New Developments in Antimicrobials
(or making the best of what we’ve got)

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A Common Scenario
A 56-year-old man with Type II DM presents to your clinic complaining of two
days of fever and a productive cough. On exam he is febrile to 38.9 but is
saturating well on room air and is no acute distress. A chest X-ray is obtained
and shows a right lower lobe consolidation. The patient is given a diagnosis
of community-acquired pneumonia and the decision is made to treat him as
an outpatient with antibiotics. Assuming equal efficacy of any given drug
regimen which of the following criteria is most important to you when
selecting an antibiotic?

A. Potential adverse effects of the medication
B. Cost to patient
C. Ease of use (i.e. daily dosing, single drug)
D. Risk of contributing to the problem of antibiotic
resistance
E. Previous experience and knowledge of the
antibiotic

Antimicrobial Resistance: Perspectives
• Survey of 800 internal medicine & ID MDs

<table>
<thead>
<tr>
<th>Statement</th>
<th>% Agree (IM/ID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Antibiotic resistance is a major public health problem”</td>
<td>82/94</td>
</tr>
<tr>
<td>“Over-prescribing of antibiotics is a major cause of antibiotic resistance”</td>
<td>86/91</td>
</tr>
<tr>
<td>“Patient demand is the major reason that physicians prescribe unnecessary antibiotics”</td>
<td>80/80</td>
</tr>
<tr>
<td>“I prescribe antibiotics more often than I should”</td>
<td>36/22</td>
</tr>
</tbody>
</table>

• Mean rank of “risk of contributing to antibiotic resistance” among 7 factors influencing antibiotic selection in hypothetical pt with CAP
  – 5.3 (last, below “ease of use” and “cost”)


Gram-Negative Bacilli Resistance Associated With Fluoroquinolone Use


Antimicrobial Prescribing: A Flawed Process

- Only ~ 50% of patients receiving antibacterials infected with bacteria
- Choice of antimicrobial to prescribe
  - Selection driven by secondary factors (cost, convenience)
- Prescription ordering
  - Dosing strategies not designed to prevent emergence of resistance
- Dispensing of antimicrobial
  - Durations of therapy essentially arbitrary (“football scores”)

Antimicrobial Stewardship

- Definition
  - “An ongoing effort...to optimize antimicrobial use in order to improve patient outcomes, ensure cost-effective therapy, and reduce adverse sequelae of antimicrobial use (including antimicrobial resistance)”
- Axioms/Assumptions
  - Antimicrobial prescribing behaviors can be changed
  - Antimicrobial use is a primary driving force in the development of antimicrobial resistance
  - Reduction in antimicrobial use will reduce the prevalence of resistance or slow its increase
  - Appropriate antimicrobial use improves patient outcomes and reduce costs

Stewardship Strategies

- Patient Evaluation
  - Education/guideline strategies
- Choice of antimicrobial to prescribe
  - Antibiotic cycling strategies
- Prescription ordering
  - Formulary/restriction strategies
- Dispensing of antimicrobial
  - Computer-assisted strategies
- Audit and feedback strategies

Technical Solution to Resistance: Antimicrobial Drug Discovery

<table>
<thead>
<tr>
<th>Year Introduced</th>
<th>Class of Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1935</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>1941</td>
<td>Penicillins</td>
</tr>
<tr>
<td>1945</td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>1946</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>1949</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>1950</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>1952</td>
<td>Macrolides, Lincosamides, Streptogramins</td>
</tr>
<tr>
<td>1956</td>
<td>Glycopeptides</td>
</tr>
<tr>
<td>1957</td>
<td>Rifamycins</td>
</tr>
<tr>
<td>1959</td>
<td>Nitroimidazoles</td>
</tr>
<tr>
<td>1962</td>
<td>Quinolones</td>
</tr>
<tr>
<td>1968</td>
<td>Trimethoprim</td>
</tr>
<tr>
<td>2000</td>
<td>Oxacephalosides</td>
</tr>
<tr>
<td>2003</td>
<td>Lipopeptides</td>
</tr>
</tbody>
</table>

Source: Food and Drug Administration (modified)
Bad Bugs- No Drugs?

