>2009</td>
<td>0.44 (0.22, 0.67)</td>
</tr>
<tr>
<td>Elgalib</td>
<td>2010</td>
<td>0.19 (0.04, 0.34)</td>
</tr>
<tr>
<td>Hathorn</td>
<td>2012</td>
<td>0.21 (0.09, 0.34)</td>
</tr>
<tr>
<td>Khosropour</td>
<td>2013</td>
<td>0.07 (-0.09, 0.23)</td>
</tr>
<tr>
<td>Khosropour</td>
<td>2014</td>
<td>0.18 (0.11, 0.25)</td>
</tr>
<tr>
<td>M-H overall</td>
<td>I^2=48.5%, P=0.101</td>
<td>0.21 (0.15, 0.27)</td>
</tr>
<tr>
<td>D-L overall</td>
<td></td>
<td>0.20 (0.11, 0.28)</td>
</tr>
</tbody>
</table>

Figure 4. Efficacy difference between 7 days of doxycycline versus single-dose azithromycin for the treatment of rectal chlamydia infections. M-H, Mantel–Haenszel (fixed) methods.

Chlamydia Treatment

Recommended Regimens
Azithromycin 1gm single dose
or
Doxycycline 100 mg BID x 7 days

Doxycycline may be better for rectal infections. LGV needs 21 days of treatment

2015 CDC STD Guidelines
Health

Man has 'world's worst' super-gonorrhoea

By James Gallagher
Health and science correspondent, BBC News

28 March 2018

A man in the UK has contracted the first case of untreatable 'super-gonorrhoea' after an encounter with a woman in south-east Asia

Alien Millington
Mar. 29, 2018, 5:29 AM 65,958


His strain is resistant to multiple first-line treatments.

Gonorrhoea is Laughing at Us

<table>
<thead>
<tr>
<th>RESISTANCE</th>
<th>WHEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfa</td>
<td>1960s</td>
</tr>
<tr>
<td>Penicillins</td>
<td>1970s</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1980s</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>2006</td>
</tr>
<tr>
<td>Cefixime</td>
<td>2012</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>2015</td>
</tr>
</tbody>
</table>

Antibiotic Resistance Threats in the United States, November 2019 cdc.gov
Gonorrhea rapidly develops resistance to antibiotics—ceftriaxone is the last recommended treatment.

Antibiotic Resistance Threats in the United States, November 2019 cdc.gov
Uncomplicated Gonorrhea
cervix, urethra, rectum, pharynx

Ceftriaxone 250 mg IM x 1
PLUS
Azithromycin 1 gram PO x 1

- This is **dual drug therapy** – always include azithromycin regardless of any chlamydia test result
- **Do not substitute** doxycycline for azithromycin
- Penicillin or cephalosporin allergy – ceftriaxone is critical and alternatives are poorly available/tolerated, refer to Allergy for testing or graded challenge
- **Partner treatment** is critical, but poorly done
- Most treatment failure is **reinfection**
- Suspect drug failure? Contact local health dept, consult ID, send culture and susceptibility testing

2015 CDC STD Guidelines

Adherence to CDC Recommendations
for the Treatment of Uncomplicated GC

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Weighted no.</th>
<th>Weighted % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone 250 mg + azithromycin 1 g</td>
<td>74,199</td>
<td>88.1 (87.2 - 88.4)</td>
</tr>
<tr>
<td>Other regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone 250 mg only</td>
<td>5,139</td>
<td>5.9 (4.8 - 7.0)</td>
</tr>
<tr>
<td>Ceftriaxone or doxycycline</td>
<td>4,574</td>
<td>4.4 (3.3 - 5.6)</td>
</tr>
<tr>
<td>Azithromycin only</td>
<td>2,884</td>
<td>3.1 (2.2 - 4.1)</td>
</tr>
<tr>
<td>Ceftriaxone + azithromycin (other or unknown dosage)</td>
<td>1,030</td>
<td>1.2 (1.1 - 1.3)</td>
</tr>
<tr>
<td>Doxycycline only</td>
<td>1,035</td>
<td>1.2 (1.1 - 1.3)</td>
</tr>
<tr>
<td>Azithromycin only</td>
<td>299</td>
<td>0.3 (0.2 - 0.5)</td>
</tr>
<tr>
<td>Ceftriaxone (125 mg or unknown dosage) only</td>
<td>539</td>
<td>0.6 (0.2 - 1.2)</td>
</tr>
<tr>
<td>Other antibiotics*</td>
<td>426</td>
<td>0.5 (0.2 - 1.0)</td>
</tr>
<tr>
<td>Ceftriaxone 1 g + azithromycin 1 g or ceftriaxone 1 g + azithromycin 1 g</td>
<td>115</td>
<td>0.1 (0.0 - 0.3)</td>
</tr>
<tr>
<td>Ceftriaxone only</td>
<td>83</td>
<td>0.1 (0.0 - 0.2)</td>
</tr>
<tr>
<td>Azithromycin 2 g + gentamicin or gemifloxacin</td>
<td>51</td>
<td>0.1 (0.0 - 0.3)</td>
</tr>
</tbody>
</table>

MMWR 2018; 67(16): 473
2015 CDC STD Guidelines
Gonorrhea Screening Recommendations

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Pregnant Women</th>
<th>Men</th>
<th>MSM</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gonorrhea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexually active &lt; 25</td>
<td>All &lt; 25</td>
<td></td>
<td>All at least annually</td>
<td>At least annually for</td>
<td></td>
</tr>
<tr>
<td>Sexually active ≥ 25</td>
<td>If at increased risk*</td>
<td></td>
<td>at sites of contact</td>
<td>for sexually active MSM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Retest 3 months after</td>
<td></td>
<td>(urethra, rectum,</td>
<td>at sites of contact</td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td>treatment</td>
<td></td>
<td>pharynx) regardless</td>
<td>(urethra, rectum,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>of condom use Every</td>
<td>pharynx) regardless</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-6 mos if at</td>
<td>of condom use Every</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>increased risk</td>
<td>3-6 mos if at</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>increased risk</td>
<td></td>
</tr>
<tr>
<td><strong>Compare to</strong></td>
<td>SAME</td>
<td>SIMILAR</td>
<td>GONE!</td>
<td>SAME</td>
<td>SAME</td>
</tr>
<tr>
<td><strong>Chlamydia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTES**
- NAAT: vaginal swab, endocervical, urethral, urine
- Rectal and throat NAAT (2 kits) cleared by FDA in May 2019
- Culture: endocervical or urethral; also rectal, throat, conjunctival
- When to do culture? Suspected or documented treatment failure

*Increased risk: new partner, > 1 partner, partner with concurrent partners, partner w/ STD

---

**Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial**

- Open label study (n=232)
  - HIV-negative high risk MSM enrolled in IPERGAY On Demand PrEP study
- On demand PEP doxycycline 200 mg vs no PEP
  - Take ~24 hours after sex, up to 72 hours
  - Syphilis serology, PCR for gonorrhea/chlamydia (3 sites)
- PEP reduced overall incidence of bacterial STD by 47% over 8.7 mos of follow-up
  - 70% relative reduction in chlamydia
  - 70% relative reduction in syphilis
  - NO effect on gonorrhea

Lancet ID 2018;18:308

Andrew Urban, MD
All Things Infectious Disease
Future Gonorrhea Management

• Higher dose current agents
  – Ceftriaxone 500 mg-1gm, Azithromycin 2gm

• Investigational agents
  – Zoliflodacin Phase 2 study: cure, uncomplicated urogenital (96%), rectal (100%), pharyngeal (50-82%)
  – Eravacycline, omadacycline, iclaprim, gepotidacin, solithromycin

• Meningococcal B vaccine?
  – Case control study New Zealand, ages 15-30, vaccine efficacy 31%

63

Pandemic sparks concerns about surging STD, HIV rates

Health departments are concerned about spikes in STIs while attention is on COVID-19

Some places are already seeing case clusters

Across Idaho, the number of people getting tested for sexually transmitted infections and HIV has cratered. The Department of Health and Welfare is screening far fewer people than they did at this time last year, and many community organizations that do rapid HIV testing shut down when the state's stay-at-home order went into effect on March 26th.


