Antimicrobial Stewardship and Rapid Diagnostic Testing

Ohio Society of Health-System Pharmacists
75th Annual Meeting
April 11, 2014

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Patient Scenario
- 55 y.o. male with recent hospitalization for acute cholecystectomy
- Presents to the ED in septic shock
  - BP 80/40
  - HR 135
  - RR 34
  - WBC 21,000
  - Temp 102°F
- Blood cultures drawn
- Fluid resuscitation, vasopressors given
- Vancomycin and piperacillin/tazobactam

Pharmacist Objectives
- Discuss the benefits and clinical impact of rapid diagnostic testing
- Describe the various rapid diagnostic tests (RDTs) used for identifying Staphylococcus spp
- Explain the stewardship implications of RDTs for Clostridium difficile
- Discuss the impact of MALDI-TOF and stewardship on patient outcomes

Without Rapid Diagnostics
- 18 hours: blood culture +
- Gram stain: GPC
- 42 hours: growth on media
- 60 hours: removed from automated ID and susceptibility system
- Enterococcus faecium: VRE
- 62 hours: vancomycin changed to daptomycin

With Rapid Diagnostics
- 18 hours: blood culture +
- Gram stain: GPC
- 21 hours: removed from Verigene GP-BC machine
- Enterococcus faecium: VRE
- 23 hours: vancomycin changed to daptomycin

Technician Objectives
- Discuss the benefits and clinical impact of rapid diagnostic testing
- Describe the various rapid diagnostic tests (RDTs) used for identifying Staphylococcus spp
- Explain the stewardship implications of RDTs for Clostridium difficile

General Principles
- Appropriate antimicrobial pharmacotherapy requires:
  - Identification and knowledge of infecting pathogen
  - Host characteristics
  - Drug’s expected activity against pathogen
- Most fundamental aspect of therapy: appropriate diagnosis
- Organism identification and susceptibility to an antimicrobial is key in determining patient’s therapy
General Principles

- **Basic Microbiology**
  - Direct examination
  - Gram stain
  - Rapid biochemical tests
  - Culture
  - Antibody and antigen detection

- Average time to deliver antimicrobial susceptibility testing results to a physician is 40 hours
- Numerous studies have demonstrated the impact of delayed appropriate antimicrobial therapy on mortality

Traditional/New Timeline

- Average time to deliver antimicrobial susceptibility testing results to a physician is 40 hours
- Numerous studies have demonstrated the impact of delayed appropriate antimicrobial therapy on mortality

New Antibacterial Agents

- Advances in rapid diagnostic tests (RDTs) provide new opportunities for stewardship programs
- Enhance function of clinical microbiology laboratories
  - Provide accurate organism identification
  - Timely antimicrobial susceptibility testing data
- RDTs benefit the individual patient but also increase the effectiveness of ASPs and infection control groups

Antimicrobial Stewardship Programs

- Multidisciplinary team
  - Physicians, pharmacists, nurses, epidemiologists
  - Infectious diseases specialists
- Goal:
  - To optimize antimicrobial therapy
  - Improve patient outcomes
  - Decrease risk for developing antimicrobial resistance

Staphylococcus spp.

- Infections caused by *Staphylococcus* spp. are an enormous burden to the health care system.
- MRSA infections are associated with increased morbidity, mortality, and health care costs.
- Vancomycin is often used empirically to treat suspected *S. aureus* infections
- Prompt identification of methicillin resistance is critical
### S. aureus Tests

