Antibiotics: Managing a Medical Treasure

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Division of Infectious Diseases,
Atlanta VA Medical Center
and Emory University School of Medicine
Objectives

- Analyze the relationship between antibiotic use and antibiotic resistance
- Review the reasons for the dearth of new antibacterial antibiotics
- Discuss the need for antibiotic stewardship and optimizing antibiotic use
- Describe the methods for optimizing antibiotic use including the use of biomarkers, newer diagnostic tools and approaches to deescalate antibiotics

Disclosures: None
Case History

A 61 yo male s/p Whipple resection in Jan. 2009 that was complicated by duodenal stump leak with drain placement.

Pt. had fascial dehiscence and colocutaneous fistula. He was placed on multiple antibiotics including imipenem. A surgical repair was done. He was discharged in mid-April.

Re-admitted 4/27 for volume depletion, acute renal failure (ARF), and sepsis. On 5/13, a blood culture showed K. pneumoniae with the following susceptibility pattern:
CULTURE RESULTS: *KLEBSIELLA PNEUMONIAE*

Comment: Cross resistance to other QUINOLONES likely

COLISTIN RESULT = S (BY DISK TEST)

ANTIBIOTIC SUSCEPTIBILITY TEST RESULTS:

<table>
<thead>
<tr>
<th></th>
<th>SUSC</th>
<th>INTP</th>
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<tbody>
<tr>
<td>AMPICILN</td>
<td>$\geq 32$</td>
<td>R</td>
</tr>
<tr>
<td>AMPICILLIN/SUL</td>
<td>$\geq 32$</td>
<td>R</td>
</tr>
<tr>
<td>CEFEPIME</td>
<td>$\geq 32$</td>
<td>R</td>
</tr>
<tr>
<td>AZTREONAM</td>
<td>$\geq 32$</td>
<td>R</td>
</tr>
<tr>
<td>CEFAZOLIN</td>
<td>$\geq 32$</td>
<td>R</td>
</tr>
<tr>
<td>PIPERACILLIN/T</td>
<td>$\geq 128$</td>
<td>R</td>
</tr>
<tr>
<td>CEFTAZIDIME</td>
<td>$\geq 32$</td>
<td>R</td>
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<tr>
<td>CEFTRIX</td>
<td>$\geq 64$</td>
<td>R</td>
</tr>
<tr>
<td>CIPROFLOXACIN</td>
<td>$\geq 4$</td>
<td>R</td>
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<tr>
<td>GENTMCN</td>
<td>8</td>
<td>I</td>
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<tr>
<td>IMIPENEM</td>
<td>$\geq 16$</td>
<td>R</td>
</tr>
<tr>
<td>NITROFURANTOIN</td>
<td>$\geq 128$</td>
<td>R</td>
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<td>TOBRMCN</td>
<td>$\geq 16$</td>
<td>R</td>
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<tr>
<td>TRMSULF</td>
<td>$\geq 320$</td>
<td>R</td>
</tr>
<tr>
<td>LEVOFLOXACIN</td>
<td>$\geq 8$</td>
<td>R</td>
</tr>
</tbody>
</table>
Hospital Course

After a small leak at the anastomosis was diagnosed, this patient was successfully treated with bowel rest and colistin.
Colistin

- A **polymyxin** antibiotic which is a mixture of cyclic polypeptides.

- Effective against most **gram-negative bacilli**

- Adverse effects: **nephrotoxicity** and **neurotoxicity**

- Available for >50 yrs — not subject to the regulations of modern drugs
  - No standardized dosing
  - No detailed trials on pharmacology or pharmacokinetics
After a small leak at the anastomosis was diagnosed, this patient was successfully treated with bowel rest and colistin.

