Microbiology's Role in Antimicrobial Stewardship-A Microbiologist’s Perspective

Yvette S. McCarter, PhD, D(ABMM)
Director, Clinical Microbiology Laboratory
UF Health Jacksonville
Professor of Pathology
University of Florida College of Medicine-Jacksonville
Jacksonville, FL

Objectives
• Discuss the need for and benefits of an antimicrobial stewardship program
• List three ways that the microbiology laboratory plays an important role in antimicrobial stewardship
• Describe the role of rapid testing for bloodstream, respiratory and neurological infections in antimicrobial stewardship
• Discuss the use of cascade reporting and reflex antimicrobial susceptibility testing to promote antimicrobial stewardship

Why do we need antimicrobial stewardship?
• Antibiotics
  ▪ 1930s-1999 – 107 antibiotics
  ▪ 2000-2009 – 20 antibiotics
  ▪ 2010- present – 14 new antibiotics
• Inappropriate use of antimicrobials lead to...
  ▪ Emergence of multidrug resistant pathogens
  ▪ Adverse effects
  ▪ Superinfections (C. difficile)
• Promote appropriate selection and use of antimicrobials
  ▪ Improve patient outcomes
  ▪ Reduce adverse effects

What is antimicrobial stewardship?
“Multidisciplinary approach to the optimal selection, dosage and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance”

Conserve the antibiotics we have

Antimicrobial Stewardship Goals
1. Work with healthcare practitioners so each patient receives most appropriate antimicrobial with correct dose and duration
   • 4 D’s of optimal therapy – Right Drug, Right Dose, De-escalation (pathogen directed therapy), Right Duration of therapy
2. Prevent antimicrobial overuse, misuse and abuse
   • Antibiotics often given for viral infections
   • Failure to tailor therapy based on culture data
3. Minimize development of resistance
   • Antibiotic use changes susceptibility patterns
   • Antibiotic exposure increases risk of colonization/infection with MDRO and C. difficile
   • Cost – antibiotic resistant infection $18,788-$29,069, increased LOS, 6.5% attributable mortality

Who should be on the team?
How do we implement it?

- Approaches
  - Preprescription – restrictive prescriptive authority
  - Postprescription – prospective review and feedback

- Techniques
  - Formulary restriction
  - Order sets/Treatment algorithms
  - Clinician guidelines
  - Education
  - Pharmacodynamic dose optimization
  - IV to oral switch programs
  - Pharmacy dosing programs
  - Antibiotic cycling

Microbiology’s Essential Role in ASP

- Timely and accurate identification of microbial pathogens
- Accurate susceptibility testing
  - Cascade reporting
  - Reflex susceptibility testing
- Development of antibiograms
  - Stratified
  - Combination
- Rapid testing
  - Respiratory viral pathogens
  - Blood cultures – appropriate therapy/de-escalation of therapy
  - Neurological infections – appropriate therapy/discontinuation of therapy

Microbiology’s Essential Role in ASP

- Guidelines for appropriate specimen collection
- Utilization controls to prevent processing of inappropriate specimens
  - Testing appropriate specimen types for *C. difficile*
- Procedures to limit workup of culture contaminants

Unnecessary and questionable laboratory testing contributes to rapid growth in healthcare costs and may harm patients by exposing them to avoidable medical interventions i.e. ANTIBIOTICS

The Role of Rapid Diagnostic Tests in Antimicrobial Stewardship

- Bloodstream Infections
- Respiratory Infections
- Meningitis and Encephalitis

RDT and ASP - Quality Measures

- Process Measures
  - Duration of antimicrobial therapy
  - Time to antimicrobial optimization
- Outcome Measures
  - Length of Stay
  - Clinical Cure
  - 30 day mortality
  - 30 day readmission
  - Hospital costs

First… A case...

- 25 year old AA male with a PMH of HIV/AIDS presented to the ED with a chief complaint of right lower extremity cellulitis/abscess secondary to a previously treated wound of the right calf
- Started on vancomycin and piperacillin/tazobactam empirically and underwent I&D on Day 2
- Wound specimens obtained during I&D grew MSSA
- Vancomycin and piperacillin/tazobactam discontinued, and nafcillin initiated
- On Day 6, ID consulted for persistent fever and neutropenia – patient changed back to vancomycin and piperacillin/tazobactam
First... A case...

