SESSION E3

Antibiotic Resistance
Brian Wood, MD

Session Description:

Presentation will review common situations in primary and acute care when antibiotic resistance should be considered, common mechanisms of antibiotic resistance, and treatment options when resistance is suspected or proven.

Learning Objectives:

Following my presentation, participants will be able to:
1. Describe common mechanisms of antibiotic resistance.
2. Apply knowledge of common antibiotic resistance patterns to clinical practice and understand clinical situations when resistance should be considered.
3. Discuss antibiotic treatment options in the setting of suspected or proven resistance.
Antibiotic Resistance

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Harborview Medical Center
University of Washington
10/9/14 Seattle, WA

Outline

• Introduction
• Antibiotic Resistance Cases
  – Staph aureus
  – Enterococcus
  – Strep pneumoniae
  – Gram-negative infections
  – Gonorrhea
• New Antibiotics

What is the problem?

• Antibiotics are misused in many settings, which impacts patients and society
• Improving antibiotic use improves patient outcomes and saves money, and should be a public health imperative

CDC 2008

What is the problem?

• 2.5 million excess hospital days and $20 billion caused by resistant infections
• 1.6% of new drugs being developed are in antibiotic class
• 36% of people correctly answered that antibiotics do not kill viruses in an EU survey
• 24.6 million pounds of antibiotics used non-therapeutically on animals in US each year

Fair FJ and Tor Y. Perspect Medizin Chem. 2014 Aug 28;6:25-64.
Association of Vancomycin Use with Resistance

Number of patients with VRE vs. Defined daily doses of vancomycin (DDD per 1000 patient days)

Kim, JID 1999;179:163

Association of Imipenem Resistance and Carbapenem Use

% Imipenem-resistant P. aeruginosa vs. Carbapenem Use Rate

r = 0.41, p = .004 (Pearson correlation coefficient)

Gould et al. ICHE 2006;27:923-5

Rising Incidence of Drug-Resistant Nosocomial Pathogens

% Incidence of MRSA, VRE, and FOQP


Number of Antibacterial New Drug Application (NDA) Approvals vs. Year Intervals

Number of antibacterial drug NDA approvals vs. Year interval


Antibiotic Prescriptions for Non-Bacterial Infections

Proportion of office visits where antibiotics prescribed vs. Proportion of office visits where antibiotics not prescribed

Furuya EY and Lowy F. Nat Rev Microbiol. 2006
Antibiotic Prescribing in Hospitals

- 30-50% of inpatient antibiotics are inappropriate
- Given when they are not needed
- Continued when they are no longer necessary
- Given at the wrong dose
- Broad spectrum agents are used to treat very susceptible bacteria
- The wrong antibiotic is given to treat an infection
- 2008 = 142,000 visits to ER for adverse events 2nd to antibiotics

“10 Commandments” of Antibiotic Use
1. Teach patients how to manage symptoms of non-bacterial infections
2. Targeted therapy is best
3. Use the shortest course that works
4. Encourage adherence
5. Use antibiotic combinations sparingly
6. Avoid sub-standard drugs
7. Discourage self-prescription
8. Follow evidence-based guidelines
9. Rely upon the clinical micro lab
10. Prescribe empirically but intelligently

Most Common Multidrug-Resistant Organisms (MDRO’s)
- Staphylococcus aureus
- Enterococcus
- Pseudomonas aeruginosa
- Clostridium difficile
- Acinetobacter baumanii
- M. tuberculosi
- Neisseria gonorrhea
- Strep. pneumoniae
- Plasmodium falciparum
- Enterobacter
- Salmonella typhi
- Klebsiella pneumoniae

A 20 y/o man with painful furuncle (boil) on buttock for last 4 days
- It is about 3.5 cm; he otherwise feels well
- Recently joined college rowing team

What does this patient need?
A) Incision and drainage (I&D)
B) Antibiotics
C) Incision and drainage (I&D) + antibiotics