<table>
<thead>
<tr>
<th>Antibacterial</th>
<th>Class</th>
<th>Year</th>
<th>Novel</th>
</tr>
</thead>
<tbody>
<tr>
<td>quinupristin/dalfopristin</td>
<td>streptogramin</td>
<td>1999</td>
<td>No</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>fluoroquinolone</td>
<td>1999</td>
<td>No</td>
</tr>
<tr>
<td>ertapenem</td>
<td>carbapenem</td>
<td>2000</td>
<td>No</td>
</tr>
<tr>
<td>linezolid</td>
<td>oxazolidinone</td>
<td>2000</td>
<td>Yes</td>
</tr>
<tr>
<td>daptomycin</td>
<td>lipopeptide</td>
<td>2003</td>
<td>Yes</td>
</tr>
<tr>
<td>telithromycin</td>
<td>ketolide</td>
<td>2003</td>
<td>No</td>
</tr>
<tr>
<td>tigecycline</td>
<td>glycylcycline</td>
<td>2005</td>
<td>No</td>
</tr>
<tr>
<td>doripenem</td>
<td>carbapenem</td>
<td>2008</td>
<td>No</td>
</tr>
<tr>
<td>telavancin</td>
<td>lipoglycopeptide</td>
<td>2010</td>
<td>No</td>
</tr>
<tr>
<td>ceftaroline fosamil</td>
<td>cephalosporin</td>
<td>2010</td>
<td>No</td>
</tr>
<tr>
<td>fidaxomicin</td>
<td>macrocyclic</td>
<td>2011</td>
<td>Yes</td>
</tr>
</tbody>
</table>

New Diagnostic Tools to Increase the Appropriate Use of Antimicrobials

Which of the following point of care tests may be useful in the diagnosis of lower respiratory tract infections and/or may allow for optimization of antibiotic therapy?

A. Sputum gram-stain
B. Pneumococcal urinary antigen
C. Serum procalcitonin level
D. ESR
E. A, B, & C

Pneumococcal Urinary Antigen test

Pros
- Rapid turn-around time (~15 min)
- Sensitivity of 50-80% and specificity of > 90%
- Remains positive after initiation of antibiotics
- Relatively inexpensive ($30 per specimen)

Cons
- False positives in patients with an episode of CAP within 3 months
- Inability to perform antibiotic susceptibilities

Usefulness of the Pneumococcal Urinary Antigen test?

- Prospective study of hospitalized patients with CAP (n = 474)
  - Pneumococcal urinary antigen test performed in 383 (81%)
  - Pneumococcal urinary antigen was performed in 153 of 171 patients with pneumococcal pneumonia (definite or probable)
  - Urinary antigen positive in 130/171
  - Sensitivity of 70.5% and specificity of 96%
  - Test allowed for the etiologic diagnosis of 75 additional cases (44% of all pneumococcal pneumonias)
  - Positive result led to reduction in antibiotic spectrum in 41 patients

Sorsa et al., Arch Intern Med 2011; 171: 166
**Etiology of CAP in hospitalized patients**

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>171 (51.4)</td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td>15 (4.4)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>13 (3.7)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>10 (2.9)</td>
</tr>
<tr>
<td>Chlamydia pneumonia</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>A. viscosus</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>M. infections</td>
<td>9 (2.5)</td>
</tr>
<tr>
<td>Other organisms</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>83 (24.2)</td>
</tr>
</tbody>
</table>

*S. pneumoniae* (other than pneumococci), M. viscosa species, M. hominis species, and Coxiella burnetii.

