Learning Objectives

• Brief highlight of major events in infectious diseases in past year
• Discuss an emerging infectious threat important to your daily practice
• Discuss 2 infection prevention strategies to reduce surgical infections
• Discuss 3 important advances in antimicrobial management
Disclosures

• Research funding from Rebiotix Inc
• Editor in Chief, AOA
• Employee, Mayo Foundation
Epidemic Infections

- Lyme disease
- West Nile Virus
- Coccidioidomycosis
- Measles
- Pertussis
- Mumps
- Norovirus
- Ebola
- MERS

- Borrelia miyamotoi
- Hartland virus
- RMSF in AZ
- Bourbon Virus
- Chikungunya
- Legionnaires – Bronx
- SLE – Arizona
- Plague - Yellowstone
Top 3 Advances in ID 2015
Which is the most important emerging threat to human health?

A. Ebola-virus disease
B. HIV infection
C. Multiply resistant bacterial infections
D. Middle Eastern Respiratory Syndrome Corona Virus Infection (MERS-CoV)
E. Lyme disease
Emerging Threats

• *Multiply resistant pathogens*

• Healthcare associated infections

*1 in 25 inpatients*
“It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body...there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”

-Alexander Fleming, Nobel prize lecture, 1945
Deaths Attributable to Antimicrobial Resistance Every Year by 2050

North America: 317,000
Europe: 390,000
Africa: 4,150,000
Latin America: 392,000
Asia: 4,730,000
Oceania: 22,000

The Discovery and Consequent Development of Antibiotic Resistance

- **Penicillin** (1930)
- **Tetracycline** (1940)
- **Methicillin** (1960)
- **Vancomycin** (1970)
- **Carbapenem** (1980)
- **Cefixime** (1990)
- **Linezolid** (2000)

Era of Antibiotic Discovery

Development of Antibiotic Resistance

Current Top 5 Healthcare Associated Infections

• Pneumonia = #1 22% of all HAI
• Surgical Site = #1 22%
• Gastrointestinal = #3 17%
• UTI (esp CAUTI) = #4 13%
• Primary BSI = #5 10%

Clostridium difficile = #1 HAI

Magill SS et al N Engl J Med 2014;370:1198
Rise of the Superbugs
Call to punish GPs over antibiotics

\[\text{BBC Health}\]
\[\text{Call to punish GPs over antibiotics}\]
\[\text{BBC News website 8/15/2015}\]

- "Soft-touch" and "hazardous" doctors should be disciplined for prescribing too many antibiotics, a leading NHS figure says.

- Prime Minister David Cameron has warned: "We are looking at an almost unthinkable scenario where antibiotics no longer work and we are cast back into the dark ages of medicine where treatable infections and injuries will kill once again."
## Causative Pathogens

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium difficile</em></td>
<td>12%</td>
</tr>
<tr>
<td><em>Staph aureus</em></td>
<td>11%</td>
</tr>
<tr>
<td><em>Klebsiella pneumonia</em></td>
<td>10%</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>9%</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>9%</td>
</tr>
</tbody>
</table>
"The last decade has seen the inexorable proliferation of a host of antibiotic resistant bacteria, or bad bugs, not just MRSA, but other insidious players as well.

...For these bacteria, the pipeline of new antibiotics is verging on empty. 'What do you do when you're faced with an infection, with a very sick patient, and you get a lab report back and every single drug is listed as resistant?' asked Dr. Fred Tenover of the Centers for Disease Control and Prevention (CDC). 'This is a major blooming public health crisis.'“

—Science magazine; July 18, 2008
Opportunities

• Has anyone in this room prescribed Azithromycin for a URI?
• Has anyone given ciprofloxacin for asymptomatic bacteriuria?
• Has anyone prescribed Amoxicillin or Clindamycin to prevent Prosthetic hip infections before dental work?
Stop killing beneficial bacteria

Collateral Damage

- Average child receives 10-20 courses of antibiotics before age 18
- Antibiotics affect our resident microbiota and may not fully recover after a course of antibiotics
- Overuse of antibiotics may be contributing to obesity, DM, IBD, allergies, and asthma