64

Andrew Urban, MD
All Things Infectious Disease
# Fluoroquinolones 2020

## Comparative Activity

<table>
<thead>
<tr>
<th>Organism</th>
<th>Ciprofloxacin</th>
<th>Levofloxacin</th>
<th>Moxifloxacin</th>
<th>Delafloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcus</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>MRSA</td>
<td></td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Enteric GNR</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Anaerobes</td>
<td></td>
<td></td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Atypical</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

Let's Discuss Each Agent by Spectrum and Use

Adapted from idstewardship.com/five-things-know-delafloxacin/
Quinolones and *C. difficile* Risk

- Considered high risk antimicrobial class
  - 2017 IDSA *C difficile* guidelines update

*Emergence of Fluoroquinolones as the Predominant Risk Factor for Clostridium difficile—Associated Diarrhea: A Cohort Study during an Epidemic in Quebec*  

**JOURNAL ARTICLE**  
A Large Outbreak of *Clostridium difficile*-Associated Disease With an Unexpected Proportion of Deaths and Colectomies at a Teaching Hospital Following Increased Fluoroquinolone Use
What Does This Really Mean?

- Side effects matter
  - Patient education
  - Clinical decisions

- Blood sugar monitoring
- Qtc monitoring
- Aneurysm risk
- Mental status changes
- Lower seizure threshold
- Neuropathy
- Tendinopathy
- *C. difficile* disease

---

What Does This Really Mean?

- Don’t use quinolones for simple infections
  - Sinusitis = amoxicillin/clavulanate or doxycycline
  - Uncomplicated UTI = nitrofurantoin, TMP/SMX, or cephalosporin
  - Bronchitis = NO antibiotics

  This is key!
  But use them when you need to
Primary Care Conference  
Wednesday, July 8, 2020

Antibiotic Alternative to Fluoroquinolones
See link for HAP and sepsis recommendations and footnotes

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Historical Empic Therapy</th>
<th>Proposed New Empic Therapy</th>
<th>Comment (Step Down Therapy)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystitis or Uncomplicated Urinary Tract Infection</td>
<td>Ciprofloxacin OR Levofloxacin</td>
<td>Nitrofurantoin Fosfomycin Ceftazidime</td>
<td>Do not treat asymptomatic bacteria. Base on final culture results: nitrofurantoin, fosfomycin, TMP/SMX, ceftazidime. Ceftriaxone susceptibility predicts activity for ceftriaxone.</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Ciprofloxacin OR Levofloxacin</td>
<td>No risk for MDR: ceftriaxone or cefotaxime</td>
<td>If no oral options, page 3333 for fluorquinolone approval. Tailor therapy based on final culture results.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With risk factors for MDR: ceftriaxone and vancomycin*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>With risk factors for MDR and IgE-mediated or severe reaction to β-lactam: ceftriaxone OR TMP/SMX.</td>
<td>Ceftriaxone susceptibility predicts activity for ceftriaxone.</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis (SBP) prophylaxis</td>
<td>Ciprofloxacin</td>
<td>Oral therapy: TMP/SMX OR ceftriaxone Intravenous therapy: ceftriaxone</td>
<td>May transition to oral equivalent of empiric regimen OR to ciprofloxacin at discharge.</td>
</tr>
<tr>
<td>Intra-abdominal infection – community or healthcare associated infection</td>
<td>Ciprofloxacin AND metronidazole</td>
<td>No risk factors for MDR:</td>
<td>Base on final culture results, some examples of potential oral options: metronidazole OR ceftriaxone PLUS azithromycin PLUS metronidazole. Amoxicillin/Clavulanate acid if final culture results require fluoroquinolone step down (e.g., Pseudomonas) single oral dose prior to discharge is acceptable.</td>
</tr>
<tr>
<td></td>
<td>Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin</td>
<td>Vancomycin OR PLUS piperacillin/tazobactam OR vancomycin PLUS plus ceftriaxone AND metronidazole.</td>
<td>With risk factors for MDR and IgE-mediated or severe reaction to β-lactam: vancomycin PLUS azithromycin PLUS metronidazole.</td>
</tr>
<tr>
<td>Community-acquired Pneumonia*</td>
<td>Meropenem OR Levofloxacin</td>
<td>No risk factors for MDR:</td>
<td>Potential oral options: ceftriaxone OR cefuroxime PLUS azithromycin OR doxycycline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ceftriaxone PLUS doxycycline OR ceftriaxone PLUS azithromycin</td>
<td>If no oral options page 3333 for fluoroquinolone approval.</td>
</tr>
</tbody>
</table>

45 Year Old Man with GERD, DM, HTN

- Admitted with fever, dysuria, flank pain
- Urine and blood cx grow pan-susceptible *E. coli*
- Renal US consistent w/ pyelonephritis
- Started on ceftriaxone. Hospital day 2 improved. Discharged on day 3 with a script for ciprofloxacin to finish 14 days.
- 4 days later fever returned and patient readmitted
What is the Most Likely Explanation for Readmission?

A. Development of ciprofloxacin resistance  
B. Infected kidney stone  
C. Development of a renal abscess  
D. Drug fever  
E. Drug interaction

But I Don’t Take My Calcium and Vitamin Pills Until Noon ... 

Me  
• Do you take your antibiotic?  
• When?  
• What time?  
• What else do you do?  
• What do you eat?  
• Do you put milk on your cereal?  

Patient  
• Yes  
• In the morning  
• About 7  
• Eat breakfast  
• Cereal  
• Well sure, I love milk and drink it all day long...
**Bioavailability**

- Rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action

**Fluoroquinolone Oral Bioavailability**

<table>
<thead>
<tr>
<th>Agent</th>
<th>% bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>70</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>86</td>
</tr>
<tr>
<td>Delafloxacin</td>
<td>59</td>
</tr>
</tbody>
</table>

However there is a critical caveat

---

**Quinolones and Cations**

- Co-administration is common and associated with treatment failure
  - Review of > 4000 doses at U Penn found 77% co-administered with cation
  - Cation reduces absorption from 25-75%
  - Most common cations: Ca, Fe, Mg, MVI, sucralfate, dairy... OTC meds not on med list
- Recommendation: dose at least 2h before or 6h after cations

---

Andrew Urban, MD
All Things Infectious Disease
Prostate: A Difficult Site for Antibiotics

Effectiveness of oral antibiotics for definitive therapy of Gram-negative bloodstream infections

Stratified 362 pts into 3 groups based on the bioavailability of oral antibiotics used for step-down therapy - low, medium, high bioavailability
70% had a urinary source of infection
Mean duration of appropriate IV antibiotics 4.4 – 4.8 days
Total duration of appropriate antibiotics 13.2-14.2 days
Risk of treatment failure higher in patients receiving moderate and low bioavailable agents
Also note cirrhosis and immunocompromised host higher risk for treatment failure


**Table 5**
Multivariate Cox model results for independent risk factors of treatment failure following Gram-negative bloodstream infection (BSI).