He was lucky!
### Antimicrobial susceptibility patterns for *Klebsiella pneumoniae* isolates

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC value, µg/mL</th>
<th>Patient 1: urine specimen</th>
<th>Patient 2: blood specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≥64</td>
<td></td>
<td>≥64</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>≥32</td>
<td></td>
<td>≥32</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>≥64</td>
<td></td>
<td>≥64</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>≥64</td>
<td></td>
<td>≥64</td>
</tr>
<tr>
<td>Cefepime</td>
<td>32</td>
<td></td>
<td>≥16</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≥64</td>
<td></td>
<td>≥64</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≥4</td>
<td></td>
<td>≥4</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≥16</td>
<td></td>
<td>≥16</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>≥128</td>
<td></td>
<td>≥128</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≥16</td>
<td></td>
<td>≥16</td>
</tr>
<tr>
<td>Trimethoprim-sulfa</td>
<td>≥320</td>
<td></td>
<td>≥320</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>256</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≥8</td>
<td></td>
<td>≥8</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≥16</td>
<td></td>
<td>≥R&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>NA</td>
<td></td>
<td>≥R&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>≥8</td>
<td></td>
<td>≥8</td>
</tr>
<tr>
<td>Polymyxin B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4</td>
<td></td>
<td>≥16</td>
</tr>
</tbody>
</table>

**NOTE.** All susceptibility testing, except for polymyxin B, was done using the Vitek 2 automated system (bioMérieux). MIC, minimum inhibitory concentration; NA, not available.

<sup>a</sup> Antimicrobial agents indicated with “R” instead of an MIC value were read as susceptible by the automated system, but findings were modified on the basis of polymerase chain reaction testing results indicating the presence of *K. pneumoniae* carbapenemase genes.

<sup>b</sup> Tested using Etest.
Antibiotics and Antibiotic Resistance

Antibiotics and Antibiotic Resistance

“But I don’t usually see antibiotic resistant bacteria when I prescribe antibiotics!”
“But I don’t usually see antibiotic resistant bacteria when I prescribe antibiotics!”

The link between antibiotic use and antibiotic resistance
### Forest plot: individual study and pooled ORs (log scale) for resistance in urinary tract bacteria (*E. coli*) and antibiotic exposure

<table>
<thead>
<tr>
<th>Time period, study</th>
<th>Antibiotic exposure</th>
<th>Resistance in unexposed (control) group (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0-1 month</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donnan 17</td>
<td>Trimethoprim</td>
<td>NR</td>
<td>4.45 (3.78 to 5.21)</td>
</tr>
<tr>
<td>Hillier 19</td>
<td>Trimethoprim</td>
<td>20</td>
<td>4.85 (2.63 to 8.94)</td>
</tr>
<tr>
<td>Hillier 19</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>
<td></td>
</tr>
<tr>
<td><strong>0-3 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donnan 17</td>
<td>Trimethoprim</td>
<td>NR</td>
<td>2.60 (2.04 to 3.33)</td>
</tr>
<tr>
<td>Hillier 19</td>
<td>Trimethoprim</td>
<td>39</td>
<td>2.62 (1.69 to 4.07)</td>
</tr>
<tr>
<td>Hillier 19</td>
<td>Amoxicillin</td>
<td>39</td>
<td>2.26 (1.41 to 3.62)</td>
</tr>
<tr>
<td>Hay 18</td>
<td>Any antibiotic</td>
<td>20</td>
<td>1.93 (1.06 to 3.51)</td>
</tr>
<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><strong>0-6 months</strong></td>
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<td></td>
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<tr>
<td>Steinke 23</td>
<td>Any antibiotic*</td>
<td>19</td>
<td>1.36 (1.14 to 1.61)</td>
</tr>
<tr>
<td>Donnan 17</td>
<td>Trimethoprim</td>
<td>NR</td>
<td>1.67 (1.32 to 2.10)</td>
</tr>
<tr>
<td>Steinke 23</td>
<td>Trimethoprim</td>
<td>19</td>
<td>3.95 (3.04 to 5.12)</td>
</tr>
<tr>
<td>Hillier 19</td>
<td>Amoxicillin</td>
<td>28</td>
<td>1.83 (1.39 to 2.42)</td>
</tr>
<tr>
<td>Donnan 17</td>
<td>Any antibiotic*</td>
<td>NR</td>
<td>1.65 (1.10 to 2.46)</td>
</tr>
<tr>
<td>Hillier 19</td>
<td>Trimethoprim</td>
<td>28</td>
<td>2.57 (1.83 to 3.61)</td>
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<tr>
<td>Metlay 24</td>
<td>ST</td>
<td>28</td>
<td>4.10 (2.20 to 7.50)</td>
</tr>
<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>
<td></td>
<td></td>
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<tr>
<td><strong>0-12 months</strong></td>
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<tr>
<td>Donnan 17</td>
<td>Trimethoprim</td>
<td>NR</td>
<td>1.22 (1.16 to 1.28)</td>
</tr>
<tr>
<td>Donnan 17</td>
<td>Any antibiotic*</td>
<td>NR</td>
<td>1.18 (1.06 to 1.32)</td>
</tr>
<tr>
<td>Hillier 19</td>
<td>Amoxicillin</td>
<td>19</td>
<td>1.62 (1.18 to 2.23)</td>
</tr>
<tr>
<td>Hay 18</td>
<td>Any antibiotic*</td>
<td>38</td>
<td>1.13 (0.79 to 1.63)</td>
</tr>
<tr>
<td>Hillier 19</td>
<td>Trimethoprim</td>
<td>19</td>
<td>2.36 (1.59 to 3.50)</td>
</tr>
<tr>
<td>Pooled odds ratio</td>
<td></td>
<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: individual study and pooled ORs (log scale) for resistance in respiratory tract bacteria and previous antibiotic prescribing