<table>
<thead>
<tr>
<th>Organism/ resistance targets</th>
<th>Detection time (hrs)</th>
<th>Technology</th>
<th>Manufacturer</th>
<th>FDA cleared</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus, CoNS</td>
<td>1.5</td>
<td>PNA FISH</td>
<td>AdvanDx</td>
<td>Yes</td>
<td>S. aureus/CNS PNA FISH</td>
</tr>
<tr>
<td>MSSA, MRSA, CoNS</td>
<td>2</td>
<td>PCR</td>
<td>BD GeneOhm</td>
<td>Yes</td>
<td>BD GeneOhm StaphSR</td>
</tr>
<tr>
<td>MSSA, MRSA, CoNS</td>
<td>1</td>
<td>PCR</td>
<td>Cepheid</td>
<td>Yes</td>
<td>Xpert MRSA/SA BC</td>
</tr>
<tr>
<td>MSSA, MRSA, CoNS</td>
<td>5.5</td>
<td>Bacteriophage amplification</td>
<td>MicroPhage</td>
<td>Yes</td>
<td>KeyPath MRSA/SSA Blood Culture</td>
</tr>
<tr>
<td>MSSA, MRSA, CoNS</td>
<td>2.5</td>
<td>Nucleic acid</td>
<td>Nanosphere</td>
<td>Yes</td>
<td>Verigene</td>
</tr>
</tbody>
</table>


### PNA FISH

- Employs fluorescent-labeled probes to target species specific rRNA sequences
- Neutral charge of synthetic molecule allows rapid hybridization
- Enables visualization of target pathogen via fluorescence microscopy
  - Large amount of set up time-often batched
  - 90 minutes from positive culture
- **QuickFISH (AdvanDx)**
  - Requires less setup time
  - Faster turnaround time- 20 minutes

### PNA FISH-Clinical Outcomes

- 101/202 patients with GPCC from blood cultures were randomly assigned to clinical notification of PNA-FISH results
- Notification was associated with:
  - Reduced mortality (17% vs 8%, p=0.05)
  - Decreased antibiotic use (median 2.5 less days, p=0.01)
  - Trends towards reduced hospital stay and charges

### Impact of PNA-FISH for Rapid Identification of Coagulase-Negative Staphylococci in the Absence of ASP

**PNA FISH groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean hospital LOS (days)</th>
<th>Mean duration (days) of vancomycin therapy (median, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-PNA FISH patients (100)</td>
<td>18.7 ± 6.5 (13.0, 20-35.3)</td>
<td>4.15 ± 4.03 (2.0, 0.3-19.2)</td>
</tr>
<tr>
<td>No-PNA FISH patients (99)</td>
<td>20.0 ± 21.0 (13.7, 18-113.5)</td>
<td>3.51 ± 3.43 (1.0, 0.3-10.8)</td>
</tr>
</tbody>
</table>

*P* value: 0.35, 0.40


### PNA FISH

- **S. aureus**
- **Coagulase-negative staph**
- **Negative**


### PNA FISH-Clinical Outcomes

- Comparison of rapid identification method with traditional methods
- Results:
  - Reduction LOS from 6 to 4 days (*p*<0.05)
  - Decreased vancomycin from 6.7 defined daily doses to 4.9 defined daily doses
  - Decrease in hospital costs of $4005 per patient

**Xpert MRSA/SA BC (Cepheid)**

- Primers and probes in the rPCR SA assay detect sequences within the staphylococcal protein A (spa) gene
- Gene for methicillin resistance (**mecA**)
- Staphylococcal cassette chromosome (**SCCmec**)
- Allows for differentiation of MSSA, MRSA, and CoNS from + blood cultures within 1 hour
- Designed to run on demand
- No batching required

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**Xpert MRSA/SA BC Assay - Clinical Outcomes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Group 2</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time to initiate MSS drug therapy, hours</td>
<td>5.2</td>
<td>4.98</td>
<td>0.007</td>
</tr>
<tr>
<td>Median time to initiate MSS drug therapy, hours</td>
<td>0</td>
<td>4.85</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean duration of MSS drug therapy, hours</td>
<td>19.7</td>
<td>20.7</td>
<td>0.09</td>
</tr>
<tr>
<td>No. (%) of patients not initially treated with MSS drug</td>
<td>2 (25)</td>
<td>1 (10)</td>
<td></td>
</tr>
<tr>
<td>No. (%) of patients treated with MSS drug for unrelated condition</td>
<td>2 (25)</td>
<td>4 (35)</td>
<td></td>
</tr>
<tr>
<td>No. (%) of patients treated with MSS drug for nephrologic infection</td>
<td>3 (38)</td>
<td>8 (85)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