<table>
<thead>
<tr>
<th>Variable</th>
<th>aHR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-stage renal disease</td>
<td>2.20 (0.44–8.53)</td>
<td>0.31</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>7.77 (2.38–21.50)</td>
<td>0.002</td>
</tr>
<tr>
<td>Immunocompromised host</td>
<td>4.62 (1.66–11.67)</td>
<td>0.005</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>1.25 (0.34–4.80)</td>
<td>0.72</td>
</tr>
<tr>
<td>Urological complications</td>
<td>1.72 (0.65–4.50)</td>
<td>0.33</td>
</tr>
<tr>
<td>BSI due to <em>Pseudomonas aeruginosa</em> or CAE</td>
<td>1.74 (0.49–4.91)</td>
<td>0.36</td>
</tr>
<tr>
<td>Bioavailability of oral regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1 (Ref.)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>5.04 (1.61–18.46)</td>
<td>0.005</td>
</tr>
<tr>
<td>Low</td>
<td>7.67 (1.90–51.52)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

aHR, adjusted hazard ratio; CI, confidence interval; CAE, chromosomally-mediated AmpC-producing Enterobacteriaceae.

**Community Acquired Pneumonia 2019 Guidelines**

**Table 3.** Initial Treatment Strategies for Outpatients with Community-acquired Pneumonia

<table>
<thead>
<tr>
<th>Standard Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No comorbidities or risk factors for MRSA or <em>Pseudomonas aeruginosa</em></strong></td>
</tr>
<tr>
<td>Aramocin or doxycycline or macrodly (if local pneumococcal resistance is &lt;25%)</td>
</tr>
<tr>
<td><strong>With comorbidities</strong></td>
</tr>
<tr>
<td>Combination therapy with amoxicillin/rifampin or cephalosporin AND macrodly or doxycycline OR monotherapy with respiratory fluoroquinolone</td>
</tr>
</tbody>
</table>

Risks for MRSA or *P. aeruginosa*
Prior respiratory isolation on culture
Hospitalization AND receipt of IV antibiotics in last 90 days

**Comorbidities**
Chronic heart, lung, liver, or renal disease; DM; alcoholism, malignancy, asplenia

**Fluoroquinolone monotherapy**
“In particular, despite the concern regarding adverse events associated with FQ, the panel believed that FQ therapy was justified for adults with comorbidities and CAP managed in the outpatient setting”

Am J Respir Crit Care Med 2019;200(7):e45-e67
Fluoroquinolones in 2020
Role in outpatient infections in Primary Care

Appropriate Use
• Prostatitis
• GI infections
• Upper tract UTI
• Pneumonia
• Beta-lactam allergy (severe)
• Resistance to other first-line agents
• Pseudomonas
• Step down for GNR bacteremia
• Osteomyelitis

Should Not be Used First-Line
• Cystitis (4th-line at best)
• Sinusitis
• COPD (most)
• Non-infections

Do not use for simple infections
Include risk/benefit in your notes
Discuss and document ADR counseling

Recurrent Cellulitis and Boils
57 Year Old Man

- Healthy, chronic LLE edema after MVA

- Hospitalized for LLE cellulitis
  - Temp 102.4, WBC 15K, Scr 1.6
  - IV vancomycin $\rightarrow$ ceftriaxone/metronidazole $\rightarrow$
    WBC up to 18K, back to IV vancomycin
  - Blood cx negative
  - MRI: Cellulitis, no abscess, no osteomyelitis

57 Year Old Man

- Additional history from he and his wife
  - Patient - “I was cleaning up Saturday night after having our relatives over to watch a football game and felt fine. Walking upstairs and then wham! I got chills then my leg started hurting”
What is This?

A. Classic streptococcal
B. Classic MRSA
C. Classic MSSA
D. Classic erysipelothrix
Streptococci = Lymphatics

Nonpurulent (nonculturable) Cellulitis

- Indurated, tender, warm
- Indistinct borders erythema
- Spreading
- Nothing to drain
- Edema
- Rapid onset
- Unilateral
- Feels lousy
- Overwhelmingly beta-hemolytic streptococci
  - Gp A,B,G streptococci
  - S dysgalactiae
**Cellulitis Fakes**  
*When to Consider Another Diagnosis*

- Bilateral  
- Chronic in nature  
- Localized, not spreading  
- Isolated color changes without other signs  
- Not responding to usual antibiotics  
- Lift the leg and it all goes away

---

**Important Exam Technique**

- Dependent rubor  
  - Gravity dependent perfusion of an extremity  
  - Red, but not XS warm or tender (clues)  
  - Lift the affected part and the redness literally drains away before your eyes (cellulitis would never do that)

---

Pictures: NEJM 2011;364:26 (e56)
Cellulitis Fakes

- Most common
  - Dependent rubor
  - Venous stasis dermatitis
  - Lipodermatosclerosis
  - DVT/superficial thrombophlebitis
  - Gout/CPPD
  - Stress fractures
  - Contact dermatitis
  - Hematoma
  - Herpes zoster
57 Year Old Man

- Additional history from he and his wife
  - Patient - “I was cleaning up Saturday night after having our relatives over to watch a football game and felt fine. Walking upstairs and then wham! I got chills then my leg started hurting”
  - Wife – “every episode is exactly like that!”
  - Me – “how many episodes total?”
  - Patient and wife – “13!”
  - This is the 3rd episode so far this year
In a Case Like This, What is the Most Important Aspect of Acute and Long-term Management?

A. Lymphedema management  
B. Lymphedema management  
C. Lymphedema management  
D. Lymphedema management  
E. Lymphedema management

Recurrent Cellulitis

[Diagram showing the relationship between Cellulitis and Lymphedema]
Management of Recurrent Cellulitis and Erysipelas

- Cycle needs to be interrupted by vigorously treating predisposing factors

- 3 management components
  - Lymphedema
  - Tinea pedis and wounds
  - Long-term antibiotic prophylaxis
Lymphedema

- Above the level of the heart elevation
  - Big stack of pillows for LE, or foam support for UE
  - Diuretics don’t help this kind of edema
- Elevate acutely and compress chronically
  - Wraps, fitted stockings, send to PT
- Doing this at home is critical but hard, and often leads to failure

Recurrent Cellulitis

After Coronary Bypass Surgery

Association With Superficial Fungal Infection in Saphenous Venectomy Limbs

Larry M. Badour, MD, Alan L. Bism, MD

- Certain patients who have undergone coronary artery bypass grafts suffer from episodes of acute cellulitis, often repeatedly, in the saphenous vein donor extremity. We describe nine patients with this entity, five of whom suffered recurrent attacks (range, two to >30). The mean interval between surgery and the initial bout of cellulitis was 15 months (range, two to 46 months). A characteristic clinical syndrome was present in the majority of patients that included the abrupt onset of chills, followed by fever (generally >38.8°C), prostration, and obvious cellulitis. Seven patients also suffered from lymph edema; in two instances, measures to control the dermatomyositis were instituted and attacks ceased. The pathogenesis of the entity may involve complex interactions between fungal and bacterial agents. Factors such as direct bacterial infection, hypersensitivity to streptococcal exotoxins, and IgG reactions to dermatomyositis are probably involved in varying combinations.

(JAMA 1984;251:1049-1052)
Penicillin to Prevent Recurrent Cellulitis

- 274 pts w/ 2 or more episodes of leg cellulitis in previous 3 years
- DB/R/PCT for 1 year, monitoring out to 3 yrs
  - Pen VK 250 mg BID vs placebo for year 1
- Exclusion criteria
  - Previous leg ulceration, surgery, penetrating trauma, allergy to pcn, other abx in past 6 mos
- Select characteristics
  - Mean BMI 35, chronic edema (68%), tinea (38%)

NEJM 2013;368:1695

Penicillin to Prevent Recurrent Cellulitis

- Prophylaxis phase, year 1
  - Penicillin 22% recurrence
  - Placebo 37% recurrence
  - 45% reduction in the risk of a repeat episode of cellulitis
    HR 0.55, 95% CI 0.35-0.86, P=0.01
- Follow-up period (off therapy), years 2 and 3
  - Penicillin 27% recurrence
  - Placebo 27% recurrence
  - Effect not sustained after prophylaxis stopped
- Overall, 53% of those in the placebo group had at least 1 recurrence during the 3 year trial

NEJM 2013;368:1695
Penicillin to Prevent Recurrent Cellulitis

**Table 3. Factors Predictive of Prophylaxis Failure.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of previous cellulitis episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>3.23 (1.82–5.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexisting edema</td>
<td>1.83 (0.97–3.47)</td>
<td>0.06</td>
</tr>
<tr>
<td>No evidence of edema</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥33</td>
<td>2.05 (1.16–3.64)</td>
<td>0.01</td>
</tr>
<tr>
<td>&lt;33</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* Failure of prophylaxis was defined as at least one confirmed episode of cellulitis during the prophylaxis phase.