Costelloe C et al. BMJ 2010;340:bmj.c2096
©2010 by British Medical Journal Publishing Group

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<td><strong>0-1 month</strong></td>
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<tr>
<td>Beekmann</td>
<td>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>Pooled odds ratio</td>
<td></td>
<td></td>
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<tr>
<td><strong>0-2 months</strong></td>
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<tr>
<td>Seaton</td>
<td>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>Clifti</td>
<td>Macrolide</td>
<td>2</td>
<td>2.37 (1.42 to 3.95)</td>
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<tr>
<td>Pooled odds ratio</td>
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<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $I^2=1.6%$, $P=0.313$</td>
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<tr>
<td><strong>0-3 months</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Schrag</td>
<td>β lactam</td>
<td>33</td>
<td>1.50 (1.20 to 1.80)</td>
<td></td>
</tr>
<tr>
<td>Samore</td>
<td>Cephalosporin</td>
<td>17</td>
<td>2.30 (1.04 to 5.10)</td>
<td></td>
</tr>
<tr>
<td>Samore</td>
<td>Penicillin</td>
<td>17</td>
<td>1.80 (0.80 to 4.20)</td>
<td></td>
</tr>
<tr>
<td>Samore</td>
<td>Macrolide</td>
<td>17</td>
<td>0.40 (0.10 to 1.30)</td>
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<tr>
<td>Pooled odds ratio</td>
<td></td>
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<tr>
<td>Test for heterogeneity: $I^2=44.2%$, $P=0.146$</td>
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<tr>
<td><strong>0-6 months</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ghaffar</td>
<td>β lactam</td>
<td>14</td>
<td>1.56 (0.50 to 4.86)</td>
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<tr>
<td>Ghaffar</td>
<td>β lactam*</td>
<td>14</td>
<td>3.93 (0.44 to 35.28)</td>
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</tr>
<tr>
<td>Pooled odds ratio</td>
<td></td>
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<tr>
<td>Test for heterogeneity: $I^2=0.0%$, $P=0.463$</td>
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<tr>
<td><strong>0-12 months</strong></td>
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</tr>
<tr>
<td>Beekmann</td>
<td>Any antibiotic</td>
<td>13</td>
<td>1.28 (0.64 to 2.54)</td>
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</tr>
<tr>
<td>Samore</td>
<td>Penicillin</td>
<td>NR</td>
<td>1.20 (0.50 to 2.50)</td>
<td></td>
</tr>
<tr>
<td>Samore</td>
<td>Cephalosporin</td>
<td>NR</td>
<td>1.60 (0.80 to 3.50)</td>
<td></td>
</tr>
<tr>
<td>Arason</td>
<td>β lactam</td>
<td>NR</td>
<td>6.75 (1.78 to 25.51)</td>
<td></td>
</tr>
<tr>
<td>Arason</td>
<td>Co-trimoxazole</td>
<td>NR</td>
<td>7.22 (1.73 to 30.05)</td>
<td></td>
</tr>
<tr>
<td>Arason</td>
<td>Erythromycin</td>
<td>NR</td>
<td>8.56 (1.14 to 64.04)</td>
<td></td>
</tr>
<tr>
<td>Pooled odds ratio</td>
<td></td>
<td></td>
<td>2.37 (1.25 to 4.50)</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $I^2=57.3%$, $P=0.039$</td>
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</tr>
</tbody>
</table>