- **Day 13**
  - Blood cultures collected @ 1330 for persistent fever; continued on vancomycin and piperacillin/tazobactam
- **Day 14**
  - Blood cultures were positive @ 1350 - Gram stain = Gram positive cocci suggestive of *Streptococcus*; bottle subcultured
- **Day 15 @ 1000**
  - Organism subculture identified as *Enterococcus* spp. and antimicrobial susceptibility testing performed
- **Day 16 @1220**
  - Organism reported as vancomycin resistant *Enterococcus* based on conventional susceptibility testing results

**Time from blood culture collection to VRE ID - 71 hours**

---

**RDT in Blood Stream Infections**

**Why do we need them?**

Sepsis... **Kills!**
- **Mortality - up to 50%**
  - MRSA/VRE bacteremia - increased mortality
  - Delays in appropriate therapy
- **MRSA - persistent bacteremia**
- **Yeast – disproportionate morbidity and mortality**

Sepsis... **Costs!**
- Most expensive condition treated in US hospitals (> $20 billion in 2011)
- Increased hospital charges and LOS
  - HA-MRSA: $27,083/case
  - VRE: $27,168/case
  - 12 days additional LOS: $27,190/case
  - 18.1 days additional LOS

---

**RDT in Blood Stream Infections**

**Why do we need them?**

Sepsis... **Costs!**

- **Inappropriate antibiotic usage**
  - Empiric use of vancomycin – Inferior to nafcillin for MSSA bacteremia
  - Empiric use of caspofungin
  - Empiric use of broad spectrum antibiotics for Gram negative bacilli
- **Potential pathogen... or not?**
  - CNS commonly isolated from blood but only ~20% represent true infection
  - UF Health - 32% of positive blood cultures = Coagulase negative *Staphylococcus* – 71% contaminants

**RDT in Blood Stream Infections**

**What’s available...**

- **PNA FISH**
- **Molecular Assays**
  - Verigene BC-GP/BC-GN
  - BioFire BCID
  - GenMark ePlex (Coming soon to a lab near you...)
  - Xpert MRSA/SA BC
  - Portrait Staph ID/R Blood Culture Panel
- **MALDI-TOF**
- **FISH & Phenotypic**
  - Accelerate Pheno™ System

---

**RDT in Blood Stream Infections**

**What’s available...**

<table>
<thead>
<tr>
<th>Assay</th>
<th>GP Targets</th>
<th>GN Targets</th>
<th>Yeast Targets</th>
<th>Resistance Markers</th>
<th>TAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNA FISH</td>
<td>2</td>
<td>2-3</td>
<td>2-3</td>
<td>1</td>
<td>20-90 min</td>
</tr>
<tr>
<td>Verigene</td>
<td>12</td>
<td>8</td>
<td>0</td>
<td>9</td>
<td>2.5 hr</td>
</tr>
<tr>
<td>BioFire</td>
<td>8</td>
<td>11</td>
<td>5</td>
<td>4</td>
<td>1 hr</td>
</tr>
<tr>
<td>Portrait</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>&lt;2 hr</td>
</tr>
<tr>
<td>Xpert</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 hr</td>
</tr>
<tr>
<td>ePlex</td>
<td>20</td>
<td>24</td>
<td>16</td>
<td>10</td>
<td>1-1.5 hr</td>
</tr>
</tbody>
</table>
RDT in Blood Stream Infections
What’s available...

PNA FISH

Multiplex – Staph
  * GeneXpert

Microarray
  * Verigene

RDT in Blood Stream Infections
What’s available...

Multiplex – Staph
  * Portrait

FISH & Phenotypic
  * Accelerate Pheno

RDT in Blood Stream Infections
What’s available...