**PROPHYLAXIS OF RECURRENT CELLULITIS DUE TO CHRONIC LYMPHEDEMA**

slide compliment of DG Maki

<table>
<thead>
<tr>
<th>Age, Years</th>
<th>Method of Therapy</th>
<th>Before Antibiotics</th>
<th>After Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>53</td>
<td>Phenoxymethyl penicillin, 250 mg twice daily, every other week</td>
<td>8 (in 5 yr)</td>
<td>0 (18 mo)</td>
</tr>
<tr>
<td>60</td>
<td>Phenoxymethyl penicillin, 250 mg twice daily, one week a month</td>
<td>5 (in 5 yr)</td>
<td>0 (18 mo)</td>
</tr>
<tr>
<td>18</td>
<td>Phenoxymethyl penicillin, 125 mg twice daily, one week a month</td>
<td>30 (in 6 yr)</td>
<td>0 (30 mo)</td>
</tr>
<tr>
<td>59</td>
<td>Benzathine penicillin G, 1,200,000 units intramuscularly, once a month</td>
<td>3 (in 3 yr)</td>
<td>0 (60 mo)</td>
</tr>
<tr>
<td>66</td>
<td>Phenoxymethyl penicillin, 125 mg four times a day, one week a month</td>
<td>6 (in 2 yr)</td>
<td>0 (48 mo)</td>
</tr>
<tr>
<td>46</td>
<td>Phenoxymethyl penicillin, 250 mg four times a day, one week a month</td>
<td>3 (in 1 yr)</td>
<td>0 (42 mo)</td>
</tr>
<tr>
<td>37</td>
<td>Erythromycin, 250 mg twice daily, every other week</td>
<td>10 (in 1 yr)</td>
<td>0 (34 mo)</td>
</tr>
<tr>
<td>64</td>
<td>Benzathine penicillin G, 1,200,000 units, intramuscularly once a month</td>
<td>4 (in 1 yr)</td>
<td>0 (24 mo)</td>
</tr>
<tr>
<td>76</td>
<td>Phenoxymethyl penicillin, 125 mg three times a day, one week a month</td>
<td>7 (in 2 yr)</td>
<td>0 (24 mo)</td>
</tr>
<tr>
<td>49</td>
<td>Phenoxymethyl penicillin, 250 mg three times a day, one week a month</td>
<td>9 (in 3 yr)</td>
<td>0 (20 mo)</td>
</tr>
<tr>
<td>51</td>
<td>Phenoxymethyl penicillin, 250 mg twice daily, one week a month</td>
<td>3 (in 4 mo)</td>
<td>0 (18 mo)</td>
</tr>
<tr>
<td>65</td>
<td>Phenoxymethyl penicillin, 250 mg four times a day, one week a month</td>
<td>12 (in 3 yr)</td>
<td>0 (18 mo)</td>
</tr>
<tr>
<td>45</td>
<td>Phenoxymethyl penicillin, 125 mg twice daily, one week a month</td>
<td>2 (in 2 mo)</td>
<td>0 (18 mo)</td>
</tr>
<tr>
<td>40</td>
<td>Phenoxymethyl penicillin, 250 mg three times a day, one week a month</td>
<td>2 (in 1 yr)</td>
<td>0 (18 mo)</td>
</tr>
<tr>
<td>60</td>
<td>Phenoxymethyl penicillin, 250 mg once daily</td>
<td>30 (in 5 yr)</td>
<td>0 (12 mo)</td>
</tr>
<tr>
<td>37</td>
<td>Benzathine penicillin G, 1,200,000 units intramuscularly, once a month</td>
<td>8 (in 1 1/2 yr)</td>
<td>0 (10 mo)</td>
</tr>
<tr>
<td>41</td>
<td>Erythromycin 250 mg four times a day, one week a month</td>
<td>6 (in 3 yr)</td>
<td>0 (10 mo)</td>
</tr>
<tr>
<td>70</td>
<td>Phenoxymethyl penicillin, 250 mg four times a day, one week a month</td>
<td>7 (in 2 1/2 yr)</td>
<td>0 (8 mo)</td>
</tr>
<tr>
<td>64</td>
<td>Phenoxymethyl penicillin, 125 mg four times a day, one week a month</td>
<td>4 (in 3 yr)</td>
<td>2 minor (36 mo)</td>
</tr>
<tr>
<td>45</td>
<td>Phenoxymethyl penicillin, 250 mg four times a day, one week a month</td>
<td>4 (in 1 1/2 yr)</td>
<td>1 minor (36 mo)</td>
</tr>
<tr>
<td>44</td>
<td>Phenoxymethyl penicillin, 250 mg three times a day, one week a month</td>
<td>20 (in 4 yr)</td>
<td>3 minor (34 mo)</td>
</tr>
</tbody>
</table>
**My Approach To Recurrent Cellulitis**

- When to use long term antibiotics?
  - 1 episode in a body part where edema cannot be reversed
  - ≥ 2 episodes involving the same body part within a year

- What to use?
  - Pen VK 500-1000 mg BID
  - *Desensitize to penicillin if needed*
  - Dicloxacillin 250-500 mg BID
  - Clindamycin 150-300 mg QD-BID

**My Approach to Recurrent Cellulitis**

- What to say about the antibiotics?
  - Let’s give it a year, then compare the number of episodes that occur with the historical rate
  - Compare effectiveness vs hassle and side effects
  - Lymphedema, wound, tinea management remain the *highest priority*

- What you’ll find
  - It works! Minimal to no side effects
Back To Our Case

- No culture data to guide us
- MRSA swabs negative
- Finish treating acute episode with Pen G
- Tinea Rx – topical ketoconazole
- PT for custom fitted compression stockings
- Pen VK 500 mg BID prophylaxis
- ASO titer 1286 IU/mL (< 200)

For completeness, let's discuss that other common, recurrent soft tissue infection that leads to many primary care visits...
Recurrent *S. aureus* Cutaneous Abscess

- Swab nares, groin, axilla for *S. aureus*
- Chlorhexidine bathing TIW-daily
  - 20 min contact time, watch for drying
- Household/Fomite/Loved Ones management
  - www.dhs.wisconsin.gov/disease/mrsa.htm
  - www.cdc.gov/mrsa/community/environment
- Mupirocin 2% BID x 5 d (nares)
- Decolonization Doxy + Rif x 2 wks (short-lived; use limited)
Urinary Tract Infections

Fundamental Truths of UTIs

• Except for 2 situations, treatment of asymptomatic bacteriuria has real harms associated with it.

• The diagnosis of UTI is a clinical diagnosis, not a laboratory diagnosis. The value of a UA and urine culture is to support or refute a clinical suspicion for UTI.
68 Year Old Diabetic Woman

- UA obtained for proteinuria screening
  - 20 WBC/HPF

- No fever, voiding complaints, or flank pain

- Because of the UA, a urine cx was obtained

Culture – *E. coli*

<table>
<thead>
<tr>
<th>Drug</th>
<th>S/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP-sulfa</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>R</td>
</tr>
<tr>
<td>Cefepime</td>
<td>R</td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>R</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>R</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>R</td>
</tr>
</tbody>
</table>
What Would You Choose?