*β lactam plus another antibiotic. NR=not reported
Carbapenem Use and Resistance to Carbapenems

- Imipenem
- Meropenem
- Doripenem
- Ertapenem
Correlation between consumption of imipenem and resistant *P. aeruginosa*

Lepper, P. M. et al. 2002. 46(9):2920-2925 Antimic Agents and Chem
Carbapenem resistance in *Enterobacteriaceae* and *Acinetobacter baumannii* is primarily mediated by carbapenemases.

These carbapenemases are class A, B or D $\beta$-lactamases with the ability to hydrolyze carbapenems.

Often these carbapenemases can inactivate other $\beta$-lactam antibiotics, thus limiting the antimicrobials available to treat infections with these pathogens.

Patel G, Bonomo R. Status report on carbapenemases: challenges and prospects
**Carbapenemases**

*K klebsiellae* carbapenemases (KPCs), reported worldwide

- Increasing KPC types (now up to 13) are described
- KPC-2 and KPC-3 most common

**New Delhi Metallo-β-lactamases, type 1 (NDM-1), increasing worldwide**

- Early cases had contact with the healthcare system in the Indian subcontinent.
Geographic distribution of NDM-1 carbapenemases
as of Dec. 31, 2010 (gray)

Patel G, Bonomo R. Status report on carbapenemases: challenges and prospects
Carbapenemases

The genetic context in which these *bla* genes are encoded carry concurrent resistance determinants to other classes of antibiotics.

Exposure to other antibiotics can select for the genes carrying carbapenemases.
Interaction effect of carbapenems and fluoroquinolones on the risk of carbapenem-resistant *K. pneumoniae* (CRKP) infection


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Carbapenemases

No single agent in development demonstrates universal activity against carbapenemases

This leaves little on the horizon for patients suffering from carbapenem-resistant, Gram-negative infections.

Patel G, Bonomo R. Status report on carbapenemases: challenges and prospects
Evaluation of a Multi-Center Approach to Optimize Carbapenem Use

1. Baseline data on carbapenem use (and resistance) and its appropriateness

2. Assess Knowledge, Attitudes and Beliefs

3. Develop Interventions to optimize carbapenem use

4. Follow up data to assess success
“If the patient has a carbapenemase-producing bacteria, what will be available soon to prescribe?”
The Dry Pipeline for New Antibacterial Antibiotics

- Remember: The average time from drug discovery to FDA approval is nine years.
New antibacterial agents approved in the U.S. per 5-year period

“There must be SOMETHING, some antibiotic in development — Right?”
Progress on newer antibiotics

Many of these agents are variations on older antibiotics:

- For example, ceftobiprole, a cephalosporin with activity against MRSA, similar to ceftaroline
- Tetracycline analogs, macrolide analogs, fluoroquinolone analogs and oxazolidinone analogs are currently under investigation

No New Antibiotics?

The *Infectious Diseases Society of America* has called for a global commitment to develop new antibacterial drugs*

“So, what do we do NOW?”
“Clinicians must realize how perilously close we are to a ‘post-antibiotic’ era.”

Jacob JT, Gaynes RP. Expert Rev Anti Infect Ther. 2010. 8(8):893-902
Another Inconvenient Truth: Addressing Antibiotic Resistance

1. Optimize antibiotic use

2. Limit the spread of resistant pathogens
No one doubts the importance of infection control practices in limiting the spread of antibiotic-resistant organisms, but optimizing antibiotic use, also known as antibiotic stewardship, remains essential for successful control of the antibiotic resistance.