Multiplex
  * BioFire
  * ePlex

RDT in Blood Stream Infections
Impact on ASP

Statistically significant reductions in
  * time to initiation of appropriate therapy
  * rates of bacteremia recurrence
  * LOS
  * mortality
  * hospital costs
when positive blood culture RDTs coupled with ASP intervention

Recommended in IDSA/SHEA guidelines on ASP implementation

  * 3 arms: standard processing, BioFire PCR +templated comments, BioFire PCR +templated comments +real-time audit/feedback by ASP team
  * PCR +templated comments reduced treatment of contaminants and use of broad-spectrum antimicrobials
  * Addition of antimicrobial stewardship enhanced antimicrobial de-escalation
RDT in Blood Stream Infections
Impact on ASP
- Pre-intervention/post-intervention
- Verigene BC-GP vs. Verigene BC-GP + reporting to ID pharmacist for enterococcal bacteremia
  - 23.4 hour reduction in time to optimal antimicrobial therapy
  - Mean LOS (13 days)
  - Mean hospital costs ($60,729)

RDT in Blood Stream Infections
Communication is the key!
- Results need to get to someone who can act on them (Pharmacist)
  - Pager
  - Email
- Use of treatment algorithms
  - Readily available
  - Organism-specific

RDT in Blood Stream Infections
Treatment algorithms

<table>
<thead>
<tr>
<th>Organism</th>
<th>Empiric treatment for bacteremic patient</th>
<th>If patient has beta lactam allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em>, methicillin susceptible</td>
<td>Cefazolin 2g Q8H IV</td>
<td>Vancomycin (trough goal (15-20)</td>
</tr>
<tr>
<td><em>S. aureus</em>, methicillin resistant</td>
<td>Vancomycin (trough goal (15-20)</td>
<td></td>
</tr>
<tr>
<td>Coagulase negative <em>S. aureus</em></td>
<td>Cefazolin 2g Q8H IV</td>
<td>Vancomycin (trough goal (15-20)</td>
</tr>
<tr>
<td><em>S. lugdunensis</em></td>
<td>Cefazolin 2g Q8H IV</td>
<td>Vancomycin (trough goal (15-20)</td>
</tr>
</tbody>
</table>

RDT in Blood Stream Infections
Not quite ready for prime time...
GeneWEAVE®
- Smarticles
  - Specifically target a species, genus, or family of bacteria
  - In the presence of antibiotics, drug-resistant bacteria targeted by Smarticles produce light (luciferase)
  - Can be used to detect MDRO in direct specimens
  - Can be used to perform AST from cultures

* Recently acquired by Roche

RDT in Blood Stream Infections
What about bypassing the blood culture altogether?
T2 Candida (T2 Biosystems)
- Requires no blood culture
- Whole blood tested
- FDA approved for 5 most common yeast
- Results in 3-5 hours
- LOD – 1-3 CFU/mL
- Sensitivity 91.1%
- Specificity 99.4%
T2 Candida
• Utilizes target amplification, nanoparticle capture and T2 magnetic resonance signal amplification
  ▫ No extraction or sample purification required
• Testing based on risk stratification and serial testing of high risk patients
  ▫ Prior to development of symptoms


Case Conclusion
• Day 13
  ▪ Blood cultures collected @ 1330 for persistent fever; continued on vancomycin and piperacillin/tazobactam
• Day 14 @1350
  ▪ Blood cultures positive - Gram stain = Gram positive cocci suggestive of Streptococcus; bottle subcultured
• Day 14@ 1650
  ▪ VRE was identified by Verigene
  ▪ The ID/critical care pharmacists paged with results
  ▪ Pharmacist notified attending physician with a recommendation to switch to daptomycin
  ▪ Daptomycin was ordered by the physician @ 1653
  ▪ Daptomycin was initiated @ 2113

Time from blood culture collection to initiation of daptomycin - 31 hours

RDT in Respiratory Infections
Then
• Rapid antigen tests
• DFA testing
• Viral culture
• Laboratory -developed molecular tests

Now
• Rapid, automated multiplex panels
  ▪ BioFire FilmArray
  ▪ Verigene RP Flex
  ▪ GenMark ePlex
  ▪ Xpert Flu/RSV
  ▪ Simplexa Flu/RSV
• POCT tests
  ▪ Alere i Flu/RSV
  ▪ Roche Liat Flu/RSV