A. Admit for IV meropenem  
B. Place PICC line for outpatient IV ertapenem  
C. High-dose levofloxacin  
D. Fosfomycin 3gm oral dose x 1  
E. No antibiotic therapy

Just Released!

Who Should Be Screened and Treated for Asymptomatic Bacteriuria?

Pregnant women  
Before urologic procedures w/ high risk of mucosal bleeding
Table 1. Prevalence of Asymptomatic Bacteriuria Reported for Different Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>&lt;1</td>
<td>[7]</td>
</tr>
<tr>
<td>Girls</td>
<td>1–2</td>
<td>[8–10]</td>
</tr>
<tr>
<td>Healthy women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>1.0–5.5</td>
<td>[11]</td>
</tr>
<tr>
<td>Pregnant</td>
<td>1.9–9.5</td>
<td>[11]</td>
</tr>
<tr>
<td>Postmenopausal (age 50–70 y)</td>
<td>2.8–8.6</td>
<td>[12]</td>
</tr>
<tr>
<td>Persons with diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>10.8–16</td>
<td>[12–13]</td>
</tr>
<tr>
<td>Men</td>
<td>0.7–11</td>
<td>[12]</td>
</tr>
<tr>
<td>Elderly persons in the community (age ≥70 y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>10.9–16</td>
<td>[12]</td>
</tr>
<tr>
<td>Men</td>
<td>3.6–19</td>
<td>[12]</td>
</tr>
<tr>
<td>Elderly persons in a long-term care facility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman</td>
<td>25–50</td>
<td>[14]</td>
</tr>
<tr>
<td>Men</td>
<td>13–50</td>
<td>[14]</td>
</tr>
<tr>
<td>Persons with spinal cord injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent catheter use</td>
<td>23–69</td>
<td>[14]</td>
</tr>
<tr>
<td>Sphincterotomy/random catheter</td>
<td>57</td>
<td>[14]</td>
</tr>
<tr>
<td>Persons with kidney transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First month post-transplant</td>
<td>23–24</td>
<td>[15–17]</td>
</tr>
<tr>
<td>1 mo–1 y post transplant</td>
<td>16–17</td>
<td>[15]</td>
</tr>
<tr>
<td>&gt;1 y post transplant</td>
<td>2–9</td>
<td>[15]</td>
</tr>
<tr>
<td>Persons with indwelling catheter use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term</td>
<td>3%–5% stay catheter</td>
<td>[19]</td>
</tr>
<tr>
<td>Long-term</td>
<td>100</td>
<td>[19]</td>
</tr>
</tbody>
</table>

Asymptomatic Bacteriuria Treatment Is Associated With a Higher Prevalence of Antibiotic Resistant Strains in Women With Urinary Tract Infections

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Resistance development</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO Abx for AsB</td>
<td>Abx for AsB</td>
</tr>
<tr>
<td>Amox-clav</td>
<td>3.8%</td>
<td>24.7%</td>
</tr>
<tr>
<td>TMP-Sulfa</td>
<td>11.5%</td>
<td>34.4%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>19.2%</td>
<td>44%</td>
</tr>
</tbody>
</table>
The Role of Asymptomatic Bacteriuria in Young Women With Recurrent Urinary Tract Infections: To Treat or Not to Treat?

<table>
<thead>
<tr>
<th>N = 673, recurrent UTI</th>
<th>Treated AsB</th>
<th>Untreated AsB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic Recurrence at 6 months</td>
<td>33%</td>
<td>8%</td>
</tr>
<tr>
<td>Symptomatic Recurrence at 12 months</td>
<td>47%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Treatment of AsB had no benefit but lead to:
Worse QOL scores
Increased risk of symptomatic recurrences at 6 and 12 mos
More drug resistance

Nursing Home Residents and Asymptomatic Bacteriuria

- Prevalence is high
  - 50% (F), 40% (M), and 100% (long-term catheter)
- UTI is #1 treated infection and #1 use of FQ
  - 50-80% of UTI antibiotics are given for asymptomatic bact
- 8.5x risk of C. difficile within 3 months of AsB Rx

The treatment of asymptomatic bacteriuria is a major contributor to emergence of MDR-GNR
Uncomplicated UTI (Women)  
IDSA 2011 Guidelines

• First-line
  – Nitrofurantoin 100 mg po BID x 5 days
  – Fosfomycin 3gm po x 1 dose
  – TMP/SMX 1DS tab BID x 3 days

• Alternatives
  – Betalactams
  – Fluoroquinolones

Do not use nitrofurantoin or fosfomycin if pyelonephritis is suspected. TMP/SMX only if local resistance < 20% and no use in past 3 months

Avoid Fluoroquinolones for Uncomplicated UTI  
FDA Black Box 2016

FDA Drug Safety Communication
FDA is advising restricting fluoroquinolone antibiotic use for certain uncomplicated infections, warn about disabling side effects that can occur together.

Safety Announcement
05-12-2016 The U.S. Food and Drug Administration is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

As an FDA safety review has shown that fluoroquinolones when used systemically (i.e., orally, by eye, and parenterally) are associated with disabling and potentially permanent serious side effects that can occur together. These side effects can involve the tendons, muscles, joints, nerves, and central nervous system.
Microbiology of UTI

Extended Spectrum Beta-Lactamases (ESBL)

- Most common in *E. coli* and *Klebsiella* spp.
- Resistance to
  - Most cephalosporins, penicillins, and aztreonam
  - Co-resistance is common to quinolones and sulfa
- Susceptible to
  - Carbapenems (best choice for systemic infections)
  - Cefepime (90%), Gentamicin (60-70%), Tigecycline
- Risk factors
  - Exposure to 3rd gen ceph, anaerobic drugs, quinolones; severity of illness; devices; ICU
ESBL-producing *E. coli* in Ambulatory UTI

- 100 ESBL *E. coli* isolates from ambulatory patients with clinically confirmed UTI

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of E. coli isolates from urine</th>
<th>No. of ESBL-producing E. coli isolates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>1,808</td>
<td>18 (1.0%)</td>
</tr>
<tr>
<td>2006</td>
<td>1,295</td>
<td>28 (2.2%)</td>
</tr>
<tr>
<td>2007</td>
<td>2,202</td>
<td>44 (1.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>5,295</td>
<td>40 (1.8%)</td>
</tr>
</tbody>
</table>

All susceptible to ertapenem

100% ESBL-producing *E. coli* isolates from ambulatory patients with clinically confirmed UTI. Low rates of susceptibility to ciprofloxacin and tmp/smx. High rates of susceptibility to fosfomycin and nitrofurantoin. Nitrofurantoin

- Advocated as first-line choice for cystitis
  - Indicated for acute uncomplicated UTI caused by susceptible *E. coli* or *S. saprophyticus*.

- Activity
  - Good activity: most *E. coli*, Citrobacter, Gp B streptococci, Enterococci, *S. saprophyticus*
  - < 50% susceptible: Klebsiella, Enterobacter
  - Usually resistant: Pseudomonas, Proteus, Serratia

- Caveats
  - Need a CrCl of at least 40 cc/min
  - Do not use for pyelonephritis
Fosfomycin

- Phosphonic acid derivative, inhibits cell wall synthesis
  - Indicated for uncomplicated UTI caused by *E. coli* and *E. faecalis* (Oral 3 gm sachet used in the US)
- Activity
  - Broad spectrum activity against Gram-positive and Gram-negative bacteria, including MDR-GNR, VRE, *P. aeruginosa* (>90%)
  - IV form used in Europe/Japan for systemic MDR-GNR
- Caveat
  - Do not use sachet for suspected pyelonephritis
  - Expensive
  - Resistance can emerge with repeated use

Simple Intervention: Hydration

- 140 premenopausal women suffering recurrent UTI (at least 3 episodes in past year) drinking less than 1.5L of water at baseline were randomized to:
  - 1.5L of water vs no intervention
  - Measured daily water and total fluid intake, urine volume and osm, number of voids, and #UTIs
- Overall:
  - 48% reduction in UTIs
  - 47% reduction in antibiotic courses

Clinical Reviews

Top Ten Myths Regarding the Diagnosis and Treatment of Urinary Tract Infections

Lucas Schulz, PharmD*, Robert J. Hoffman, MD†, Jeffrey Pothof, MD‡, Barry Fox, MD§
Received 27 January 2016, Accepted 5 February 2016, Available online 7 April 2016

Myth 1: The urine is cloudy and smells bad. My patient has a UTI
Urine color and clarity or odor should not be used alone to diagnose or start antibiotic therapy in any patient population. Foul smelling urine is an unreliable indicator of infection in catheterized patients and is usually dependent on patient’s hydration status and concentration of urea in the urine.