When you ask:

**INTERNAL MEDICINE JOURNAL**


**EDITORIAL**

**Why can’t I prescribe that antibiotic? The role of antimicrobial stewardship programmes in modern medicine**

Although all drugs may have an additional effect damage.¹ This refers to the antibiotic on the colonizing bacterial species. The use of antibiotic resistant organisms may cause suboptimal infection control. The transmission of these organisms may lead to inappropriate antibiotic use. Physicians who do not know how to proceed by Bannan et al. demonstrated telephone approval was ribers. Nineteen per cent of respondents to the survey believed an infringement on their autonomy that it was reasonable to implement policy. Important majorit...
Autonomy in Medicine

In a recent survey, 19% of prescribers believed that Antimicrobial Stewardship Programs were an infringement on their autonomy.
Doctors have not distinguished themselves when using antibiotics!

**Antibiotic Use**
- Patients receive an antibiotic on 80-90% of ICU days
- Patients receive an antibiotic on 40% of non-ICU days

**Inappropriate Use**
- 25-45% among hospitalized patients
- 20-50% among community patients
Indiscriminate Antibiotic Use is **NOT** an option

1. As a drug class, antibiotics are virtually unique; once an antibiotic is released for wide-scale use, its efficacy diminishes.*

2. Infections caused by antibiotic-resistant pathogens are threatening ALL progress in medicine—transplantation, surgeries, and invasive procedures.

* Gaynes R. Preserving the Effectiveness of Antibiotics. *JAMA.* 2010;303(22):2293-2294
Remember our patient?

He survived a Whipple’s Procedure, but nearly died from an antibiotic-resistant infection.
Ways to Optimize Antimicrobial Prescribing

- Streamlining therapy based upon microbiology culture and susceptibility results
- Dose optimization
- Antimicrobial de-escalation
- Computer-assisted decision support
- Infectious disease consultation
- Formulary restriction
- Development of guidelines for antibiotic use
- Policies for parenteral to oral antibiotic conversion
- Prospective audit and feedback of antibiotic use data
- Pre-approval policies
Ways to Optimize Antimicrobial Prescribing:

What works??
Interventions to change professional practice: Antimicrobial Stewardship

- Cochrane reviews
  

- Impact of antimicrobial stewardship in critical care: a systematic review
Interventions to change professional practice: Antimicrobial Stewardship

**Generally effective:**

- Detailing
- Computerized decision support
- Formal reassessment (or antibiotic de-escalation)
- Infectious diseases consultation
- Multifaceted interventions
A Note about Drug Detailing...

- "In the case of obtaining information from detailers, physicians' prescribing practices are less appropriate as a result of the interaction."

- Approximately 1/3 of the pharmaceutical workforce is in sales/drug detailing

Interventions to change professional practice: Antimicrobial Stewardship

**Generally effective:**

- Detailing
- Computerized decision support
- Formal reassessment (or antibiotic de-escalation)
- Infectious diseases consultation
- Multifaceted interventions
Impact of antimicrobial stewardship in critical care: a systematic review

“Studies of computer-assisted decision support, formal reassessment, and the impact of an infectious diseases consultant all demonstrated decreases in antibiotic use among several classes of antibiotics without a pronounced compensatory increase in other agents with a similar spectrum.”

Computerized Decision Support

- Computerized Protocols
  - Dynamic
  - Explicit
  - Patient-specific
  - Point-of-care
Theradoc’s Antibiotic Wizard

**Admit Diagnosis:** DEHYDRATION

**SCR:** 1 mg/dL (07/17/2007)

**CrCl:** 83 mL/min (Cockcroft Gault)

**Admit Date:** 07/13/2007 17:20

**Height:** 74 in (188 cm)

**BSA:** 2.01 m²

**Attending:** JURADO, RAFAEL L

**Weight:** 169 lb (77 kg)

**IBW:** 180 lb (82 kg)

**Location:** 9SURG 9C136 1

**Allergies:** No Known Allergies

**ANTIBIOTIC WIZARD**

**MRN:**

**Room:** 9C136  **Bed:** 1  **Attending:** JURADO, RAFAEL L

**Patient:** 62 Year Male

**Height:** 74 in (188 cm)

**Weight:** 169 lb (77 kg)

**BSA:** 2.01 m²

**Allergies:** NO KNOWN ALLERGIES

**Syndrome:** Bacteremia

**SCR:** 1 mg/dl

**CrCl:** 83 mL/min (Mild Impairment)

**IBW:** 181 lb (82 kg)

**Recommendation**
Antimicrobial De-escalation

What is it actually??