**Risk Factors for Drug-Resistant Pneumococcal Pneumonia**

- Age < 2 year or > 65 years
- β-lactam antibiotics within 3 months
- Alcoholism
- Immunocompromised patients
- Multiple comorbidities
- Exposure to children in day care centers

**S. pneumoniae Susceptibility: Revised Breakpoints for Penicillin**

- **Oral PCN & Meningeal Isolates**
  - Susceptible: MIC ≤ 0.06 μg/mL
  - Intermediate: MIC = 0.12 – 1 μg/mL
  - Resistant: MIC ≥ 2 μg/mL

- **Non-Meningeal Isolates Treated with IV PCN**
  - Susceptible: MIC ≤ 2 μg/mL
  - Intermediate: MIC = 4 μg/mL
  - Resistant: MIC ≥ 8 μg/mL

**IDSA/ATS Inpatient CAP: Treatment Recommendations**

- **Empirical**
  - Inpatients, non-ICU treatment
    - A respiratory fluoroquinolone or a beta-lactam plus a macrolide or doxycycline
  - Inpatients, ICU treatment
    - A beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a respiratory fluoroquinolone
- **S. pneumoniae** with PCN MIC < 2 mcg/ml
  - IV penicillin G, PO amoxicillin
  - In a recent surveillance study only 7% of 1647 US isolates tested was resistant to IV PCN based on the revised breakpoints

Procalcitonin & C-Reactive Protein

- Biomarkers of inflammation
  - PCT > CRP specificity for bacterial infection

Procalcitonin in Primary Care

- Briel et al Arch Intern Med 2008
  - Design/Setting: OL-RCT-NI in primary care practices in Switzerland
  - Subjects: 458 patients with acute respiratory tract infection (upper and lower tract)
  - Group assignments: Patients randomized to standard care or procalcitonin-guided care
  - Outcomes:
    - Days of restricted activities (RAs)
    - Symptoms at day 28
    - Antibacterial prescribing
    - Antibacterial adverse effects

Study Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PCT-guided therapy</th>
<th>Difference (95%) CI</th>
<th>Standard therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT analysis</td>
<td>N = 232</td>
<td>N = 226</td>
<td></td>
</tr>
<tr>
<td>Days with RAs</td>
<td>8.7</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>Adjusted difference in days</td>
<td>0.1 (-0.6 to 0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. prescribed abx</td>
<td>58 (25%)</td>
<td>219 (97%)</td>
<td></td>
</tr>
<tr>
<td>Adjusted odds ratio</td>
<td>0.01 (0002 to 0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days on abx</td>
<td>6.2</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Adjusted difference in days</td>
<td>-1.0 (-1.7 to -0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with adverse abx effects within 14 days</td>
<td>2.3</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Adjusted difference in days</td>
<td>-1.1 (-2.1 to -0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with any symptoms, ongoing or relapsed at 28 d.</td>
<td>69 (30)</td>
<td>67 (30)</td>
<td></td>
</tr>
<tr>
<td>Adjusted odds ratio</td>
<td>1.0 (0.7 to 1.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Bouadma L et al. Use of procalcitonin to reduce patients’ exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010; 375: 463-74

**PRORATA Trial Methodology**

- **Objective**: To establish whether a strategy based upon procalcitonin serum concentration monitoring would result in a reduction in antibiotic exposure with no associated harm to patients
- **Prospective, multicenter RCT including a total of 140 ICU beds (n= 621 patient)**
- **Inclusion**: All adults with suspected bacterial infection and received antibiotics for <24 hrs
- **Exclusion**: <18 yo, BMT, neutropenic, clear infection requiring long-term therapy (e.g. osteomyelitis, endocarditis)
- **Patients randomized to the procalcitonin group or controls**
PRORATA Trial: Mortality Results

- While procalcitonin has utility in the management of infectious diseases, it still is a relatively nonspecific test
- Similar to the use of antimicrobial serum levels (e.g. vancomycin, aminoglycoside levels), the procalcitonin level must be used in context of the specific patient
  - Recommendations not followed in 219 instances
    - 65 patients received antibiotics despite PCT <0.5 mcg/L
    - 4 patients did not receive antibiotics despite PCT >0.5 mcg/L
    - 39 patients had antibiotics stopped despite PCT >0.5 mcg/L
    - 79 patients had antibiotics continued despite PCT <0.5 mcg/L

A final pearl on the treatment of CAP
What is the optimal antibiotic regimen in the treatment of severe CAP requiring ICU admission?

A. ceftriaxone plus levofloxacin
B. ceftriaxone plus azithromycin
C. vancomycin
D. daptomycin

Superiority of macrolide-based regimens in severe CAP?