Myth 7: All Findings of Bacteria in a Catheterized Urine Sample Should be Diagnosed as a UTI
Virtually 100% of patients with an indwelling Foley catheter are colonized within 2 weeks of placement with 2-5 organisms. Catheter colony counts define bacteriuria but must be taken in a clinical context for diagnosis of UTI.


WHAT SHOULD ALL CLINICIANS KNOW ABOUT HIV TESTING?
### Primary Care Guidelines for the Management of Persons Infected With HIV: 2013 Update by the HIV Medicine Association of the Infectious Diseases Society of America

**Table 7. Routine Healthcare Maintenance in the HIV-Infected Adult**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure check</td>
<td>Perform annually in all patients</td>
<td>Impose adverse events, malignancy, protein abnormalities in men</td>
</tr>
<tr>
<td>Pneumonia and chest</td>
<td>Perform annually in all patients</td>
<td></td>
</tr>
<tr>
<td>Depression screening</td>
<td>Perform annually in all patients</td>
<td>Use conventional mental health intervention or standardized tool</td>
</tr>
<tr>
<td>Fasting glucose and lipids</td>
<td>Perform annually in all patients</td>
<td>Consider testing 1–3 mo after starting or modifying antiretroviral therapy, if it may be used for screening. Consider thyroid function if 5.3. Would be best if performed every 6 mo in patients with diabetes mellitus.</td>
</tr>
<tr>
<td>Periphery blood pressure</td>
<td>Perform annually in all patients</td>
<td>Consider testing 1–3 mo after starting or modifying antiretroviral therapy.</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>Perform annually in patients at risk for HTN</td>
<td>Measure frequent testing may be indicated in patients at high risk for HTN.</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Perform annually in patients at risk for HTN</td>
<td>Measure frequent testing may be indicated in patients at high risk for HTN.</td>
</tr>
<tr>
<td>Cholesterol screening</td>
<td>Perform at baseline and annually in patients at risk for hypercholesterolemia</td>
<td>No need to repeat in patients with prior positive 75% additional cholesterol testing may be indicated depending on individual risk profile.</td>
</tr>
<tr>
<td>Pap smear</td>
<td>Perform annually in women age 25 to 65 yr</td>
<td>Some authorities advise initiation of screening starting at age 50 based on individual risk assessment.</td>
</tr>
<tr>
<td>Bone density scan</td>
<td>Perform baseline exam in postmenopausal women and men age 50+ yrs</td>
<td>Measure of hip/forearm bone mass. Risk factors for hip fracture are age, body mass index, smoking, alcohol, estrogen use, and history of osteoporosis.</td>
</tr>
<tr>
<td>Abnormal chest X-ray</td>
<td>Perform annual exam in men aged 55+ yrs who have ever smoked</td>
<td>Screening test for chronic obstructive pulmonary disease.</td>
</tr>
<tr>
<td>Mental health evaluation</td>
<td>Address every in all patients</td>
<td>Screen for anxiety, depression, and suicidal ideation.</td>
</tr>
</tbody>
</table>

**HTN prevalence 42%**

Undiagnosed 13%

[Open Forum Inf Dis 2018](Doi.org/10.1093/ofid/ofy/028)

**DM prevalence 10.3%**

BMJ Open Diabetes Res Care 2017;5(1):e000304

Updated HTN prevalence 42%

Undiagnosed 13%

[Open Forum Inf Dis 2018](Doi.org/10.1093/ofid/ofy/028)

Reduced BMD 67%

Osteoporosis 15%

[Clin Cases Miner Bone Metab 2011; 8(1):33-33](Clin Cases Miner Bone Metab 2011; 8(1):33-33)

---

**28 Year Old Diagnosed with Influenza (swab negative) in the ER, on Oseltamivir.**

These HIV Testing Results Appear in Your Inbasket

![Testing Results](image)

**This is**

- A. Chronic HIV-1
- B. Acute HIV-1
- C. False positive
27 Year Old Female Presents 48 Hours After Receptive Vaginal Intercourse with a Man Who Later Disclosed He had HIV with a “Negative” Viral Load. A Condom was Used But May have Broke. She is Very Worried about Her Risk of Acquiring HIV and Asks about PEP and PrEP.

What Would You Recommend?

A. Too late for PEP
B. Start PEP (TDF/FTC + raltegravir x 28 days)
C. PEP not indicated w/ partner’s negative viral load
D. Start PrEP (TDF/FTC once daily)

HIV is Alive and Well

- US 1.1 million living with HIV
  - 15% do not know they have HIV
  - 45% are over the age of 50

- 39,000 newly diagnosed in 2016
  - 40% got HIV from those unaware they have HIV
  - 17% were over the age of 50

https://www.cdc.gov/hiv/statistics/overview/ataglance.html
Screening Recommendations

- CDC 2006 – Opt-out testing
  - All persons 13-64, routine screen*
  - All pregnant women
  - Those starting TB meds, attending STD clinics
  - If high-risk, rescreen at least once per year

*Unless prevalence of undiagnosed HIV < 0.1%
Screening Recommendations

- **CDC 2006 – Opt-out testing**
  - All persons 13-64, routine screen*
  - All pregnant women
  - Those starting TB meds, attending STD clinics
  - If high-risk, rescreen at least once per year

- **USPSTF 2013 – Grade A recommendations**
  - All persons 15-65 (older/younger if at risk)
  - All pregnant women, each pregnancy
  - Very high risk, rescreen at least annually; increased risk, rescreen 3-5 yrs; no increased risk, no rescreen if (-)

  *Unless prevalence of undiagnosed HIV < 0.1%

---

HIV Testing Options

- **Conventional blood (Ag/Ab, Ab)**
  - Collected by HCP, tested at lab

- **Conventional oral fluid (Ab)**
  - Collected by HCP, tested at lab

- **Rapid tests (Ab, Ag/Ab)**
  - Collected by HCP, POC test
  - **Must be confirmed**

- **Home tests (Ab)**
  - 2 approved tests. Blood sent to lab, rapid oral fluid at home

- **Urine tests (Ab)**
  - Collected by HCP, tested at lab

---

HIV Testing in the US Henry J Kaiser Family Foundation June 2017
https://www.dhs.wisconsin.gov/aids-hiv/faq-clinician.htm
HIV Ag/Ab Testing
(4th Generation HIV Testing)

HIV-1 Ab / HIV-2 Ab / HIV-1 p24 Ag

Advantages
• Built in way to diagnose Acute HIV (p24Ag)
• Keeps accuracy for HIV-1 & HIV-2 Ab detection
• Closes the (seroconversion) window more
• Faster turnaround time
• Used for screening and targeted diagnosis
• Used to confirm a positive non-traditional test

Figure 1. Sequence of appearance of laboratory markers for HIV-1 infection

Laboratory Testing for the Diagnosis of HIV Infection
Updated Recommendations. CDC June 27, 2014
**Combination Ag/Ab immunoassay**

3 parts: HIV-1 Ab, HIV-2 Ab, HIV-1 p24 Ag

When it returns POSITIVE, it means one of those 3 parts is POSITIVE. But which one?

