Confronting Antimicrobial Resistance: Stewardship and Diagnostics

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SHADOW EPIDEMIC
The Growing Menace of Antimicrobial Resistance

2005
“Nightmare Bacteria”

- 2 million people/yr. acquire serious resistant bacterial infections
- 23,000 people die as a direct result

Source: CDC
Causes

• Unnecessary antibiotic use
  - 30% of all prescriptions not needed
  - More than $1.1 billion spent annually on unnecessary prescriptions for adult respiratory infections

• Improper use

• Lack of rapid diagnostics

• Dwindling antibiotic pipeline
Spain transplants
MDR gram-neg BSI 19%*

Germany -CRKP
Transplants/cancer 80%

Pakistan
Infants with Acinetobacter 47%

India infant BSI
ESBL+ gram-neg: 33%
NDM-1: 100%

US transplants
MDR infections 38%

Tanzania BSI
Pediatric gram-neg 43%

*Death or graft loss
Source: ReAct facts, May 2012
## Mortality: Resistant vs. Sensitive Strains

<table>
<thead>
<tr>
<th>Species</th>
<th>Site</th>
<th>Death Rate (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Resistant strain</td>
<td>Sensitive strain</td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Euro. tert care ctrs (13)</td>
<td>32</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td><em>A. baumannii</em></td>
<td>U.K.</td>
<td>16.4</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>Greece, Israel, NYC</td>
<td>42.9, 43.8, 38</td>
<td>18.9, 12.5, 12</td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>75 countries, U.S.</td>
<td>36.4, 23.6</td>
<td>27.0, 11.5</td>
<td></td>
</tr>
</tbody>
</table>

*Source: ReAct facts May 2012*
### Annual Cost of Antibiotic Resistance

#### US: > 20 Billion Dollars

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>EUROPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Societal costs</td>
<td>$35 B</td>
<td>€1.5 B</td>
</tr>
<tr>
<td>Additional hospital days</td>
<td>8 M</td>
<td>2.5 M</td>
</tr>
</tbody>
</table>

Roberts et al. CID 49:1175 (2009)
ReAct Facts 2013
Antimicrobial Stewardship urgently needed to:

- Achieve optimal clinical outcomes
- Decrease adverse drug events
- Minimize development of antimicrobial resistance
- Preserve antimicrobial resources
- Reduce costs
Combating Antimicrobial Resistance: Core Actions

1. Prevent infections and the spread of resistance
2. Track resistance patterns
3. Develop new antibiotics and diagnostic tests
4. Improve antibiotic use
Under-utilized Stewardship Initiatives

A. Treat only when necessary

B. Use narrow-spectrum agents whenever possible

C. Consider:
   - higher doses
   - shorter duration

D. Utilize rapid diagnostics
A. Treat only when necessary

30% of 1941 antimicrobial days of therapy deemed unnecessary

Most Common Reasons for Unnecessary Therapy

Inappropriate Antimicrobial Therapy: Impact on Mortality

B. Use narrow-spectrum agents whenever possible

<table>
<thead>
<tr>
<th>Colonization strain</th>
<th>Penicillin-tobramycin regimen</th>
<th>Amoxicillin-cefotaxime regimen</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative bacillus resistant to empiric therapy of unit*</td>
<td>1.2</td>
<td>21.4</td>
<td>17.98</td>
</tr>
</tbody>
</table>

Data are: (colonizing events/patient days at risk) x 1000.

*Tobramycin resistant in unit using penicillin-tobramycin regimen and cefotaxime resistant in unit using amoxicillin-cefotaxime regimen.

P de man et al. The Lancet 2000, 355:973
C. Consider:

- **Higher doses**
  Generally safe (with exceptions)
  Continuous IV Rx – Beta Lactams – gaining acceptance

- **Shorter Duration**
  Longer is not necessarily better!

<table>
<thead>
<tr>
<th>Infection</th>
<th>Treatment days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-acquired pneumonia (CAP)</td>
<td>Std  8</td>
</tr>
<tr>
<td>Hospital-acquired pneumonia (VAP)</td>
<td>15</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>10</td>
</tr>
<tr>
<td>Cystitis</td>
<td>7-10</td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
<td>14</td>
</tr>
</tbody>
</table>

* with FQ
D. Utilize rapid diagnostics

- Know the organism
- Know the treatment
Rapid Diagnostics

Support antimicrobial stewardship
• Speed targeted therapy
• Reduce unwanted antibiotic side effects

Reduce costs
• Avoids additional tests (eg., colonoscopy, imaging)
• Improved therapy increases pharmacy savings
• Reduced infection transmission increases infection control savings

Source: Goff, Pharmacother 2012, 32:677
The Ideal Diagnostic Test

- Affordable
- Sensitive, few false -
- Specific, few false +
- User-friendly
- Rapid, 30 minutes
- Equipment-free
- Deliverable