Which antibiotic should be AVOIDED?
A) Clindamycin
B) TMP/SMX
C) Doxycycline
D) Linezolid

Drug Interpretation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>Oxacillin</td>
<td>RESISTANT</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>RESISTANT</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>SUSCEPTIBLE</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>SUSCEPTIBLE</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>SUSCEPTIBLE</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>SUSCEPTIBLE</td>
</tr>
</tbody>
</table>
Clindamycin Resistance

Mechanism:
- ERM gene, alters 50S ribosome target
- Constitutive or inducible

Detection:
- Put clinda disk next to eryth disk, look for "D-zone"

Clinical Significance:
- Treatment failures reported with clindamycin

Take Home Point
- If erythromycin resistance, don’t use clindamycin!

Methicillin Resistance

Mechanism:
- Expression of MecA gene
- On staphylococcal chromosome cassette (SCCmec)
- Altered penicillin binding protein (PBP2a)
- Resistant to beta-lactams (methicillin/oxacillin/nafcillin)

Detection:
- Generally easy to detect PBP2a in the lab

70 y/o woman with dementia & diabetic nephropathy admitted from SNF for sepsis.
- H/o foot ulcers with VRE & MRSA.
- Urine grows MRSA → Vanco begun.
- There is also concern for pneumonia.
- On high dose SSRI’s for depression.
- Remains febrile after 6 days with borderline blood pressures. Vanco trough 15.5.

A. Continue current therapy
B. Push for higher vancomycin troughs
C. Switch to daptomycin
D. Switch to linezolid
E. Switch to ceftaroline

Drug | MIC | Interpretation
---|---|---
Oxacillin | >1 | RESISTANT
Chloramphenicol | SUSCEPTIBLE
Linezolid | SUSCEPTIBLE
Keflogin | SUSCEPTIBLE
TMP/SMX | >8 | SUSCEPTIBLE
Vancomycin | 2 | SUSCEPTIBLE

MRSA: Risk Factors

<table>
<thead>
<tr>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
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<tbody>
<tr>
<td>No apparent risk factors</td>
<td>Healthcare in the last year</td>
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<tr>
<td>Athletes</td>
<td>Nosocomial outbreak</td>
</tr>
<tr>
<td>Men who have sex with men (MSM)</td>
<td>Indwelling lines and urinary catheters</td>
</tr>
<tr>
<td>Family clusters</td>
<td></td>
</tr>
<tr>
<td>IVDU</td>
<td></td>
</tr>
<tr>
<td>Jail</td>
<td></td>
</tr>
<tr>
<td>Homeless/shelter</td>
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</table>
**MRSA: Biology**

<table>
<thead>
<tr>
<th>CA-MRSA</th>
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</thead>
<tbody>
<tr>
<td>SCCmec IV</td>
<td>SCCmec II</td>
</tr>
<tr>
<td>More toxins</td>
<td>Fewer toxins</td>
</tr>
<tr>
<td>PVL common</td>
<td>PVL rare</td>
</tr>
<tr>
<td>Less resistant</td>
<td>More resistant</td>
</tr>
<tr>
<td>Skin abscesses</td>
<td>Blood and catheter infections</td>
</tr>
</tbody>
</table>

**MRSA Transmission & Colonization**

<table>
<thead>
<tr>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most commonly transmitted by contact with a colonized or infected person</td>
<td>Most commonly transmitted by transiently contaminated hands of healthcare workers</td>
</tr>
<tr>
<td>Sites of colonization: anterior nares, axillae, perineum, etc (decontamination protocols available)</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment Options for MRSA**

**Oral**
- TMP-SMX
- Clindamycin
- Doxycycline
- Linezolid

*Rifampin: may be added; never use as monotherapy*

**Intravenous**
- Vancomycin
- Linezolid
- Daptomycin
- Ceftaroline
- Tigecycline
- Telavancin
- Quinupristin/dalfopristin

*New oral and IV options just approved!*
- Tedizolid
- Dalbavancin
- Oritavancin

**What if the GPC’s turn out to be MSSA?**

**Oral**
- TMP-SMX
- Clindamycin
- Doxycycline
- Linezolid
- Augmentin
- Dicloxacillin
- Levo/Moxi
- Cephalexin

*New oral and IV options just approved!*
- Tedizolid
- Dalbavancin
- Oritavancin

**Intravenous**
- Nafcillin
- Cefazolin

**Strep Cellulitis**
- 35-year-old injection drug user presented 5 days ago with painful erythema of forearm.
- Started TMP-SMX. Returns because erythema progressing and pain worsening.
- What happened?