**Differentiation Ab immunoassay**

Determines if a detectable antibody to HIV-1 or HIV-2 is the reason for the combination assay being positive.

**HIV-1 NAT (nucleic acid test)**

Determines if a detectable p24Ag (and therefore Acute HIV) is the reason for the combination assay being positive.

---

**Acute HIV Infection**

- Transient nonspecific viral syndrome that occurs 2-6 weeks after exposure to HIV
  - “Flu-like or Mono-like” illness

- Characterized by
  - High levels of HIV-RNA (transmissibility)
  - Presence of p24, a transient early viral antigen
  - Negative or indeterminate HIV antibody testing
Figure 1. Sequence of appearance of laboratory markers for HIV-1 infection

**Table 1. Frequency of Symptoms and Findings Associated with Acute HIV-1 Infection.**

<table>
<thead>
<tr>
<th>Symptom or Finding</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>&gt;80–90</td>
</tr>
<tr>
<td>Fatigue</td>
<td>&gt;70–90</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>&gt;40–80</td>
</tr>
<tr>
<td>Headache</td>
<td>30–70</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>40–70</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>50–70</td>
</tr>
<tr>
<td>Myalgia or arthralgia</td>
<td>50–70</td>
</tr>
<tr>
<td>Nausea, vomiting, or diarrhea</td>
<td>30–60</td>
</tr>
<tr>
<td>Night sweats</td>
<td>50</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>24</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>10–20</td>
</tr>
<tr>
<td>Genital ulcers</td>
<td>5–15</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>45</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>40</td>
</tr>
<tr>
<td>Elevated hepatic enzyme levels</td>
<td>21</td>
</tr>
</tbody>
</table>

**Clues to HIV**

NEJM 1998;339:33-39
Let’s Go Over 3 Testing Scenarios

“I Want to Get Screened for HIV

• Order HIV Ag/Ab
**Scenario #1**

**Combination Differentiation**

<table>
<thead>
<tr>
<th>Combination</th>
<th>POSITIVE</th>
<th>NEGATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 Ab DETECTED</td>
<td>HIV-1/2 Ab detected</td>
<td>NO RESULT</td>
</tr>
</tbody>
</table>

**Laboratory Testing for the Diagnosis of HIV Infection**

*Updated Recommendations CDC June 27, 2014*

**This is chronic, established HIV. This is “HIV positive.”**

**“I Want to Test for Acute HIV”**

- Order HIV Ag/Ab
Scenario #2

Combination POSITIVE
Differentiation NEGATIVE or INDETERMINATE
HIV-1 NAT POSITIVE

HIV-1/2 antigen/antibody combination immunoassay

HIV-1/HIV-2 antibody differentiation immunoassay

HIV-1 (+) HIV-1 (-) HIV-2 (+) HIV-2 (-)

HIV-1 antibodies detected HIV-2 antibodies detected HIV antibodies detected HIV-1 NAT

(+) indicates reactive test result
(-) indicates nonreactive test result
NAT: nucleic acid test

This is Acute HIV

28 Year Old Diagnosed with Influenza (swab negative) in the ER, on Oseltamivir.
These HIV Testing Results Appear in Your Inbasket

Combination POSITIVE
Differentiation INDETERMINATE
HIV-1 NAT POSITIVE

This is
A. Chronic HIV-1
B. Acute HIV-1
C. False positive

Key Point: Recognize how Acute HIV is reported on Ag/Ab test results
Scenario 3
In Your Inbasket

Combination: POSITIVE
Differentiation: NEGATIVE
HIV-1 NAT: NEGATIVE

Laboratory Testing for the Diagnosis of HIV Infection
Updated Recommendations   CDC June 27, 2014

This is most likely a False Positive Combination Assay, But could be Very Early HIV, or the Lab Having a Bad Day
Scenario #3  Explained

• Before concluding a test is a False Positive
  – Why was it ordered – high risk or routine screen?
  – Ask about recent vaccines, illness, autoimmune conditions, gammopathy, chronic liver disease, pregnancy
  – Repeat the HIV Ag/Ab in 1-3 months if risks
  – SOMETIMES LABS HAVE BAD DAYS TOO, don’t be afraid to repeat the test and order another method (standard HIV-RNA) if acute HIV is suspected
  – Ask for help on these
  – Counsel the individual in person

No Assumptions

Woman Misdiagnosed With HIV Awarded $2.5M

(27 Comments)  Email Story  Share This  Tweet This
[Have Your Say]  [Send to a Friend]  [Tell Your Friends]  [Tweet This]

(27 Comments)  Email Story  Share This  Tweet This
[Have Your Say]  [Send to a Friend]  [Tell Your Friends]  [Tweet This]

(AP) A jury has awarded $2.5 million in damages to a woman who received HIV treatments for almost nine years before discovering she never actually had the virus that causes AIDS.

ALWAYS get a HIV test in someone new to you

Can’t Sneak It In

Surprise HIV test at Brooklyn clinic outrages woman, so she sues doctor over bad news

Harlem woman claims doctor violated law by giving her test against her wishes and gave her result without mandated counseling. She seeks damages for ‘terror, confusion, embarrassment and emotional distress.’


Opt-out Testing – is an opportunity to opt out

Red Flag List

Should make you consider HIV

* ALWAYS check HIV

- Thrush
- Aseptic meningitis
- Cytopenias
- Adenopathy, especially multifocal
- Unexplained neurologic, nephropathy or skin problem
- Shingles in young person
- TB*
- Hepatitis B*
- Hepatitis C*
- Any STD*
- Recurrent pneumonia
- Recurrent infections
- Unexplained weight loss, constitutional symptoms

Andrew Urban, MD
All Things Infectious Disease
Test today. Don’t delay

1 in 2 people with HIV have had the virus at least 3 years before diagnosis.

About **40%** of new HIV infections come from people who don’t know they have HIV.

7 in 10 people at high risk for HIV who weren’t tested last year saw a healthcare provider during that year.

---

Urgent Referral to HIV Specialist

- Acute HIV
- Active opportunistic infection
- Active malignancy + HIV
- ARV complications/side effects
- Pregnancy and HIV
- Testing questions
WHAT SHOULD ALL CLINICIANS KNOW ABOUT PrEP and PEP?

HIV Pre-Exposure Prophylaxis (PrEP)

- Prevention option
- Efficacy correlates with drug levels and adherence
  - Risk reduction 90% (sexual), 70% (injection drug use)
- Stops HIV from entering cells and replicating
- Maximum concentration achieved in rectal tissue by 7 days and cervicovaginal and serum by 20 days
- Daily use of one of two fixed-dose combinations
  - Truvada (Tenofovir DF + Emtricitabine)$^1$
  - Descovy (Tenofovir AF + Emtricitabine)$^2$

$^1$ FDA approved July 2012  $^2$ FDA approved October 2019
**Preexposure Prophylaxis for the Prevention of HIV Infection**

**US Preventive Services Task Force**

**Recommendation Statement**

**CONCLUSIONS AND RECOMMENDATION** The USPSTF recommends offering PrEP with effective antiretroviral therapy to persons at high risk of HIV acquisition.