Blaser M et al Nature 2011;476:393
Infectious Disease Mortality in the United States During the 20th Century

US deaths declined by ~220 per 100,000 in 15 years

Sulfa

Penicillin

Other medical technologies reduced deaths by ~20 per 100,000 over the next 45 years

Why We Need to Improve Antibiotic Use

- Antibiotics are misused across the continuum of care
- Use of antibiotics in animals
- Antibiotic misuse adversely impacts patients and society
- **Antibiotics are the only drug where use in one patient can impact the effectiveness in another.**
- Improving antibiotic use improves patient outcomes and saves money
- Improving antibiotic use is a public health imperative- WHO considers AR an emerging threat to global stability
How Big is the Problem?

- Antibiotics are the second most commonly used class of drugs in the United States
- More than 8.5 billion dollars spent annually
  - 200-300 million antimicrobials prescribed annually
  - 53% for outpatient use
  - Bronchitis, pharyngitis and sinusitis account for 75% of all office-based Rx for antibiotics
- Almost half of hospitalized patients receive antibiotics
- **50%** of antibiotic use is either unnecessary or inappropriate across all type of health care settings

*BMC Med 2014;12:96*  
*Clin Infect Dis 2007; 44:159-177*
Trends in overall antibiotic prescribing.
Temporal trends in the proportion of all antibiotics prescribed for each antibiotic class.
Prevention of Unnecessary Abx Use

- URTIs - >50% Rxs are inappropriate
- Pharyngitis – adults – not Strep
- UTI – 30-50% are inappropriate
- Prophylaxis – not in line with guidelines
But it won’t impact MY patients..

- Impact on urinary, respiratory and skin flora
- Effect is greatest in month after but may last 12 months
- Potential driver of community resistance
- Dose response for Amox and TMP-SMX

_Fewest Abx for shortest duration_

_BMJ 2010; 340 doi: http://dx.doi.org/10.1136/bmj.c2096_
Forest plot showing individual study and pooled ORs (log scale) for resistance in urinary tract bacteria (E coli) and antibiotic exposure.

<table>
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<tr>
<th>Time period, study</th>
<th>Antibiotic exposure</th>
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<tbody>
<tr>
<td>0-1 month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donnan <em>17</em></td>
<td>Trimethoprim</td>
<td>NR</td>
<td>4.45 (3.78 to 5.21)</td>
</tr>
<tr>
<td>Hillier <em>19</em></td>
<td>Trimethoprim</td>
<td>20</td>
<td>4.85 (2.63 to 8.94)</td>
</tr>
<tr>
<td>Hillier <em>19</em></td>
<td>Amoxicillin</td>
<td>20</td>
<td>3.11 (1.57 to 6.17)</td>
</tr>
<tr>
<td>Pooled odds ratio</td>
<td></td>
<td></td>
<td>4.40 (3.78 to 5.12)</td>
</tr>
<tr>
<td>Test for heterogeneity: $I^2=0.0%$, $P=0.576$</td>
<td></td>
<td></td>
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<tr>
<td>0-3 months</td>
<td></td>
<td></td>
<td></td>
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<td>Donnan <em>17</em></td>
<td>Trimethoprim</td>
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<td>2.60 (2.04 to 3.33)</td>
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<tr>
<td>Hillier <em>19</em></td>
<td>Trimethoprim</td>
<td>39</td>
<td>2.62 (1.69 to 4.07)</td>
</tr>
<tr>
<td>Hillier <em>19</em></td>
<td>Amoxicillin</td>
<td>39</td>
<td>2.26 (1.41 to 3.62)</td>
</tr>
<tr>
<td>Hay <em>18</em></td>
<td>Any antibiotic</td>
<td>20</td>
<td>1.93 (1.06 to 3.51)</td>
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<tr>
<td>Pooled odds ratio</td>
<td></td>
<td></td>
<td>2.48 (2.06 to 2.98)</td>
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<tr>
<td>Test for heterogeneity: $I^2=0.0%$, $P=0.796$</td>
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<tr>
<td>0-6 months</td>
<td></td>
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<tr>
<td>Steinke <em>27</em></td>
<td>Any antibiotic*</td>
<td>19</td>
<td>1.36 (1.14 to 1.61)</td>
</tr>
<tr>
<td>Donnan <em>17</em></td>
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<td>NR</td>
<td>1.67 (1.32 to 2.10)</td>
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<td>Steinke <em>27</em></td>
<td>Trimethoprim</td>
<td>19</td>
<td>3.95 (3.04 to 5.12)</td>
</tr>
<tr>
<td>Hillier <em>19</em></td>
<td>Amoxicillin</td>
<td>28</td>
<td>1.83 (1.39 to 2.42)</td>
</tr>
<tr>
<td>Donnan <em>17</em></td>
<td>Any antibiotic*</td>
<td>NR</td>
<td>1.65 (1.10 to 2.46)</td>
</tr>
<tr>
<td>Hillier <em>19</em></td>
<td>Trimethoprim</td>
<td>28</td>
<td>2.57 (1.83 to 3.61)</td>
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<tr>
<td>Metlay <em>24</em></td>
<td>ST</td>
<td>28</td>
<td>4.10 (2.20 to 7.50)</td>
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<tr>
<td>Pooled odds ratio</td>
<td></td>
<td></td>
<td>2.18 (1.57 to 3.03)</td>
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<tr>
<td>Test for heterogeneity: $I^2=89.2%$, $P=0.000$</td>
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<tr>
<td>Hay <em>18</em></td>
<td>Any antibiotic*</td>
<td>38</td>
<td>1.13 (0.79 to 1.63)</td>
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<tr>
<td>Hillier <em>19</em></td>
<td>Trimethoprim</td>
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<td>2.36 (1.59 to 3.50)</td>
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<td>Pooled odds ratio</td>
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<td></td>
<td>1.33 (1.15 to 1.53)</td>
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<tr>
<td>Test for heterogeneity: $I^2=71.9%$, $P=0.007$</td>
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</tbody>
</table>