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**Xpert MRSA/SA Assay**

- All inpatients admitted between 9/08-12/08 (pre-Xpert test) and 3/09-6/09 (post-Xpert test) with SA bacteremia
- Microbiology laboratory personnel called the ID PharmD with the Xpert results
- ID PharmD recommended appropriate targeted therapy after reviewing the medical record

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**Time to Antibiotic Switch**

![Graph showing time to antibiotic switch for MSSA and MRSA](image)


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**Hospital Costs**

![Cost comparison chart](image)


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**Impact of **mecA** Gene Testing and Intervention by ID PharmD on Time to Optimal Therapy**

![Graph showing impact of meca gene testing and intervention](image)

**Verigene Blood Culture Test**

- Multiplexed, automated nucleic acid test
- Identification of genus, species, and genetic resistant determinants
- Broad panel of the most common Gram-positive and Gram-negative blood culture isolates
- Results within 2.5 hours of blood culture positivity
- Enables 24/7 on demand testing

**Verigene Gram Positive Blood Culture (BC-GP) Test**

<table>
<thead>
<tr>
<th>Available Test Panels</th>
<th>Species</th>
<th>Genus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>Staphylococcus spp.</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>Streptococcus spp.</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus lugdunensis</td>
<td>Micrococcus spp.</td>
<td></td>
</tr>
<tr>
<td>Streptococcus anginosus Group</td>
<td>Listeria spp.</td>
<td></td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>Resistance Markers</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>meca</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>vanA</td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>vanB</td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Verigene Gram Negative Blood Culture (BC-GN) Test**

<table>
<thead>
<tr>
<th>Available Test Panels</th>
<th>Genera and Species</th>
<th>Resistance Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter spp.</td>
<td>CTX-M (blaCTX-M)</td>
<td></td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>KPC (blaKPC)</td>
<td></td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>NDM (blaNDM)</td>
<td></td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>VIM (blaVIM)</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>IMP (blaIMP)</td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>OXA (blaOXA)</td>
<td></td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Enterococcus spp.**

- Enterococcus spp. are the fourth most common bacterial cause of hospital-acquired bacteremia
  - Enterococcus faecalis
  - Enterococcus faecium
- Treatment decisions are challenging due to antibiotic resistance
- Leads to inappropriate and excess antimicrobial therapy and significant extra hospital costs

**PNA-FISH-Enterococcus**

- Differentiate *E. faecalis* from other Enterococcus spp., including *E. faecium* from + blood cultures
- Results within 90 minutes

**Clinical Impact**

- Species identification in a median of 2.3 days earlier (p<0.001)
- Decreases in time to initiate effective therapy (1.3 vs 3.1 days, p<0.001)
- Reduced 30-day mortality (26% vs 45%, p=0.04)

**Verigene- Enterococcus**

- Determines *E. faecalis* vs. *E. faecium* and detects vanA/vanB
- Results in 160 minutes from positive blood culture

**Clinical Impact**

- ID and/or critical care PharmD contacted with Verigene results
- Time to appropriate therapy 23.4 hours shorter (p=0.005)
- LOS 13 days shorter (p=0.048)
- Mean hospital costs $60,729 lower (p=0.02)


**Clostridium difficile**

- Increasingly challenging infection associated with high morbidity, mortality, and healthcare costs.
- Epidemiology has markedly changed with the emergence of a hypervirulent strain (NAP1/027/BI).
- Higher proportion of severe disease, reduced response to traditional therapy, and increased rates of recurrences have led to significant challenges in the management of *C. difficile* infection (CDI).