- Is the patient actually infected at all?
- Is the patient actually infected with bacteria?
- How long do you need to treat with antimicrobials?
Antimicrobial De-escalation

Is the patient actually infected with bacteria?

- Pathogens are isolated in a minority of cases where infection is suspected and antibacterial antibiotics are used.

Was therapy altered at 72 hrs using microbiology cultures when Pip/Tazo was appropriate empiric therapy? (N=135 cases)

- Yes: 27%
- No: 8%
- Indeterminate: 65%

Why empiric therapy was NOT altered at 72 hrs (N=88 Indeterminate cases)

Cultures taken but not revealing, 56%

Cultures taken AFTER antibiotic, 33%

No culture taken, 11%
The biomarker, Procalcitonin, is a precursor of calcitonin and is rapidly released in blood in presence of an infection.

Antimicrobial therapy has been discouraged with low levels of procalcitonin for lower respiratory tract infections with no difference in outcome but significant reductions in antibiotic use.*

## Use of Procalcitonin

### Table 1. Randomized Controlled Trials That Used Procalcitonin (PCT) Serum Levels to Guide Antibiotic Therapy in Adult Patients With Respiratory Tract Infections

<table>
<thead>
<tr>
<th>Reference</th>
<th>Clinical syndrome(s)</th>
<th>Study site (location)</th>
<th>No. of evaluable patients</th>
<th>Percentage of patients who started antibiotic therapy</th>
<th>Duration of antibiotic therapy, mean days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control group</td>
<td>PCT group</td>
<td>Control group</td>
</tr>
<tr>
<td>[21]</td>
<td>Pneumonia, AECOPD, acute bronchitis</td>
<td>Emergency department (Basel, Switzerland)</td>
<td>119</td>
<td>124</td>
<td>77.3</td>
</tr>
<tr>
<td>[22]</td>
<td>Community-acquired pneumonia</td>
<td>Emergency department (Basel, Switzerland)</td>
<td>151</td>
<td>151</td>
<td>99</td>
</tr>
<tr>
<td>[23]</td>
<td>AECOPD</td>
<td>Emergency department (Basel, Switzerland)</td>
<td>106</td>
<td>102</td>
<td>72</td>
</tr>
<tr>
<td>[24]</td>
<td>Rhinosinusitis, tonsillitis, pharyngitis, acute otitis media, tracheobronchitis, AECOPD, community-acquired pneumonia</td>
<td>General practices at multiple outpatient facilities (Switzerland)</td>
<td>226</td>
<td>232</td>
<td>97</td>
</tr>
<tr>
<td>[25]</td>
<td>Community-acquired pneumonia</td>
<td>Hospitals (Denmark)</td>
<td>107</td>
<td>103</td>
<td>79</td>
</tr>
<tr>
<td>[26]</td>
<td>Acute bronchitis, AECOPD, community-acquired pneumonia</td>
<td>Emergency departments at 6 hospitals (Switzerland)</td>
<td>688</td>
<td>671</td>
<td>87.9</td>
</tr>
</tbody>
</table>

**NOTE.** AECOPD, acute exacerbation of chronic obstructive pulmonary disease.
Antimicrobial De-escalation

How long do you need to treat with antimicrobials?

**Use of Procalcitonin**

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<tr>
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<td>Pneumonia, AECOPD, acute bronchitis</td>
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<td>119</td>
<td>124</td>
<td>77.3, 44.4</td>
</tr>
<tr>
<td>[22]</td>
<td>Community-acquired pneumonia</td>
<td>Emergency department (Basel, Switzerland)</td>
<td>151</td>
<td>151</td>
<td>99, 85</td>
</tr>
<tr>
<td>[23]</td>
<td>AECOPD</td>
<td>Emergency department (Basel, Switzerland)</td>
<td>106</td>
<td>102</td>
<td>72, 40</td>
</tr>
<tr>
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<td>Rhinosinusitis, tonsillitis, pharyngitis, acute otitis media, tracheobronchitis, AECOPD, community-acquired pneumonia</td>
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<td>226</td>
<td>232</td>
<td>97, 25</td>
</tr>
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<td>671</td>
<td>87.9, 75.4</td>
</tr>
</tbody>
</table>

