Antimicrobial Stewardship and Rapid Diagnostic Testing

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

Eric Wenzler, PharmD, BCPS
Specialty Practice Resident, Infectious Diseases
The Ohio State University Wexner Medical Center
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
Patient Scenario

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
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
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
New Antibacterial Agents

Introduction

- 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</td>
<td>5.5</td>
<td>Bacteriophage amplification</td>
<td>MicroPhage</td>
<td>Yes</td>
<td>KeyPath MRSA/MSSA 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

S. aureus
Coagulase-negative staph
Negative
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

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

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

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Mean hospital LOS (days) ± SD (median; range)</th>
<th>Mean duration (days) of vancomycin treatment ± SD (median; range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-PNA FISH patients (100)</td>
<td>18.7 ± 16.5 (13.0; 2.0–83.3)</td>
<td>4.15 ± 4.03 (2.9; 0.3–19.2)</td>
</tr>
<tr>
<td>Post-PNA FISH patients (99)</td>
<td>20.9 ± 21.0 (13.7; 1.8–113.5)</td>
<td>3.51 ± 3.43 (1.8; 0.3–10.8)</td>
</tr>
</tbody>
</table>

*P value*

0.35

0.49

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
### Table 2. Data on Drug Therapy for Patients with Bacteremia due to Methicillin-Susceptible *Staphylococcus aureus* at the Michael E. DeBakey Veterans Affairs Medical Center in Houston, Texas (2008–2009)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (^a) (n = 12)</th>
<th>Group 2 (^b) (n = 48)</th>
<th>(P^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time to initiate MSS drug therapy, hours</td>
<td>5.2</td>
<td>49.8</td>
<td>.007</td>
</tr>
<tr>
<td>Median time to initiate MSS drug therapy, hours</td>
<td>0</td>
<td>48.5</td>
<td>.004</td>
</tr>
<tr>
<td>Mean duration of MRS drug therapy, hours</td>
<td>19.7</td>
<td>80.7</td>
<td>.003</td>
</tr>
<tr>
<td>No. (%) of patients not initially treated with MRS drug</td>
<td>3 (25.0)</td>
<td>5 (10.4)</td>
<td>.003</td>
</tr>
<tr>
<td>No. (%) of patients treated with MRS drug for unrelated condition</td>
<td>3 (25.0)</td>
<td>4 (8.3)</td>
<td>.025</td>
</tr>
<tr>
<td>No. (%) of patients treated with MRS drug for staphylococcal bacteremia</td>
<td>6 (50.0)</td>
<td>39 (81.3)</td>
<td>.025</td>
</tr>
</tbody>
</table>

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

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

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
## Available Test Panels

<table>
<thead>
<tr>
<th>Species</th>
<th>Genus</th>
<th>Resistance Markers</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></td>
<td>Resistance Markers</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>
## Available Test Panels

<table>
<thead>
<tr>
<th>Genera and Species</th>
<th>Resistance Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter spp.</td>
<td>CTX-M ((\text{blaCTX-M}))</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>KPC ((\text{blaKPC}))</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>NDM ((\text{blaNDM}))</td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>VIM ((\text{blaVIM}))</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>IMP ((\text{blaIMP}))</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>OXA ((\text{blaOXA}))</td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></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 identify of the organism by analyzing the mass-to-charge ratio
MALDI-TOF

Electrodes

Free-field region (drift tube)

Acceleration region

Time-of-Flight

Detector

Intensity

Research use only – not for use in diagnostic procedures.
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 onset</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 MALDI TOF Combined with ASP Intervention in Patients with Bacteremia and Candidemia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Preintervention (n = 256)</th>
<th>Intervention (n = 245)</th>
<th>Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day all-cause mortality</td>
<td>52 (20.3)</td>
<td>31 (12.7)</td>
<td>83 (20.7)</td>
<td>.021</td>
</tr>
<tr>
<td>Time to microbiological clearance, d</td>
<td>3.3 ± 4.8</td>
<td>3.3 ± 5.7</td>
<td>3.3 ± 4.9</td>
<td>.928</td>
</tr>
<tr>
<td>Length of hospitalization, d&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14.2 ± 20.6</td>
<td>11.4 ± 12.9</td>
<td>12.8 ± 18.1</td>
<td>.066</td>
</tr>
<tr>
<td>Length of ICU stay, d&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14.9 ± 24.2</td>
<td>8.3 ± 9.0</td>
<td>11.5 ± 16.7</td>
<td>.014</td>
</tr>
<tr>
<td>Recurrence of same BSI</td>
<td>15 (5.9)</td>
<td>5 (2.0)</td>
<td>10 (4.0)</td>
<td>.038</td>
</tr>
<tr>
<td>30-day readmission with same BSI</td>
<td>9 (3.5)</td>
<td>4 (1.6)</td>
<td>6.5 (2.9)</td>
<td>.262</td>
</tr>
<tr>
<td><strong>Treatment-related outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to effective therapy, h</td>
<td>30.1 ± 67.7</td>
<td>20.4 ± 20.7</td>
<td>25.3 ± 25.7</td>
<td>.021</td>
</tr>
<tr>
<td>Time to optimal therapy, h</td>
<td>90.3 ± 75.4</td>
<td>47.3 ± 121.5</td>
<td>63.6 ± 100.7</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
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</td>
<td>75 [45-96]</td>
<td>28 [1-52]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Clinical cure at 7 days</td>
<td>8 (11)</td>
<td>24 (36)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mortality at 14 days</td>
<td>14 (20)</td>
<td>15 (23)</td>
<td>0.22</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>21 (30)</td>
<td>19 (29)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Hospital LOS, days</td>
<td>20 [13-36]</td>
<td>19 [12-30]</td>
<td>0.12</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
Antimicrobial Stewardship and Rapid Diagnostic Testing

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

Eric Wenzler, PharmD, BCPS
Specialty Practice Resident, Infectious Diseases
The Ohio State University Wexner Medical Center