**C. difficile**

- Produces two toxins, A and B.
  - Toxin B more potent damaging to human colonic epithelium.
- **Cytotoxin neutralization assay** has been considered the gold standard.
  - Only 70% sensitive.
- **Rapid enzyme immunoassays (EIA)**
  - Toxins A, B, or both toxins.
  - Lack sensitivity.
  - Not recommended for routine use.

**C. difficile Tests**

<table>
<thead>
<tr>
<th>Detection time (hrs)</th>
<th>Technology</th>
<th>Manufacturer</th>
<th>FDA cleared</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LAMP</td>
<td>Meridian Bioscience</td>
<td>Yes</td>
<td>Illumigene C. difficile</td>
</tr>
<tr>
<td>2</td>
<td>PCR</td>
<td>BD GeneOhm</td>
<td>Yes</td>
<td>BD GeneOhm C diff</td>
</tr>
<tr>
<td>0.75</td>
<td>PCR</td>
<td>Cepheid</td>
<td>Yes</td>
<td>Xpert C. difficile</td>
</tr>
<tr>
<td>0.75</td>
<td>PCR</td>
<td>Cepheid</td>
<td>Yes</td>
<td>Xpert C. diff Epi</td>
</tr>
<tr>
<td>3</td>
<td>PCR</td>
<td>Gen-Probe desse</td>
<td>Yes</td>
<td>Progastro Cd</td>
</tr>
</tbody>
</table>

**C. difficile-Important Stewardship Implications**

- PCR technology is more sensitive.
  - Rate of positive tests can more than double.
- Important to educate medical staff and hospital administration.
- Implement strict criteria for testing.
  - ≥ 3 unformed watery stools in a 24-hour period.
  - Formed stool rejected unless lab notified of ileus.
  - Samples should not be sent as test of cure.

**Gram-negatives**

- Infections caused by Gram-negative organisms have become a healthcare priority.
- Associated with significant increases in hospital length of stay, mortality, and healthcare costs.
- Increased number have become multidrug-resistant, resulting in the use of combination therapy, more expensive antibiotics or relatively toxic agents.

**GNR Traffic Light Assay**

- Distinguishes *P. aeruginosa* from *E. coli* or *K. pneumoniae* within 90 minutes after the recognition of Gram-negative bacilli of + blood cultures.
- Provides a key opportunity for stewardship programs to deescalate therapy.
  - Combination therapy.
  - Antipseudomonal therapy.
Candida spp.

- Candida spp. represent the 4th most common cause of nosocomial bloodstream infections.
- Attributable mortality as high as 49%
- Additional cost per episode is approximately $40,000
- Early diagnosis remains challenging
  - Criteria for initiating empiric antifungal therapy remain undefined.


Yeast Traffic Light PNA FISH Assay

- Identifies five different Candida spp. within 1.5 hours after growth is detected in + blood cultures
- Fluorescent hybridization probes

C. albicans/parapsilosis
C. tropicalis
C. glabrata/krusei

MALDI-TOF

- Rapid, precise, and cost-effective identification of intact organisms compared to conventional phenotypic techniques
- Allows identification of organisms directly from samples (blood cultures)
- Sample is converted into charged particles which are then separated to produce a molecular “signature” for the organism
- Simultaneously screens a multitude of molecules to determine the identity of the organism by analyzing the mass-to-charge ratio

MALDI-TOF and Stewardship

Provide appropriate therapy and de-escalation sooner

Initiation of appropriate therapy
- Staphylococcus aureus- Recommend starting vancomycin
- Acinetobacter baumannii- Recommend starting double coverage with minocycline + colistin

De-escalation of therapy
- Not Pseudomonas aeruginosa- Recommendations for discontinuing second antibiotic

Additional management
- Recommend
  - follow-up blood cultures
  - appropriate duration of therapy
  - appropriate laboratory monitoring