* Any antibiotic other than trimethoprim. ST=sulfamethoxazole-trimethoprim. NR=not reported.
Forest plot showing individual study and pooled ORs (log scale) for resistance in respiratory tract bacteria and previous antibiotic prescribing.

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<tr>
<td>0-1 month</td>
<td>Beekmann²⁹ Any antibiotic</td>
<td>13</td>
<td>2.10 (1.05 to 4.26)</td>
<td>2.10 (1.04 to 4.23)</td>
</tr>
<tr>
<td></td>
<td>Pooled odds ratio</td>
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<td></td>
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<tr>
<td>0-2 months</td>
<td>Seaton³⁰ Any antibiotic</td>
<td>13</td>
<td>2.10 (1.20 to 3.60)</td>
<td>4.19 (1.23 to 14.26)</td>
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<tr>
<td></td>
<td>Cliffr³¹ Macrolide</td>
<td>2</td>
<td>2.37 (1.42 to 3.95)</td>
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<tr>
<td></td>
<td>Pooled odds ratio</td>
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<tr>
<td>Test for heterogeneity: $\chi^2=1.6%, P=0.313$</td>
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<tr>
<td>0-3 months</td>
<td>Schrag³² β lactam</td>
<td>33</td>
<td>1.50 (1.20 to 1.80)</td>
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</tr>
<tr>
<td></td>
<td>Samore³³ Cephalosporin</td>
<td>17</td>
<td>2.30 (1.04 to 5.10)</td>
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</tr>
<tr>
<td></td>
<td>Samore³³ Penicillin</td>
<td>17</td>
<td>1.80 (0.80 to 4.20)</td>
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<tr>
<td></td>
<td>Samore³³ Macrolide</td>
<td>17</td>
<td>0.40 (0.10 to 1.30)</td>
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<tr>
<td></td>
<td>Pooled odds ratio</td>
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<td>1.48 (0.95 to 2.32)</td>
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<td>Test for heterogeneity: $\chi^2=44.2%, P=0.146$</td>
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<tr>
<td>0-6 months</td>
<td>Ghaffar³⁴ β lactam*</td>
<td>14</td>
<td>3.93 (0.44 to 35.28)</td>
<td></td>
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<tr>
<td></td>
<td>Ghaffar³⁴ β lactam</td>
<td>14</td>
<td>1.90 (0.69 to 5.21)</td>
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<td>Pooled odds ratio</td>
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<tr>
<td>Test for heterogeneity: $\chi^2=0.0%, P=0.463$</td>
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<tr>
<td>0-12 months</td>
<td>Beekmann²⁹ Any antibiotic</td>
<td>13</td>
<td>1.28 (0.64 to 2.54)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Samore³³ Penicillin</td>
<td>NR</td>
<td>1.20 (0.50 to 2.50)</td>
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<tr>
<td></td>
<td>Samore³³ Cephalosporin</td>
<td>NR</td>
<td>1.60 (0.80 to 3.50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arason³⁶ β lactam</td>
<td>NR</td>
<td>6.75 (1.78 to 25.51)</td>
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</tr>
<tr>
<td></td>
<td>Arason³⁶ Co-trimoxazole</td>
<td>NR</td>
<td>7.22 (1.73 to 30.05)</td>
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<tr>
<td></td>
<td>Arason³⁶ Erythromycin</td>
<td>NR</td>
<td>8.56 (1.14 to 64.04)</td>
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<td></td>
<td>Pooled odds ratio</td>
<td></td>
<td>2.37 (1.25 to 4.50)</td>
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<tr>
<td>Test for heterogeneity: $\chi^2=57.3%, P=0.039$</td>
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</tbody>
</table>