**Meningitis Case**
- A 28-year-old grad student presents to the emergency room for fever, stiff neck, and photophobia.
- LP is performed and he is started on vancomycin, ceftriaxone, and corticosteroids.
- Why does he need vancomycin?
  - A) He may have MRSA
  - B) He may have Enterococcus
  - C) He may have Strep pneumo resistant to ceftriaxone
  - D) He may have Neisseria meningitidis resistant to ceftriaxone
**Strep Pneumo Resistance**

- Susceptible to penicillin and many other antibiotics until mid-1970's
- Resistance began in areas where children with viral infections treated “prophylactically” with abx
- Mechanism: decreased affinity of PBP; in some circumstances, may be overcome by higher antibiotic concentration (meningitis = exception)
- In US, 96% susceptible to ceftriaxone (3% intermediate, 1% resistant)

**Vancomycin-Resistant Enterococcus (VRE)**

- VRE has become endemic in many hospitals
- Initially developed in part due to glycopeptide use for growth promotion in animals
- Mechanism: alteration of vancomycin target (D-ala-D-ala becomes D-ala-D-lac)
- Vancomycin resistance much more common with *E. faecium* than *E. faecalis*; both worsening
- May colonize the GI tract and skin
- Treatment: dapto, linezolid, sometimes others

**Emerging Resistance: ESBL**

**Extended Spectrum β-Lactamases**

- Mutant β-lactamases that hydrolyze beta-lactam antibiotics, including 3rd generation cephalosporins
- Usually in *Klebsiella* spp. and *E.coli*
- Consider in all nosocomial infections with these organisms (overall prevalence may be >10%)

**Beta-Lactamase**

- Beta-lactamase: enzyme that opens beta-lactam ring, inactivating the antibiotic
- Discovered in 1960’s
- Hydrolyze penicillins and narrow-spectrum cephalosporins (ie. cefazolin)
- Present in many gram-negative bacteria (*Enterobacteriacae, Neisseria, Haemophilus, etc*)
- Later generation cephalosporins still work: cefotaxime, ceftriaxone, cefazidime, cefepime

**Extended-Spectrum Beta-Lactamase (ESBL)**

- Klebsiella developed resistance to cefotaxime, ceftazidime, & ceftriaxone shortly after they were introduced in Europe
- Developed from mutations in beta-lactamase
- Transferrable (plasmid-mediated)
- Generally susceptible to cephemycins (cefotetan, cefoxitin), beta-lactamase inhibitors, and carbapenems
- Treatment of choice: carbapenem

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**What should be done?**

A) Switch to levo or cipro
B) Switch to pip/tazo
C) Switch to cefepime
D) Switch to meropenem
E) Continue current therapy
**ESBL**

- **Treatment of choice:**
  - Carbapenem  **Variable success:**
    - FQ
    - Aminoglycoside
    - Cefoxitin (generally not reported as sensitive)
    - Beta-lactam/beta-lactamase inhibitor or cefepime (suffer from inoculum effect)

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**AmpC: What’s in a Name?**

| S | P | I | C | E | M | +/- Acinetobacter- SPICEMA |

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**Serratia marcescens**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prior</th>
<th>Today</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cipro</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Amp</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Amp / Sulbactam</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Cefotixin</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>Cefepime</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Meropenem</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

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**Emerging Resistance: AmpC**