RDT in Respiratory Infections
Impact on ASP
• Pre-intervention/post-intervention
  ▪ In patients with influenza – decrease in LOS, duration of antimicrobial administration, and number of chest x-rays
  ▪ No differences seen with other respiratory viruses
  ▪ Rogers et al. 2015. Arch Pathol Lab Med 139:636-641
  ▪ Pre-intervention/post-intervention – Pediatric
  ▪ No change in LOS overall
  ▪ Decreased LOS in patients with positive BioFire result
  ▪ Reduction in antimicrobial days

RDT in Respiratory Infections
Opportunities for ASP
• Respiratory virus detected → unnecessary antibiotics not given or discontinued early
• Flu/RSV – expediting treatment with antivirals
• ? Benefit of detection of other respiratory viruses
• IDSA/SHEA
  ▫ Advocate use of RDT for respiratory viruses in effort to reduce use of inappropriate antibiotics
• Need to better define how to optimize role of ASP in RDT for respiratory viruses

RDT in Neurological Infections
• What’s available
  ▪ Xpert EV – Enterovirus
  ▪ Simplexa HSV 1/2
  ▪ FilmArray Meningitis/Encephalitis panel
• RDTs facilitate optimization of antimicrobials already started
  ▪ Enterovirus – discontinuation of antibiotics
  ▪ Decreased LOS and unnecessary antibiotic days
  ▪ HSV – discontinuation of antibiotics, continuation of acyclovir if positive; potential discontinuation of acyclovir if negative
Susceptibility Testing
Catching Unusual Results
Cascade Reporting

Antibiograms
Reflex Susceptibility Testing

Susceptibility Testing
Catching Unusual Results
Cascade Reporting

Susceptibility Testing
Catching Unusual Results
Cascade Reporting

Susceptibility Testing
Catching Unusual Results
Cascade Reporting

E. coli

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>R</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>R</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>R</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>S</td>
</tr>
</tbody>
</table>

Susceptibility Testing
Catching Unusual Results
- Susceptibility results compared against current antibiogram data
- Unusual results are repeated
  - Resistant results repeated if antibiogram shows >90% susceptible
  - Susceptible results are repeated if antibiogram shows >90% resistant
- Organisms with no known resistance
  - *Streptococcus pyogenes* – penicillin resistant
  - *Streptococcus pneumoniae* – vancomycin resistant

UF Health Jacksonville
Antibiogram

UF Health Jacksonville
Urine Antibiogram

UF Health Jacksonville
ICU Antibiogram
Combination Antibiogram
- Data predicts the likelihood of having at least one susceptible agent when combination antimicrobial therapy is initiated
  - Does not predict an \textit{in vivo} synergy

Fluoroquinolone Days of Therapy/1000 Patient Days 2011 – 92.1 2016 – 51.8

Reflex Testing
- Implementation of reflex fosfomycin susceptibility testing on ESBL-producing E. coli and Klebsiella urine isolates resulted in a statistically significant decrease in the incidence of carbapenem use
- Increased use of fosfomycin did not negatively impact microbiologic cure

- Confronting antimicrobial resistance requires a multidisciplinary effort – Microbiology is an integral part of the ASP team
- Use of rapid diagnostic tests result in positive patient outcomes and promote appropriate antimicrobial use – only when used in conjunction with ASP
- Communication is key
- Utilize microbiology colleagues to promote ASP
Assessment Question 1
Which of the following is a role that the microbiology laboratory plays in antimicrobial stewardship?

a. Establish antibiotic duration  
b. Perform accurate antimicrobial susceptibility testing  
c. Determine appropriate antibiotic dosing  
d. Increase antimicrobial utilization

Assessment Question 2
Which of the following best describes a benefit of rapid diagnostic testing in bloodstream infections coupled with antimicrobial stewardship intervention?

a. Increased time to appropriate therapy  
b. Increased hospital costs  
c. Decreased patient length of stay  
d. Decreased antibiotic optimization