*β lactam plus another antibiotic. NR=not reported

Céire Costelloe et al. BMJ 2010;340:bmj.c2096
Forest plot showing individual analytic and pooled ORs (log scale) for resistance in respiratory tract streptococci of healthy volunteers from the Malhotra-Kumar study and previous antibiotic prescribing.

<table>
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<tr>
<th>Time period</th>
<th>Odds ratio (95% CI)</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>At 1 week post-antibiotic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>14.67 (6.14 to 35.00)</td>
<td>10.44 (4.65 to 23.44)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>12.22 (6.76 to 22.10)</td>
<td></td>
</tr>
<tr>
<td>Pooled odds ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At 2 weeks post-antibiotic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>11.59 (5.08 to 26.47)</td>
<td>5.37 (2.58 to 11.17)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>7.70 (3.63 to 16.34)</td>
<td></td>
</tr>
<tr>
<td>Pooled odds ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At 1 month post-antibiotic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>9.25 (4.21 to 20.31)</td>
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</tr>
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<td>Clarithromycin</td>
<td></td>
<td>6.08 (2.76 to 13.39)</td>
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<td><strong>At 2 months post-antibiotic</strong></td>
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<td>4.37 (2.13 to 8.98)</td>
<td>3.00 (1.48 to 6.08)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td>3.61 (2.18 to 5.97)</td>
</tr>
<tr>
<td>Pooled odds ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At 6 months post-antibiotic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1.89 (0.88 to 3.77)</td>
<td>2.47 (1.20 to 5.07)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td>2.16 (1.30 to 3.61)</td>
</tr>
<tr>
<td>Pooled odds ratio</td>
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</tbody>
</table>
The Response

• Prevention
  – Screening and surveillance
  – Hygiene and Environmental controls

• Dx/Treatment
  – Differentiate bacterial infections from others
  – Biomarkers
  – Reliable bacterial identification and resistance tests

• Outbreak Management

• Education
The FilmArray BCID Panel
Simultaneous detection of 27 targets:

**Gram + Bacteria**
- Staphylococcus
- Staphylococcus aureus
- Streptococcus
- Streptococcus agalactiae
- Streptococcus pyogenes
- Streptococcus pneumoniae
- Enterococcus
- Listeria monocytogenes

**Gram - Bacteria**
- Klebsiella oxytoca
- Klebsiella pneumoniae
- Serratia
- Proteus
- Acinetobacter baumannii
- Haemophilus influenzae
- Neisseria meningitidis
- Pseudomonas aeruginosa
- Enterobacteriaceae
- Escherichia coli
- Enterobacter cloacae complex