Integrating Rapid Pathogen Identification and Antimicrobial Stewardship

- Microbiology laboratory implemented MALDI-TOF MS for routine species identification of gram-negative bacteria directly from + blood cultures
- Microbiology laboratory personnel called the ID PharmD 24/7
- ID PharmD recommended deescalation to targeted therapy or escalation of therapy when appropriate

Integrating Rapid Pathogen Identification and Antimicrobial Stewardship

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-intervention cohort</th>
<th>Intervention cohort</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital LOS</td>
<td>11.9 ± 9.3</td>
<td>9.3 ± 7.6</td>
<td>.01</td>
</tr>
<tr>
<td>Hospital LOS after BSI</td>
<td>9.9 ± 7.1</td>
<td>8.1 ± 6.4</td>
<td>.01</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>7.3 ± 8.5</td>
<td>6.3 ± 8.7</td>
<td>.05</td>
</tr>
<tr>
<td>ICU LOS after BSI onset</td>
<td>6.1 ± 6</td>
<td>4.9 ± 6.7</td>
<td>.09</td>
</tr>
<tr>
<td>Mean hospital costs/patient</td>
<td>$45,709 ± $61,806</td>
<td>$26,162 ± $28,996</td>
<td>.009</td>
</tr>
</tbody>
</table>

Impact of MALDI TOF Combined with ASP Intervention in Patients with Bacteremia and Candidemia

- 501 patients with bacteremia or candidemia
- ASP team were informed of MALDI TOF results in real time through decision support software
- ID PharmD provided recommendations for optimization of antimicrobial and antifungal therapy
- 210 interventions were made, 90% were accepted by prescribers

Impact of Rapid Identification of Acinetobacter Baumannii via MALDI-TOF and ASP Intervention in Patients with Pneumonia and/or Bacteremia.

- 136 patients with pneumonia and/or bacteremia due to Acinetobacter baumannii
- ID PharmD was informed of MALDI TOF results during the intervention period and provided antimicrobial therapy recommendations
- Primary outcome was time to effective therapy
- Secondary outcomes of clinical cure, 14-day mortality, length of stay

Impact of Rapid Identification of Acinetobacter Baumannii via MALDI-TOF and ASP Intervention in Patients with Pneumonia and/or Bacteremia.

<table>
<thead>
<tr>
<th>Characteristic/outcome</th>
<th>Pre-intervention (n=70)</th>
<th>Intervention (n=66)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58 [49-68]</td>
<td>54 [39-65]</td>
<td>0.23</td>
</tr>
<tr>
<td>Male</td>
<td>43 (61)</td>
<td>43 (65)</td>
<td>0.39</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>19 [16-23]</td>
<td>18 [14-23]</td>
<td>0.75</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>3 (4)</td>
<td>12 (18)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>66 (94)</td>
<td>52 (79)</td>
<td>0.07</td>
</tr>
<tr>
<td>Time to effective therapy, hours</td>
<td>30 ± 67.7</td>
<td>20 ± 20.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time to optimal therapy, hours</td>
<td>90.3 ± 70.4</td>
<td>47.3 ± 121.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Additional Molecular Techniques

- Xpert MRSA/SA SSTI assay
  - Can be used to detect staphylococcal species directly from wound swabs
- SeptiFast Light Cycler
  - Can detect up to 25 of the most common causes of bloodstream infections
  - Gram positive, gram negative, fungal
  - Detects directly from blood sample within 6 hours
  - Sensitivity and specificity results have varied
Stewardship Implications

- RDTs provide numerous collaborative opportunities for stewardship programs to work with physicians and microbiology laboratory to optimize patient outcomes
- Important to understand how results will be presented
  - Must provide education to medical staff
- Stewardship can be instrumental in cost justifying and implementing the technology
  - Purchase vs lease
  - Laboratory space
  - Complexity of the test

Stewardship Implications

- Stewardship programs evaluate clinical and economic impact of RDTs
- Improve antimicrobial therapy
- Reduce transmission of organisms
- Decrease length of stay
- Decrease mortality

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The Ohio State University Wexner Medical Center