- **AmpC β-Lactamases**
  - Enzymes hydrolyze penicillins & Gen 1-3 cephalosporins
  - Chromosome of “SPICEM” organisms, but often not expressed until drug pressure applied
  - Can be transferred on plasmids also
  - Consider in all infections with SPICEM bugs when initial improvement fails (“induction of AmpC”)

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**GNR Resistance Detection Summary**

<table>
<thead>
<tr>
<th>MOA</th>
<th>Location</th>
<th>Bugs</th>
<th>1 gen Ceph</th>
<th>2 gen Ceph</th>
<th>3 gen Ceph</th>
<th>4 gen Ceph</th>
<th>Cefotax + Clav</th>
<th>Carbapenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL</td>
<td>Plasmid</td>
<td>E.coli, Klebsiella</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>R / S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

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- A 58 y/o man with *Serratia marcescens* hardware-associated osteomyelitis of the tibia, doing well.
- Treated for 4 weeks with IV amp/sulbactam, no problems
- Unexpected fever develops → BCx grows *Serratia*. 
AmpC: What’s in a Name?

S  Serratia
P  Pseudomonas, Providencia
I  Indole + Proteus (vulgatis)
C  Citrobacter
E  Enterobacter
M  Morganella

+/- Acinetobacter- SPICEMA
GNR Resistance Detection Summary

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<tr>
<td>4 gen Ceph</td>
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<tr>
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<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Carbapenem</td>
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</tr>
</tbody>
</table>

- A 75 y/o woman is admitted with massive myocardial infarction.
- After five days on the ventilator, she develops hypoxemia, fever, leukocytosis, and infiltrates. She is treated empirically for VAP using pip/tazo and then meropenem.
- Sputum gram stain shows 3+ GNR’s.
- Clinical illness worsens on therapy….

Emerging Resistance: KPC

KPC Carbapenemases
- Enzymes hydrolyze carbapenems
- Klebsiella pneumoniae strongest association… also seen in Enterobacteriaceae & Pseudomonas aeruginosa
- Can be transferred on plasmids
- Consider in all infections with Klebsiella pneumoniae or other Enterobacteriaceae which fail to improve on carbapenem therapy

Treatment Options
- Beta-lactams are generally ineffective
- Plasmids often contain resistance determinants for numerous other drugs
- Test aminoglycosides, FQ’s, tetracyclines, tigecycline, TMP/SMX, colistin/polymixin B…

Emerging Resistance: KPC

A 24 yo man flown to your hospital from India following a car accident. You receive a call from the team that the wound is growing Pseudomonas and E. coli. What’s next?

- Put the patient in contact precautions
- Call infection control
- Call the microbiology lab
### Pseudomonas aeruginosa

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MICM Interp</th>
<th>Microtiter MIC (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>R</td>
<td>&gt;32</td>
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<tr>
<td>Aztreonam</td>
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<td>&gt;8</td>
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<tr>
<td>Cefepime</td>
<td>I</td>
<td>16</td>
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<tr>
<td>Ceftazidime</td>
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<td>Levofloxacin</td>
<td>R</td>
<td>&gt;4</td>
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<tr>
<td>Meropenem</td>
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<td>&gt;8</td>
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<tr>
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<tr>
<td>Tobramycin</td>
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<td>&gt;8</td>
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</table>

Colistin MIC 4 mcg/mL

### Escherichia coli

<table>
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<tr>
<th>Antibiotic</th>
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</tr>
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<tbody>
<tr>
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<tr>
<td>Ampicillin</td>
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<td>&gt;16</td>
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<td>&gt;8</td>
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<tr>
<td>Cefazolin</td>
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<td>&gt;16</td>
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<tr>
<td>Cefepime</td>
<td>R</td>
<td>&gt;16</td>
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<tr>
<td>Cefotetan</td>
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<tr>
<td>Ceftazidime</td>
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<td>Ceftriaxone</td>
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<td>Ciprofloxacin</td>
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<td>R</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Trimeth_Sulfamethoxazole</td>
<td>R</td>
<td>&gt;4</td>
</tr>
</tbody>
</table>