**Fungi**
- Candida albicans
- Candida glabrata
- Candida krusei
- Candida parapsilosis
- Candida tropicalis

**Antibiotic Resistance**
- mcrA
- vanA / vanB
- KPC

**Simple:**
Only 2 minutes of hands-on time

**Easy:**
No precise pipetting required

**Fast:**
Run time of only 1 hour
## Rapid Tests for MRSA

<table>
<thead>
<tr>
<th>Test</th>
<th>Time</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeneOhm MRSA ACP Assay</td>
<td>2 hrs</td>
<td>Nasal, Groin, Wound</td>
</tr>
<tr>
<td>GeneOhm StaphSR Assay</td>
<td>2 hrs</td>
<td>Blood*</td>
</tr>
<tr>
<td>Xpert MRSA/SA BC, MRSA/SA SSTI</td>
<td>1 hr</td>
<td>Blood*, Wound</td>
</tr>
<tr>
<td>Lightcycler MRSA</td>
<td>2 hrs</td>
<td>Nasal</td>
</tr>
<tr>
<td>Nanosphere Verigene</td>
<td>2.5 hrs</td>
<td>Blood*</td>
</tr>
</tbody>
</table>

*Blood Tests Detect: MSSA, MRSA, Coagulase-negative staphylococcus
Why all the Overuse?
Diagnostic Uncertainty

- Physicians often prescribe due to this
- Fail to think about the consequences
  - Individual and public health
- How to relieve uncertainty?
- What new tools may help?
Adults with suspected AMS were referred by GPs for Xrays of the maxillary sinus.

Those with radiographic abnormalities (n = 214) were randomly assigned treatment with amoxicillin (750 mg three times daily for 7 days; n = 108) or placebo (n = 106).

Clinical course was assessed after 1 week and 2 weeks, and reported relapses and complications were recorded during the following year.

- At 2 weeks, symptoms improved substantially or disappeared
- 83% AMOX and 77% placebo.
- No influence on the clinical course, frequency of relapses during the 1-year follow-up.
- Radiographs had no prognostic value.
- Side-effects were recorded in 28% of patients given amox and in 9% of those taking placebo (p < 0.01). The occurrence of relapses was similar in both groups (21 vs 17%) during the follow-up year.

Van Buchem *Lancet*. 1997 May 17;349(9063):1476
Rhinosinusitis

- One in 7 Americans, diagnosed each year
- In top 5 for Abx Rxs
- But... 90-98% of these are viral
- When to prescribe....
  1. Symptoms >10 days w/o improvement
  2. Severe sxs with fever>102, nasal dc & facial pain>3 days
  3. Viral sinus sxs that worsen over 506 days and associated with new fever, headache, more nasal dc
What to treat ABRS with?

- Amox-Clav for 5-7 days in adults
- Nasal saline irrigation
Otitis Media – the evidence base

- 80% of acute OM resolves in 3 days without Rx
- ABX do not influence subsequent OM or deafness at 1 month
- May reduce no of children still in pain 2-7 days but for each 1 improved 3 will develop ABX related side effects
- Repeated courses may make recurrent infection more likely
Viral Infections don’t require antibiotics

- Acute bronchitis
- Common colds
- Sinusitis with symptoms less than 7 days
- Pharyngitis not due to Group A *Streptococcus spp.*

URTIS – Improving Care

• Use Biomarkers
  – Procalcitonin

• Use Rapid Diagnostic tests – Multiplex PCR

• Patient education

• CDC Get Smart program

• Opportunity to Vaccinate
  – Influenza, Pertussis, Strep pneumoniae

• OMT?
Bacterial infection and cytokines stimulate production of PCT in parenchymal tissues

- PCT is rapidly released into bloodstream
- Cytokines produced by viral infection inhibit this
Evidence levels
? Still undefined
+ Moderate
++ Good
+++ Strong

Procalcitonin data

Schuetz et al. BMC Medicine 2011 9:107
Antibiotic prescribing per 1000 persons by state (sextiles) in 2011 for all ages (A) and persons aged ≤2 (B), 3–64 (C), or ≥65 (D) years.