<table>
<thead>
<tr>
<th>Rapid Diagnostics</th>
<th>Test</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POSITIVE CULTURE</strong></td>
<td>PNA-FSH&lt;sup&gt;1&lt;/sup&gt;</td>
<td>MRSA, CoNS, <em>Enterococcus</em>, <em>E. coli</em>, <em>Pseudomonas</em>, <em>Klebsiella</em>, <em>Candida spp.</em></td>
</tr>
<tr>
<td></td>
<td>MALDI-TOF&lt;sup&gt;3&lt;/sup&gt;</td>
<td>multiple bacterial and yeast pathogens</td>
</tr>
<tr>
<td><strong>PRIMARY SPECIMEN</strong></td>
<td>Polymerase chain reaction (PCR)</td>
<td>MRSA, MSSA, CoNS, <em>C. difficile</em>&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>LAMP&lt;sup&gt;2&lt;/sup&gt;</td>
<td><em>C. difficile</em></td>
</tr>
<tr>
<td></td>
<td>Rapid Antigen tests</td>
<td><em>S. pneumoniae</em>, <em>Legionella pneumophila</em>, <em>S. pyogenes</em>, <em>Staph aureus</em>, MRSA, <em>C. difficile</em></td>
</tr>
<tr>
<td></td>
<td>Procalcitonin</td>
<td>general sepsis</td>
</tr>
<tr>
<td></td>
<td>C-reactive protein (CRP)</td>
<td>general inflammatory condition</td>
</tr>
</tbody>
</table>

<sup>1</sup>Pepptide nucleic acid fluorescence in situ hybridization  
<sup>2</sup>Loop-mediated iso-thermal amplification  
<sup>3</sup>Matrix-assisted laser desorption ionization- time of flight mass spectrometry  
* requires stewardship team monitoring as pos predictive value decreases with repeat testing)
**Hazard Level**

**URGENT**

*Clostridium difficile*, Carbapenem-resistant Enterobacteriaceae (CRE), ABR *Neisseria gonorrhoeae* (cephalosporin resistance)

**Hazard Level**

**SERIOUS**

MDR *Acinetobacter*, ABR *Campylobacter*, Fluconazole-resistant *Candida* (a fungus), Extended Spectrum β-lactamase producing Enterobacteriaceae (ESBLs), Vancomycin-resistant *Enterococcus* (VRE), MDR *Pseudomonas aeruginosa*, ABR Non-typhoidal *Salmonella*, Drug-resistant *Salmonella* Typhi, ABR *Shigella*, Methicillin-resistant *Staphylococcus aureus* (MRSA), ABR *Streptococcus pneumonia*, ABR tuberculosis (MDR and XDR)

**Hazard Level**

**CONCERNING**

Vancomycin-resistant *Staphylococcus aureus* (VRSA), Erythromycin-resistant *Streptococcus* Group A, Clindamycin-resistant *Streptococcus* Group B

Source: CDC
Diagnostics and their Role in Antimicrobial Stewardship

Kavita K. Trivedi, MD

Public Health Medical Officer
Healthcare Associated Infections Program
California Department of Public Health
Traditional Microbiology vs. Rapid Approach

Patient

Specimen

Culture Detection

Specimen Plated to Media
Day 1

Presumptive Identification
Day 2

Report susceptibilities and Final Identification
Day 3-4

Rapid Detection

Preparation
30 min

Results
1 Hour

Patient outcome

Traditional Microbiology vs. Rapid Approach
Benefits of Rapid Organism Identification

- Implement appropriate early goal directed therapy for sepsis
  - Best studies show only 50-70% initial antibiotic correctly selected
- Leads to earlier de-escalation of antibiotic therapy
  - Current methods take 3-4 days
- Identify outbreaks of resistant organisms earlier
- May be useful for clinical studies
  - Better inclusion criteria
  - Target specific organisms
Non-Culture Methods

• Procalcitonin
  ▪ Precursor to hormone calcitonin
  ▪ Produced in response to bacterial toxins and cytokines (IL-6 & TNF)
    ▪ Specific to bacterial infection
  ▪ Rises 3-4 hrs after insult and peaks in 14-24 hrs
  ▪ Distinguishes blood culture contamination

* Available in Europe only
PCT and Stewardship

- Most data in PNA and COPD
  - Stopping therapy when viral infection
  - More data on using PCT to stop narrow therapy
- PCT may be useful for stopping antibiotic therapy
How PCT Used at Community Hospital H

- 600+ bed community hospital
- Unrestricted use of PCT by all clinicians
  - Reference ranges for PCT available on intranet for PNA and COPD
  - Added PCT to PNA order set
    - At baseline and 24 hours
    - Noted as a tool for antimicrobial stewardship
- Cost to hospital: $90/level
- Turn-around time: 2 hours
# PCT Interpretation

<table>
<thead>
<tr>
<th>PCT (ng/mL)</th>
<th>Interpretation</th>
<th>Antibiotic Suggestion</th>
<th>Start Antibiotics?</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.1</td>
<td>Indicates absence of bacterial infection.</td>
<td>Antibiotics strongly discouraged.</td>
<td>NO!</td>
</tr>
<tr>
<td>0.1 – 0.25</td>
<td>Bacterial infection unlikely.</td>
<td>Antibiotics discouraged.</td>
<td>No.</td>
</tr>
<tr>
<td>≥ 0.25 - &lt; 0.5</td>
<td>Bacterial infection possible.</td>
<td>Antibiotics encouraged.</td>
<td>Yes.</td>
</tr>
<tr>
<td>≥ 0.5</td>
<td>Suggestive of the presence of bacterial infection.</td>
<td>Antibiotics strongly recommended.</td>
<td>YES!</td>
</tr>
</tbody>
</table>
Hospital H PCT Study