**NOTE.** AECOPD, acute exacerbation of chronic obstructive pulmonary disease.
Is the patient infected with bacteria?
More help is on the way...
Rapid diagnostics for identifying and characterizing the pathogen
<table>
<thead>
<tr>
<th>Test</th>
<th>Technology</th>
<th>Disease/agent detected</th>
<th>Test sample</th>
<th>Detection time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary antigen test</td>
<td>Immunochromatographic membrane test (ICT) for pneumococcal antigen</td>
<td>Community-acquired <em>S. pneumoniae</em> in adults</td>
<td>Urine</td>
<td>15 mins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Streptococcal meningitis</td>
<td>CSF</td>
<td></td>
</tr>
<tr>
<td>Urinary antigen test</td>
<td>Immunochromatographic membrane test (ICT) for <em>Legionella pneumophila</em> sero-group 1 antigen</td>
<td><em>Legionella pneumophila</em> (<em>Legionnaire's disease</em>)</td>
<td>Urine</td>
<td>15 mins</td>
</tr>
<tr>
<td>Strep A</td>
<td>Immunochromatographic assay</td>
<td><em>Streptococcus pyogenes</em> Group A (pharyngitis)</td>
<td>Throat swab</td>
<td>&lt;10 mins</td>
</tr>
<tr>
<td><em>Staph aureus</em></td>
<td>Immunochromatographic assay</td>
<td><em>S. aureus</em> bacteremia</td>
<td>Blood with clustered cocci</td>
<td>30 mins</td>
</tr>
<tr>
<td>MRSA</td>
<td>Immunochromatographic assay for penicillin binding protein 2a (PBP2a)</td>
<td>Methicillin-resistant <em>S. aureus</em></td>
<td>Plated cfu</td>
<td>6 mins</td>
</tr>
<tr>
<td><em>C. difficile</em></td>
<td>Rapid Enzyme Immunoassay cartridge</td>
<td>Toxin-positive <em>C. difficile</em></td>
<td>Feces</td>
<td>&lt;30 mins</td>
</tr>
<tr>
<td>Influenza</td>
<td>Immunochromatographic assay for influenza A &amp; B nucleoproteins</td>
<td><em>Influenza A, influenza B</em></td>
<td>Nasal swab</td>
<td>15 mins</td>
</tr>
</tbody>
</table>
Can the broad-spectrum antimicrobials be narrowed?

Multiplex polymerase chain reaction (PCR) panels for *S. pneumoniae*, *Legionella pneumophila*, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Mycoplasma pneumoniae*, and *Chlamydothila (Chlamydia) pneumoniae* were compared with conventional cultures.*

- The sensitivity and specificity varied from 93% to 100%
- Multiplex PCR Panels can also detect viruses

Antimicrobial De-escalation

Rapid Microorganism Identification by MALDI-TOF*

Matrix-assisted laser desorption/ionisation-time of flight

*Pulsed Laser Beam
N₂ 50 Hz variable repetition

UV-adsorbing matrix mixed with sample

Sample holder

Data analysis – organism identification

Detector

Voltage Potential

Time of Flight Mass Analysis
(Mass to charge ratio)

Desorbed sample and matrix ions

Voltage Potential

Time of Flight Mass Analysis
(Mass to charge ratio)

Detector

UV-adsorbing matrix mixed with sample

Sample holder
Disadvantages of broad-spectrum antibiotics:

- Interrupt or destroy normal flora of the host
  - Opportunistic pathogens, e.g., *Candida* spp.
  - Superinfection, e.g., *Clostridium difficile*

- Development of Resistance

- Cost

Can the broad-spectrum antimicrobials be narrowed?
Antimicrobial De-escalation

Can the broad-spectrum antimicrobials be narrowed?