Outpatient UTI Management

Uncomplicated Cystitis

• Women with at least 2 sxs: dysuria, urgency, frequency and no vaginal discharge - >90% probability of acute cystitis
  – Studies found no benefit to doing testing

Women with relapse or recurrent UTI (>2/6m), complicated infections, Abx exposure or resistance should have a urine culture done
Treatment of Acute Cystitis

- **Women**
  - Nitrofurantoin 100 mg BID x 5 days
  - Fosfomycin 3g x 1 dose
  - TMP-SMX DS BID x 3 days (if resistance<20%)

- **Men**
  - 7-14 days
Treat Bacterial Infection, not Colonization

- $\geq 10^5$ colony forming units is often used as a diagnostic criteria for a positive urine culture
- **It does NOT prove infection**; it is just implies the culture is unlikely due to contamination
- **Pyuria is not predictive** on its own
- Symptoms AND pyuria AND bacteruria denotes infection

Grigoryan L et al *JAMA* 2014;312:1677-84
### Asymptomatic Bacteriuria is Common

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>70</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>&gt;70 + long-term care</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>(with intermittent catheterization)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic urinary catheter</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Ileal loop conduit</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Treatment of Asymptomatic Bacteriuria in the Elderly

Multiple prospective randomized clinical trials have shown no benefit

- No improvement in “mental status”
- No difference in the number of symptomatic UTIs
- No improvement in chronic urinary incontinence
- No improvement in survival
Inappropriate Abx Use in Asymptomatic Bacteriuria

- Dalen 2005 Ottawa 52%
- Ghandi 2009 Michigan 33%
- Cope 2009 Houston 32%

- 1/3-50% get antibiotics despite evidence of no benefit
A Second Opportunity - UTIs

- Much of the antibiotic use here is not appropriate and avoidable.
- Wrong treatment, Wrong Drug, Wrong Duration are common
- **Resistance to Fluoroquinolones**
  - Trimethoprim-Sulfa
- Ensure the patient has a UTI not an alternate diagnosis
- When catheters in place - all are bacteriuric
What Causes the Pain in UTI

• Visceral pain is usually projected over the dermatome that shares common spinal innervation
• In murine models – strains which cause ASB elicit different responses than symptomatic UPEC strains – **It is LPS which induces the pain through TLR4**
• Inflammatory cells in urine are not the cause of pain and do not correlate with UTI in ASB
• New therapeutic approach? Probiotics with LPS

Rudick CN  *J Infect Dis* 2010:201:1240
Biotherapeutics in UTI

- Vaginal application of *L. crispatus* reduces UTI
- ASB E. coli – bacterial interference
- Strain 83972 of E. coli
- Use of these strains in mice prevents symptomatic infection
- Reduces pain more than ciprofloxacin
- Promotes clearance

Rudick CN *PLOS One* 2014;9:e109321
Review 322 cases of SSTI @400 bed hospital in Denver 2007

- Positive cultures: 145/150 (97%) – *S. aureus* or streptococci

  Treatment -70% got Abx for GNRs

- Imaging (151): Yield-1%

- Abx duration (median): 14 days

Jenkins T. *Clin Infect Dis* 2010;51:895
Every time antibiotics are prescribed:

1. Order recommended cultures before antibiotics are given and start drugs promptly.

2. Make sure indication, dose, and expected duration are specified in the patient record.

3. Reassess within 48 hours and adjust Rx if necessary or stop Rx if indicated.

Specific recommendations for common prescribing situations:

- **Rx for urinary tract infections**
  - Make sure that culture results represent true infection and not just colonization.
  - Assess patient for signs and symptoms of UTI.
  - Make sure that urinalysis is obtained with every urine culture.
  - Treat for recommended length of time and ensure that planned post-discharge treatment takes into account the antibiotics given in the hospital.

- **Rx for pneumonia**
  - Make sure that symptoms truly represent pneumonia and not an alternate, non-infectious diagnosis.
  - Treat for the recommended length of time and ensure that planned post-discharge treatment takes into account the antibiotics given in the hospital.

- **Rx for MRSA infections**
  - Verify that MRSA is growing in clinically relevant cultures. Do not use vancomycin to treat infections caused by methicillin-susceptible staph (and not MRSA).