Colistin MIC 2 mcg/mL
Almost complete beta-lactam resistance
- Resistant to aminoglycosides, FQ’s, and some other classes of antimicrobials.
- Some even resistant to tigecycline and colistin
- K. pneumoniae, E. coli, Citrobacter freundii, Pseudomonas
- Has been seen in many countries, including the US, Australia, Canada, Japan, Balkan nations, Kenya

**New Delhi beta-lactamase-1 (NDM-1)**

**MOA**

<table>
<thead>
<tr>
<th>MOA</th>
<th>AmpC</th>
<th>ESBL</th>
<th>KPC</th>
<th>NDM-1</th>
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<tbody>
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<td>Plasmid</td>
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<tr>
<td>Bugs</td>
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<td>Klebsiella, enterobacteriaceae</td>
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<td>R</td>
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<td>R</td>
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<tr>
<td>3 gen Ceph</td>
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<td>R</td>
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<td>4 gen Ceph</td>
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<td>R</td>
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<tr>
<td>Carbopenem</td>
<td>S</td>
<td>S</td>
<td>R</td>
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</tbody>
</table>

**2012 Updated Gonorrhea Treatment Guidelines**

Uncomplicated Gonococcal Infection of Cervix, Urethra, or Rectum

**Recommended Therapy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>250 mg IM x 1</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1 g PO x 1</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg PO bid x 7d</td>
</tr>
</tbody>
</table>

**Notes:**
- Dose of ceftriaxone now 250 mg (previously 125 mg)
- Azithromycin preferred over doxycycline because of high rate of tetracycline resistance
- Ceftriaxone NOT first line anymore
- Fluoroquinolones NOT recommended
- If giving second-line therapy (cefixime or azithromycin), must do test of cure at 1 week

**Last Case.** A 20-year-old man presents for urethral pain and discharge. Nucleic acid amplification test (NAAT) of urine is positive for *Neisseria gonorrhoea*. NAAT for *Chlamydia trachomatis* is negative.

Which of the following is the recommended treatment for this patient (according to 2012 CDC guidelines):

1. Ceftriaxone 250 mg IM x 1
2. Cefixime 400 mg PO x 1
3. Ceftriaxone 250 mg IM x 1 plus azithromycin 1 g PO x 1
4. Ciprofloxacin 250 mg PO x 1
5. Azithromycin 2 g PO x 1

**Neisseria gonorrhoea**

- #2 most common reported infectious disease in U.S.
- ~600,000 cases/yr
- Causes PID, organ damage, infertility
- Can be asymptomatic
"10 Commandments" of Antibiotic Use

1. Teach pts how to manage symptoms of non-bacterial infections
2. Targeted therapy is best
3. Use the shortest course that works
4. Encourage adherence
5. Use antibiotic combos sparingly
6. Avoid sub-standard drugs
7. Discourage self-prescription
8. Follow evidence-based guidelines
9. Rely upon the clinical micro lab
10. Prescribe empirically but intelligently

+ 5 recommendations

1. Wash your hands
2. Consider an “antibiotic time-out” on day 2 or 3 (or when the test results return)
3. Use guidelines (ex. IDSA recs for acute rhinosinusitis or skin/soft tissue infections)
4. Help educate your staff and patients
5. Get active in your facility, clinic, hospital, program!

Teaching Pearl: Antibiotics that Treat Pseudomonas

- Aminoglycosides
- Pip/tazo
- Imipenem (or meropenem)
- Cipro (or levo)
- Ceftazidime, cefepime

*Colistin or polymixin B if desperate

*New Antibiotics*

- FDA Approved: for skin/soft tissue infections (including MRSA)
  - Tedizolid: like linezolid but shorter course
  - Oritavancin: single dose
  - Dalbavancin: once-weekly dosing
- Coming:
  - Ceftipibrole: 5th gen ceph active against MRSA and Pseudomonas

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