• Retrospective chart review of PNA patients
• Inclusion criteria:
  ▪ ICD-9 code PNA
  ▪ ID consult or ICU stay
• No PCT Group: July 1 2008 – December 31 2008
• PCT Group: July 1 2010 – December 31 2010

**Hospital H: Average Antibiotic Days and Cost**

![Bar chart comparing average antibiotic days between No PCT Group and PCT Group](chart.png)

<table>
<thead>
<tr>
<th>N = 116</th>
<th>No PCT (n = 66)</th>
<th>PCT (n = 50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average Antibiotic Cost ($)</strong></td>
<td>926 ± 881</td>
<td>622 ± 528</td>
<td><strong>0.023</strong></td>
</tr>
</tbody>
</table>

Data are mean ± SD

*Personal communication with Kook JL*
PNA FISH

- Peptide Nucleic Acid Fluorescent in-situ Hybridization
- Identifies *Staphylococcus aureus*/Coag Neg Staph, *Enterococcus faecalis* and other enterococci, *Candida*, *E. coli*, *Klebsiella* and *Pseudomonas*
- Turn around time of 90 min in total
  - Retains morphology of organism
  - Fluorescent microscope and water bath
  - Only works on a positive Gram Stain
- Costs approximately $60/test
PNA FISH: Impact on Clinical Care

<table>
<thead>
<tr>
<th>Reference</th>
<th>Assay</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forrest et al AAC 2008:52:3358</td>
<td>PNA FISH <em>Enterococcus faecalis</em>/OE Qausi-experimental (Pretest and posttest design) Twice/day testing HAI infections only N=224</td>
<td>ASP intervention both arms <em>E. faecalis</em> pts.– Mortality same <em>E. faecium</em> pts. Decreased time to effective Rx 3 days (P &lt; 0.001) Lower mortality post – intervention 26% vs. 45% (P=0.04)</td>
</tr>
<tr>
<td>Ly et al, <em>Ther Clin Risk Management</em> 2008;4:637</td>
<td>PNA FISH <em>S. aureus</em>/CoNS dual probe twice daily—all pts. Prospective study</td>
<td>202 pts. randomized to intervention, call to treating physician, or just LIS report; intervention group—reduced mortality (P=0.05); 25% reduction in vancomycin use (p=0.01) Saved $1500 CNS, $6000 <em>S. aureus</em> Study confounded by differences in morbidity</td>
</tr>
</tbody>
</table>
PNA FISH with Stewardship

- Sustained cost-saving and reduction in echinocandin over several years
  - $514,237 over three years

Forrest et al. Sustained Effect of Peptide Nucleic Acid Fluorescent in-situ Hybridization (PNA FISH) on Antimicrobial Utilization and Costs. Poster D787, ICAAC 2009
**S. aureus PCR**

- Limited data
- Compared 3 month periods pre- and post-Gene Xpert® implementation
- 156 patients evaluated

Bauer et al CID 2010:51;1074-80
**S. aureus** PCR and Stewardship

**Figure 2.** Mean time to antibiotic switch from vancomycin to cefazolin or nafcillin for methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia and vancomycin to daptomycin for methicillin-resistant *S. aureus* (MRSA) bacteremia. rPCR, rapid polymerase chain reaction MRSA/SA blood culture test.

Bauer et al CID 2010:51;1074-80
S. aureus PCR

- MSSA
  - Mean time to stop vancomycin 1.7 days earlier
- MRSA
  - Decreased mean LOS by 6 days
  - Saved $21,600

Bauer et al CID 2010:51;1074-80
## Rapid testing without Stewardship

### PNA FISH
- Compared Pre – Post PNA FISH and Vancomycin usage
- GPC in clusters batched and run overnight
- Reported in EMR for morning shift
  - No verbal notification to providers
- No impact on vancomycin use, costs or LOS
- All other data showing benefits of PCR or PNA FISH utilized ASP support

### MRSA PCR
- Pre-Post Gene Xpert® PCR
- GPC in clusters batched and run daily
- No ASP program
- Reported in EMR
  - No verbal notification to providers
- Decreased time to identification by 13 hours
- No impact on time to antibiotic change or LOS

Holtzman et al. J Clin Micro 2011;49;1581-2
Frye A et al. J Clin Micro 2012;50;127-33
Conclusion

- Rapid diagnostic methods may lead to better direct care of infections by:
  - Shortening time to appropriate therapy
  - Reducing toxicities from unnecessary antibiotics
- PCT and other rapid methods appear to be useful for reaching stewardship goals
- Limitations
  - Better education of providers
  - Need for larger multicenter studies
  - Ineffectual without stewardship support