SOURCE: CDC Vital Signs, 2014
A Challenging UTI

- A 53 year old man with Parkinson’s disease and a seizure disorder presents with his 4\textsuperscript{th} urinary tract infection in the past year.

- He has back pain and dysuria. His current urinalysis shows pyuria and bacteriuria

- Urine culture is growing \textit{Klebsiella pneumoniae} Resistant to: Ciprofloxacin, Gentamicin, Trimethoprim-Sulfa, Pip-Tazo, Cefepime, Ertapenem, Imipenem, Meropenem

- What antibiotic is \textbf{most likely to be effective} for treatment of his \textit{Klebsiella pneumoniae} infection?
Management of Carbapenem-resistant Enterobacteriaceae (CRE)

• Any Enterobacteriaceae isolate non-susceptible to all 3rd generation Cephs and Imipenem, Doripenem or Meropenem

• CALL FOR BACK-UP!!
CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

9,000 drug-resistant infections per year
600 deaths

Carbapenem-resistant Klebsiella spp. 7,900
Carbapenem-resistant E. coli 1,400

CRE have become resistant to all or nearly all available antibiotics

THREAT LEVEL URGENT
This bacteria is an immediate public health threat that requires urgent and aggressive action.

CRE germs kill up to half of patients who get bloodstream infections from them.

Vitalsigns™
www.cdc.gov/vitalsigns
New Drugs for MDROs

Ceftazidime-Avibactam (Avycaz)

• New non-beta-lactam beta-lactamase inhibitor added to Ceftazidime which enhances activity against some MDR GNRs including CRE
• Most KPCs, ESBL, AmpC
• *NOT* Metallo-beta lactamases!
• 2.5 g IV q 8h (over 2h)
  – 2 g Taz plus 500 mg Avibactam
Epidemiology of Carbapenem-Resistant Enterobacteriaceae in 7 US Communities, 2012-2013

- 87% from urine; 11% blood
- Device associated or hospitalized
- Fatal in 9%
- Higher rates in GA, MD, NY vs CO, NM, OR lower
- Median age 66
- Incidence 2.93/100k vs MRSA 25, CDI 147

Guh AY et al JAMA Oct 5, 2015;doi10.10001/jama2015.12480
New Cephalosporins for Resistant Gram Negatives

- **Ceftolozane/tazobactam (Zerbaxa)**
  - Similar to ceftazidime w/modified sidechain at position 3 - antiPseudomonal
  - Tazo protects the ceph from ESBLs
  - Better than Ceftaz vs P. aeruginosa
  - **Not active vs KPCs or MBLs**
  - Approved for IAI, UTI
More MDROs

A 32 yo woman presents with severe dyspnea, hemoptysis and fever. She refused flu vaccination this year because it makes her sick.

8 days ago she had *influenza* A and was just beginning to improve when this struck.

Her past history is remarkable for recurrent skin boils and severe depression for which she takes Sertraline and Venlafaxine

Her CXR shows diffuse multilobar infiltrates and a sputum gram stain reveals the following:

![Image of bacteria](image.png)
Which antibiotic would you recommend to treat her pneumonia?

A. Telavancin (Vibativ)
B. Vancomycin
C. Dalbavancin (Dalvance)
D. Daptomycin (Cubicin)
E. Tedizolid (Sivextro)
THE ANTI-MRSA BRIGADE

Vancomycin, Daptomycin, Telavancin, Linezolid, Tedizolid, Dalbavancin, Oritavancin, Clindamycin, Trimethoprim-Sulfa, Tigecycline, Minocycline, Ceftaroline, Quinupristin-dalfopristin
Telavancin (Vibativ)

• Lipoglycopeptide - daughter of Vancomycin
  Longer half life (7.5h) – dosed 10 mg/kg q24h over 1 hr  **IV only**
• Approved for SSTI – MRSA $$$
• Side effects – altered taste, nausea, foamy urine; Red Person
• Prolongation of Qtc; interferes with INR
• Been used in HAP and VAP
Ceftaroline fosamil (Teflaro)