Disadvantages of broad-spectrum antibiotics:

- Interrupt or destroy normal flora of the host
  - Opportunistic pathogens, e.g., *Candida* spp.
  - Superinfection, e.g., *Clostridium difficile*

- Development of Resistance

- Cost

Remember: Antibiotic use is NOT always benign!!
Antimicrobial De-escalation

How long do you need to treat with antimicrobials?

Few studies or guidelines illustrate the required lengths of therapy for bacterial infections.*

- Traveler’s Diarrhea (3 days)
- Meningitis (7-21 days)
- Lower extremity infections in diabetics (1-6 wks)

CAP: “We are not aware of any controlled trials that have specifically addressed the questions of how long pneumonia should be treated.”**

Probability of survival for 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia (Kaplan-Meier estimates)

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Number of Studies</th>
<th>Short vs. Long Duration (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-acquired pneumonia</td>
<td>9 studies</td>
<td>5 vs. 7-10 days</td>
<td>No difference or non-inferiority in all studies</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>1 study</td>
<td>8 vs. 15 days</td>
<td>No difference in mortality</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>1 study</td>
<td>14 days with combination Rx vs. 28 days w/sing Rx</td>
<td>No difference in clinical cure rate and microbiological eradication</td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
<td>4 studies</td>
<td>5-7 days vs. 10-14d</td>
<td>No difference or non-inferiority in all studies</td>
</tr>
</tbody>
</table>

Optimizing Antibiotic Use

1. Is the patient infected with **bacteria**?

2. Can the broad-spectrum antimicrobials be narrowed?

3. How long do you need to treat with antimicrobials?
Antimicrobial Agents: Overriding Premise for Use

- Because of the potential to develop resistance, antimicrobials are fundamentally different from all other classes of pharmacotherapy.

- Antimicrobials should be viewed as medical treasures and a precious resource.
THE END
Finding Benchmarks: Inpt Antibiotic Use Per Pt - FY2009
20 Largest VA Hospitals

Facility Complexity: all sites are level 1A

Inpatient (DDD/1,000 pt-days)
Since the beginning of 2008, the US Food and Drug Administration has approved only 2 new antibacterial antibiotics:

- Telavancin
- Ceftarolne
“Why no antibiotic drug discovery?”
Why no antibiotic drug discovery?!

No Guarantee of Success

Finding new antimicrobial compounds, particularly new classes of antibiotics, has always been exceedingly difficult, e.g., penicillin
Why no antibiotic drug discovery?!

Fewer pharmaceutical companies are looking

- Due to consolidations, in the last 25 years, the number of pharmaceutical companies performing drug discovery has dropped from 70 to 12.

- Only 6 companies are working on antibiotic drug discovery!
Lack of profitability:

The profitability of any drug can be expressed as its ‘NPV<sub>R</sub>’: the return in future dollars after adjustment for the investment and any lost income, expressed as the # of millions of dollars

- Antibiotics: NPV<sub>R</sub> of 100
- Oncologic drugs: NPV<sub>R</sub> of 300
- Neurologic drugs: NPV<sub>R</sub> of 720
- Musculoskeletal drugs: NPV<sub>R</sub> of 1150

Why no antibiotic drug discovery?!

Need for Constant Marketing

Need for antibiotic marketing works against pharmaceutical efforts in antibacterial antibiotics since these drugs must be ‘marketed’ to prescribers each time an infection occurs. In contrast, an anti-hypertensive or lipid-controlling drug usually requires one-time marketing since they are often lifelong agents.
Penicillin’s Discovery and Production

- In 1929, Alexander Fleming found a *Penicillium* mold growing on a plate of staphylococci, but he could not purify the compound.

- A team of Oxford scientists finally did purify penicillin 10 years later, but had to go to the U.S. for large-scale production.

- In 1941, two members of the Oxford team headed to a U.S. agriculture station in Peoria, Ill where Charles Thom identified Fleming’s strain as *Penicillium notatum*. 
Penicillin Production

- Of 1,000 *Penicillium* strains in Charles Thom’s collection, only 3 produced penicillin:
  - Fleming’s strain
  - one in Thom’s collection
  - a strain from a spoiled cantaloupe, which produced six times more than other strains and was the one used in large-scale penicillin production.