(A recommendation)


---

**Who Should Consider Taking PrEP?**

**HIV negative** AND

- Anal or vaginal sex in the past 6 months and:
  - Sexual partner with HIV, or
  - Inconsistent condom use, or
  - STD in the past 6 months

- Injection drug use and:
  - Injection partner with HIV, or
  - Share injection equipment

- Use of nPEP and:
  - Continued risk behavior, or
  - Multiple courses of nPEP

nPEP = non-occupational post-exposure prophylaxis

aidsinfo.nih.gov fact sheet
Truvada vs Descovy: Drug Differences

- Truvada has **TDF/FTC**, Descovy has **TAF/FTC**
  - TDF and TAF are prodrugs of tenofovir
  - TAF higher intracellular and lower plasma levels than TDF
  - Both have been used in HIV care for many years
  - CrCl > 60 ml/min for Truvada
  - CrCl > 30 ml/min for Descovy

TAF = tenofovir alafenamide  TDF = tenofovir disoproxil fumarate  FTC = emtricitabine

Truvada vs Descovy: Populations Studied

- Descovy PrEP indication excludes those at risk from receptive vaginal intercourse
  - DISCOVER trial, 5387 enrolled cisgender MSM or transgender women who have sex with men
  - 1:1 randomization Descovy daily vs Truvada daily
  - Descovy non-inferior to Truvada (7 vs 15 infections)

Additional studies planned

FDA.gov. FDA approves second drug to prevent HIV infection as part of ongoing efforts to end the HIV epidemic.
CROI 2019 Abstract 104 The Phase 3 DISCOVER Study: Daily F/TAF or F/TDF for HIV Preexposure Prophylaxis
**Adverse Effects**

- Diarrhea (5-6%), nausea (4-5%), headache (2%), fatigue (2%), abd pain (2-3%)
- Renal impairment
- Bone mineral density
- Hepatitis B exacerbations
- Lactic acidosis

---

**Truvada vs Descovy: Adverse Effects**

- **Switch Truvada to Descovy for PrEP**
  - 4.5 ml/min gain in GFR at week 48
  - BMD gain 1.13% (hip), no change (spine)

- **Switch TDF to TAF for HIV treatment**
  - Median weight gain 3 lbs, BMI up 0.5 kg/m²
  - Median LDL increase 98.6 to 112.1 mg/dL
  - Median ASCVD risk score increase 6.9 to 8.1%

---

ID Week 2019, Abstract 1962 and 1288, Subsets of Discover Trial
Open Forum Inf Dis 6:e06414. 2019. n=110 viral suppressed, TDF ≥1 yr, age 40-75, 80% men, 64% AA
HIV median 12 years, CD4 median 628 cells/mm³
Do You Take Truvada? Or Know Someone?

• Truvada Class Action Lawsuits, 2018

Guidance for PrEP Use

<table>
<thead>
<tr>
<th>Men Who Have Sex with Men</th>
<th>Heterosexual Women and Men</th>
<th>Persons Who Inject Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-positive sexual partner</td>
<td>HIV-positive sexual partner</td>
<td>HIV-positive injecting partner</td>
</tr>
<tr>
<td>Recent bacterial STIs</td>
<td>Recent bacterial STIs</td>
<td>Sharing injection equipment</td>
</tr>
<tr>
<td>High number of sex partners</td>
<td>High number of sex partners</td>
<td></td>
</tr>
<tr>
<td>History of inconsistent or no condom use</td>
<td>History of inconsistent or no condom use</td>
<td></td>
</tr>
<tr>
<td>Commercial sex work</td>
<td>Commercial sex work</td>
<td></td>
</tr>
<tr>
<td>In high HIV prevalence area or network</td>
<td>In high HIV prevalence area or network</td>
<td></td>
</tr>
</tbody>
</table>

Clinically eligible:

- Documented negative HIV test result before prescribing PrEP
- No signs/symptoms of acute HIV infection
- Normal renal function or no contraindicated medications
- Documented hepatitis B virus infection and vaccination status

Prescription:

- Daily, continuing, oral doses of TDF/FTC (Truvada), 280-day supply
- Or Descovy

Other services:

- Follow-up visits at least every 3 months to provide the following:
  - HBV test, medication adherence counseling, behavioral risk reduction support
  - Side effect assessment, STI symptom assessment
  - At 3 months and every 6 months thereafter, assess renal function
  - Every 3-6 months, test for bacterial STIs

Follow-up:

- HIV test every 3 months
- No signs/sx acute HIV
- Creatinine at 3 mos then q6 mos
- STD screening q 3-6 mos
- Adherence
- Desire to continue

Baseline:

- Documented negative HIV Ag/Ab testing
- No symptoms/signs of acute HIV
- Check creatinine, pregnancy, drug interactions
- **Check Hepatitis B: HBsAg, antiHBC, antiHBs**
- STD screening
- Educate: combination strategy, condoms, STD screening
- Vaccines (HAV, HBV, HPV)
- 90 day supply of medication

Comment: I also check baseline CBC, ALT and serial ALT


Andrew Urban, MD

All Things Infectious Disease
• Changes in STI incidence in a PrEP cohort
  – PrEPX Study, Australia, n = 4275, July16-Apr18
  – 2981 had > 1 post enrollment visit
  – 98% MSM/bisexual males, 30% PrEP prior use
  – Quarterly screening: Chlamydia, Gonorrhea, Syphilis
  – Follow-up 1.1 years

Table 2. Incidence of Sexually Transmitted Infections During Follow-up Among Included Participants (N = 2981)

<table>
<thead>
<tr>
<th>STI Type</th>
<th>No. of Infections</th>
<th>Person-Years of Follow-up (n = 3183.00)</th>
<th>Incidence Rate per 100 Person-Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All STIs</td>
<td>2928</td>
<td>91.9 (88.7-95.3)</td>
<td></td>
</tr>
<tr>
<td>Chlamydia</td>
<td>1434</td>
<td>45.0 (42.7-47.4)</td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>1091</td>
<td>34.3 (32.3-36.3)</td>
<td></td>
</tr>
<tr>
<td>Urethral</td>
<td>381</td>
<td>12.0 (10.8-13.2)</td>
<td></td>
</tr>
<tr>
<td>Pharyngeal</td>
<td>127</td>
<td>4.0 (3.3-4.7)</td>
<td></td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>1242</td>
<td>39.6 (36.9-41.2)</td>
<td></td>
</tr>
<tr>
<td>Rectalb</td>
<td>719</td>
<td>22.6 (21.0-24.3)</td>
<td></td>
</tr>
<tr>
<td>Urethralb</td>
<td>233</td>
<td>7.3 (6.4-8.3)</td>
<td></td>
</tr>
<tr>
<td>Pharyngealb</td>
<td>629</td>
<td>19.7 (18.3-21.3)</td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>252</td>
<td>8.0 (7.1-9.0)</td>
<td></td>
</tr>
<tr>
<td>SIVC</td>
<td>118</td>
<td>56.8 (53.4-60.4)</td>
<td></td>
</tr>
</tbody>
</table>

• 76% of infections occurred in 25% of participants
• STI incidence pre/post enrollment
  – 69.5 to 98.4 per 100 person/years (IRR, 1.41, 1.29-1.56)
• STI risk
  – Younger age, more partners, group sex
  – Inconsistent or no condom use not associated
The CDC estimates over 1.1 million Americans have indications for PrEP. By 2018 only 200,000 were using it. (CDC, 2018)

Post-Exposure Prophylaxis

Any Questions?
Call the National PEPline
1-888-448-4911

Truvada + Raltegravir 28 day course

Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV – United States, 2016
27 Year Old Female Presents 48 Hours After Receptive Vaginal Intercourse with a Man Who Later Disclosed He had HIV with a “Negative” Viral Load. A Condom was Used But May have Broke. She is Very Worried about Her Risk of Acquiring HIV and Asks about PEP and PrEP.

What Would You Recommend?

A. Too late for PEP
B. Start PEP (TDF/FTC + raltegravir x 28 days)
C. PEP not indicated w/ partner’s negative viral load
D. Start PrEP (TDF/FTC once daily)

Key Point: Recognize the role of PEP and distinguish PEP from PrEP
Other Common Questions

- **PEP to PrEP transition**
  - For ongoing high risk

- **On-demand PrEP**
  - Not FDA approved
  - 86% relative risk reduction

- **Family planning**
  - Serodiscordant couples
  - Undetectable VL +/- PrEP
  - See Perinatal Guidelines aidsinfo.nih.gov