- “Ceph with enhanced gram positive activity
  - MRSA, VRE, VISA, hVISA, MDR-Strep; common gram negatives
  - Minimal activity vs *E. faecalis*
  - Not active vs *E. faecium*
- Lacks broad gram negative coverage – think RTI only!
- Approved for cSSTI, CAP (not MRSA) $$$
  - 600 mg IV q12H IV
  - Similar to Vanco for SSTI; Ceftriaxone for RTI
  - Side effects of nausea, diarrhea
Tedizolid (Sivextro)

- Oxazolidinone similar to Linezolid
- Bacteriostatic
- 200 mg tab **once daily orally** for 6 days for SSTI
Dalbavancin (Dalvance)  
Oritavancin (Orbactiv)  

• These are long half-life lipoglycopeptides vs Gram positive infections – approved SSTI  
• Redman syndrome like Vanco  
• Allow once weekly dosing – IV only  
  – Dalba 1g day 1, 500 mg day 8  
  – Orita 1200 mg x 1 over 3 h  
    • Increase PTT, PT for 48h  

• $$$$$$
SSI Prevention

• A 68 year old woman presents with 3 weeks of left hip pain. She had a left THA 6 weeks ago at her local community orthopedic hospital for avascular necrosis.

• She was seen pre-operatively by an anesthesiologist who assessed her operative risk and okayed her for surgery. No special precautions were taken.

• Today an aspiration of the hip showed 45,000 WBC, 90% polys and gram stain showed numerous gram positive cocci in clusters.
Surgical Site Infections

• Most are due to Staph aureus
• Prevention
  – Screen with nasal swab 10-14 days pre-op or history of prior colonization
  – Decolonize carriers of Staph aureus
    • Mupirocin nasal ointment BID x 5 days
    • CHG wash daily for 5 days
    • If MRSA – use IV Vancomycin + Cefazolin px
    • If MSSA – Cefazolin – 1 dose
STOP-SSI Trial

• 43,087 operations
  – 28,593 before and 14,494 after
  – 90 day follow-up
  – 101 pre vs 29 after – OR 0.6

*Still unclear whether all should be screened*

Given that 400,000 cardiac and 1 million joint replacements done annually – the reduction in infections could have a huge impact

Schweizer M et al JAMA 2015:313:242
Duration of Antibiotics in Surgical Infections – Peritonitis STOP-IT Trial

- 500 pts – 23 US and Canadian sites
- 34% CRS  14% small bowel
- 11% Cancer  10% IBD 15% Diabetic
- Abx for 4 days vs up to 10 days
  - 33% percutaneous drainage
  - 26% surgery
  - 21% surgical drainage
- No difference in SSI/recurrent intrabdominal infection or death in 30 days

Antibiotic exposure is the #1 risk factor for the development of *Clostridium difficile* infection (CDI).

- Up to 85% of patients with CDI have antibiotic exposure in the 28 days before infection

20% of patients admitted to the ICU with CDI were receiving antibiotics without evidence of infection with an accompanying 28% in-hospital mortality

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2. *BMC Infect Dis* 2007; 7:42
CDI: Incidence and Mortality are Increasing in US

Its not just in hospitals - CDI
Control of *C. difficile* infection

- Appropriate use of antimicrobials
- Infection prevention measures
- New Monoclonal Ab vs CD toxin B (coming)
- *Microbiota replacement therapy*
Some Final Tips to Optimize Duration of Antibiotic Therapy

• Avoid generic 10-14-day therapy

  – Uncomplicated urinary tract infection: 3-5 days
  – Community-acquired pneumonia: 3-7 days
  – Ventilator-associated pneumonia: 8 days
  – CR-BSI Coagulase-negative staphylococci: 5-7 days
  – Acute Hem Osteomyelitis in children: 21 days
  – Meningococcal meningitis: 7 days
  – Uncomplicated secondary peritonitis with source control: 4-7 days
  – Uncomplicated SSTI: 5 days

3. JAMA 2003; 290:2588-2598
Summary
To Control Antimicrobial Resistance

- Develop New Drugs and Vaccines
- Improved Diagnostics
- Infection Prevention
- Research & Public Policy
- Education
- Antimicrobial Stewardship
- Reduce Resistance Reservoirs