- Macrolides have immunomodulatory properties (↓ IL-1,-6,-8; TNF-α)
- The improved mortality seen with the use of macrolides may be due to properties unrelated to antimicrobial effects

Treatment of Urinary Tract Infections

According to the 2010 Updates IDSA guideline which of the following antibiotics is not recommended as a first-line choice for uncomplicated cystitis?

A. nitrofurantoin  
B. fosfomycin trometamol  
C. ciprofloxacin  
D. TMP/SMX (in areas where resistance prevalence is < 20%)

Increasing resistance in urinary pathogens

- TMP/SMX resistance in E.coli > 20% in many parts of the United States
- Resultant shift to use of quinolones as first-line empirical therapy over the past 10-20 years
- Quinolones have been associated with “collateral damage”
  - Increased rates of MRSA
  - Selection for resistant GNRs including ESBL-producers
  - Clostridium difficile-associated diarrhea

2010 IDSA recommended treatment regimens for uncomplicated cystitis

**First Line Regimens**
- Nitrofurantoin macrocrystals (Macrobid®) 100 mg BID X 5 days (avoid if early pyelo suspected)
- Trimethoprim-sulfamethoxazole one DS tablet BID X 3 days (avoid if resistance prevalence exceeds 20% or if used for a UTI in previous 3 months)
- Fosfomycin trometamol 3 grams x 1 dose (lower efficacy than some other agents, avoid if early pyelo suspected)

**Second Line Regimens**
- Fluoroquinolones (including ciprofloxacin, levofloxacin, & ofloxacin; resistance prevalence high in some areas)
- Oral β-lactams (including amoxicillin/clavulante, cefdinir, cefpodoxime, cephalaxin (less data); avoid ampicillin or amoxicillin alone; lower efficacy than other available agents, requires close follow up)


Treatment of cystitis: Back to the future

**Nitrofurantoin (Macrobid®)**

**PROS**
- As effective as TMP/SMX
- Minimal drug resistance
- Low propensity for collateral damage

**CONS**
- Blood levels not sufficient to treat early pyelonephritis
- Avoid in pts with CrCl < 50 ml/min
- Nausea, headache (similar adverse effect rate as TMP/SMX)
- Rare pulmonary hypersensitivity

**Fosfomycin trometamol**

**PROS**
- Clinical efficacy similar to TMP/SMX and nitrofurantoin
- Low propensity for collateral damage
- Single dose therapy

**CONS**
- Microbiologic efficacy lower than TMP/SMX and nitrofurantoin
- Blood levels not sufficient to treat early pyelonephritis
- Susceptibility testing not routinely performed
- Diarrhea, nausea, headache (similar adverse effect rate as nitrofurantoin)
UTIs caused by resistant GNRs: Case 1

A 31-year-old sexually active woman presents to your clinic complaining of two days of dysuria. She has been treated for cystitis 3 times in the past 12 months. She has no other significant past medical history. She received one 3-day course of TMP/SMX and two courses of ciprofloxacin (1 3-day course and 1 7-day course). No cultures were obtained with these past episodes. Because of the history of multiple recurrences a culture was obtained in clinic today. The culture grows *E. coli* that was reported to be an ESBL-producer that was also resistant to TMP/SMX and fluoroquinolones.

UTIs caused by resistant GNRs: Case 1

All of the following oral treatment options may be effective for treatment of this case of cystitis except:

A. Nitrofurantoin (Macrobid) 100 mg po BID x 5 days
B. Fosfomycin trometamol 3 gram po X1 dose
C. Amoxicillin/clavulanate 875/125 mg po BID X 7 days
D. Cefaclor 500 mg po TID X 7 days

UTIs caused by resistant GNRs: Case 2

A 80-year-old man lives in a nursing home and is catheterized for incontinence. This morning he becomes altered and spikes a fever to 38.5. He has no specific urinary symptoms. A urine culture is obtained from his indwelling catheter and he is started on oral levofloxacin pending culture results. His past medical history is significant for DM Type II, dementia, and a recent episode of pneumonia treated with ceftriaxone plus azithromycin. On day 3 his culture results return with ESBL-producing *E. coli* resistant to quinolones and TMP/SMX, he remains clinically stable.

UTIs caused by resistant GNRs: Case 2

All of the following oral treatment options may be effective for treatment of this presumed complicated UTI except:

A. Nitrofurantoin 100 mg po BID x 7 days
B. Fosfomycin trometamol 3 grams po q72hrs x 3 doses
C. Methenamine hippurate 1 gram po QID x 7 days
D. Cefpodoxime 200 mg po BID + Augmentin 875/125 mg po TID x 7 days
UTIs caused by resistant GNRs: Case 3

A 56-year-old woman presents to the ED acutely ill with fever, CVA tenderness, and signs of sepsis. She returned one week ago from a vacation in India. While there she took 7 days of ciprofloxacin for travelers diarrhea. She is admitted to the hospital with a diagnosis of urosepsis, blood and urine cultures are obtained, and she is started on piperacillin/tazobactam per hospital guidelines. She improves clinically however on Day 2 her blood culture and urine cultures grows an ESBL-producing *K. pneumoniae*, sensitive to all carbapenems, gentamicin, & piperacillin-tazobactam; the isolate is resistant to all cephalosporins, fluoroquinolones, and TMP/SMX.

**ESBL Bacteremia: Treatment Outcomes**

- Time to receiving active antibiotics
  - 11.5 hours (non-ESBL) versus 72 hours (ESBL) (p<0.001)
- Treatment outcomes for ESBL-*Klebsiella* bacteremia
  - Observational study in which 19% (85/445) of *Klebsiella* blood stream isolates produced an ESBL
  - 24% 14-day overall mortality
    - 64% mortality if no active antibiotic within 5 days
    - 14% mortality with active antibiotic in 5 days
  - 49 patients received monotherapy with an active antibiotic
  - Use of a carbapenem associated with a significantly lower 14-day mortality
    - Carbapenems (5%) (p<0.017)
    - FQ (36%)
    - Other beta-lactams (44%)

**β-Lactam/β-Lactamase Inhibitor: Treatment of ESBL Producers?**

- ESBLs are inhibited by beta-lactamase inhibitors however beta-lactam/inhibitor combinations (i.e. Zosyn) are NOT recommended for treatment of serious infections caused by ESBL producers
- Even when susceptible an inoculum effect occurs; the amount of ESBL produced may be able to overcome the amount of inhibitor present leading to clinical failure

<table>
<thead>
<tr>
<th>MIC of ESBL producers based on inoculum size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
</tr>
<tr>
<td>Organism</td>
</tr>
<tr>
<td><em>E.coli</em></td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
</tr>
</tbody>
</table>

3. Thompson et al. AAC. 2001;45:3548-54
Microdilution method of ESBL detection

ESBL positive defined as ≥ 3 two-fold MIC dilution drop (i.e. a 3 well decrease) in presence of clavulanic acid as compared to the MIC value of the antibiotic tested alone

New CLSI Breakpoints for Enterobacteriaceae

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC</th>
<th>NEW</th>
<th>OLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin 2 g q8h</td>
<td>≤ 4</td>
<td>8</td>
<td>≥ 16</td>
</tr>
<tr>
<td>Ceftriaxone 1 g q24h</td>
<td>≤ 1</td>
<td>2</td>
<td>≥ 4</td>
</tr>
<tr>
<td>Ceftazidime 1 g q8h</td>
<td>≤ 4</td>
<td>8</td>
<td>≥ 16</td>
</tr>
<tr>
<td>Cefepime 1 g q12h</td>
<td>No change</td>
<td>≤ 8</td>
<td>16</td>
</tr>
<tr>
<td>Ertapenem 1 g q24h</td>
<td>≤ 0.25</td>
<td>0.5</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Imipenem 1 g q8h/Meropenem 1 g q8h/Doripenem 500 mg q8h</td>
<td>≤ 1</td>
<td>2</td>
<td>≥ 4</td>
</tr>
</tbody>
</table>

Answer Key

1) N/A
2) E
3) B
4) C
5) D
6) C
7) B