Value of Diagnostics to Enhance Antimicrobial Stewardship

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Disclosures: consultant bioMerieux
Objectives

• Introduction
• Summarize the basic principles of an antimicrobial stewardship program (ASP)
• What is diagnostic stewardship
• Point of Care Nucleic Acid Amplification Tests (NAAT)
• Biomarkers
• Rapid Diagnostics
Introduction
Crisis in Infectious Diseases

- Widespread antimicrobial drug resistance
- Increasing number of patients who are immunosuppressed
- Emergence of new pathogens
- Reemergence of older pathogens
- Decrease new drug development
- Dysbiosis due to antimicrobial therapy
OLD
Antibiotics as miracles
(“No downside risk, so why not try?”)

New
Antibiotics: Good when used well, better when used thoughtfully
Outcomes of antibiotic misuse

- Development of resistant organisms
- *Clostridioides difficile* infections
- Patient harm such as treatment failure, adverse drug events and increased mortality
- Increase healthcare and societal costs.
Estimate: **By 2050, 10 Million Deaths Attributed to AMR Every Year Costing World Economy $100 Trillion**

[Map showing global dimensions of antimicrobial resistance with numbers of deaths for different regions.]
How do we define antibiotic stewardship?

Antibiotic stewardship is the effort to:

• Measure antibiotic prescribing
• Improve antibiotic prescribing so that antibiotics are only prescribed and used when needed
• **Minimize misdiagnoses or delayed diagnoses leading to underuse or overuse of antibiotics**
  - **diagnostic stewardship**
• Ensure that the right drug, dose, and duration are selected when an antibiotic is needed

It’s about patient safety and delivering high-quality healthcare.
Four Moments of Antibiotic Decision Making

1. **Does my patient have an infection that requires antibiotics?**

2. **Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate?**

3. **A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from IV to oral therapy?**

4. **What duration of antibiotic therapy is needed for my patient's diagnosis?**

*JAMA* 2019; 321:119-121
Linking Diagnostics to Stewardship: The Right Test for the Right Patient at the Right Time

- Is the test appropriate for the clinical setting?
  - Sending the correct specimens is critical
- Will the clinical care of the patient be affected by the test result?
- Will the result be available in time to optimally affect care?
Roles of diagnostic and antimicrobial stewardship in the implementation of rapid molecular infectious disease diagnostics

Basic Principles

• If antimicrobial stewardship is to be successful then appropriate specimen collection must be embraced by the medical and nursing staff
• Cultures should have an indication
• Appropriate specimen collection is critical
• Cultures should be collected before starting antibiotics whenever possible and labeled properly.
• Specimens of poor quality should be rejected
• A swab specimen should be discouraged
Roles of Labs and ASP in Implementation of Diagnostic Stewardship continued

• Key ASP considerations
  • Will the physician understand the test result?
  • Will the physician appropriately modify antimicrobials based on test results?
  • Will the physician act promptly on the test result?
  • Both diagnostic and antibiotic stewardship are required to optimize use of resources and outcomes

Historical Perspectives

• Cultivation of bacteria
  • Joseph Lister, ~1880

• New method of staining bacteria
  • Hans Christian Gram, 1884

• New container for cultivation
  • R. J. Petri, 1887
Obtain Cultures Prior to Starting Antibiotics!

• Develop a process to ensure cultures are properly and consistently ordered
  • Nursing to ensure safe/timely collection of specimens from appropriate source

• Develop processes to ensure cultures are properly and promptly transported and processed and labeled correctly
Clinical Pearl: Appropriate Specimen Collection and Cultures

Culture results guide better patient care decisions

• Wounds
  • Recommend against superficial swab, likely colonizing organisms
  • Preferred samples are pus and tissue
  • Surgical wounds – recommend contacting MD prior to culture collection, consider wound care consult if available for cleansing/debridement prior to sample

• Blood cultures
  • Separate peripheral venipunctures using aseptic technique are preferred
  • Drawing blood for cultures from indwelling catheters should be avoided unless the catheter is thought to be the source of bacteremia
  • Label specimen and collection site and time

• Urine
  • Evaluation of the patient’s symptoms is critical before ordering urine culture
  • Screening for asymptomatic bacteriuria (ABU) is not recommended except in pregnancy and before an invasive urological procedure
  • A urinalysis should be performed before a urine culture is ordered. Urine with >10 WBC/HPF with symptoms should have a urine culture if patient has symptoms.
Clinical Pearl: Appropriate Specimen Collection and Cultures (2)

• Stool for *C. difficile*
  • clinically significant diarrhea is defined as 3 or more unformed stools samples within 24 hours
  • Only watery or unformed loose stool should be submitted (Bristol 7)
  • If patient has been on laxatives in the last 48 hours cancel order and allow at least 48 hours without laxatives to reassess
  • Testing to evaluate for cure is not recommended.
  • PCR does not distinguish colonization versus infection, therefore indications for testing are very important.
A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiologya

J. Michael Miller,1 Matthew J. Binnicker,2 Sheldon Campbell,3 Karen C. Carroll,4 Kimberle C. Chapin,5 Peter H. Gilligan,6 Mark D. Gonzalez,7 Robert C. Jerris,7 Sue C. Kehl,8 Robin Patel,2 Bobbi S. Pritt,2 Sandra S. Richter,9 Barbara Robinson-Dunn,10 Joseph D. Schwartzman,11 James W. Snyder,12 Sam Telford III,13 Elitza S. Theel,2 Richard B. Thomson Jr,14 Melvin P. Weinstein,15 and Joseph D. Yao2

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Highlights

1. Specimens of poor quality should be rejected
2. Physicians should not demand that the laboratory report “everything that grows”
3. Specimens from sites such as lower respiratory tract (sputum), nasal sinuses, superficial wounds, fistulae, and others require care in collection
4. The laboratory requires a specimen, not a swab of a specimen
5. A specimen should be collected prior to administration of antibiotics
6. Susceptibility testing should be done only on clinically significant isolates, not on all microorganisms recovered in culture
7. Specimens must be labeled accurately and completely so that interpretation of results will be reliable.
Point of Care (POC) NAAT
Original POC Test

• Rapid Antigen Tests
  • Group A Streptococcus
    • Sensitivity/Specificity
      86%/92% in children, 91%/93% in adults\(^1\)
  • Influenza EIA
    • Sensitivity/Specificity \textit{50-70\%/90-95\%}\(^2\)

\(^2\)www.cdc.gov/flu/professionals/diagnosis/rapidclin
<20 minute POC NAAT
Influenza A/B, RSV, Group A strep

- Swab used to collect specimen → placed in liquid medium
- Liquid pipetted into reaction container
- Barcode scanned
- Reaction container placed into instrument
Biomarkers Procalcitonin (PCT)
PCT

- Sensitivity 89%/Specificity 94% lower respiratory track infection
- Sensitivity 77%/Specificity 78% sepsis
- Negative predictive value 89-94%
- Evaluate bacterial burden
- Not affected by corticosteroids
- Can use with disease modifying drugs
- Use with other drugs affecting inflammatory mediators
- Not affected by most autoimmune diseases
- Not affected by decreasing immune function/oncology therapy
PCT Kinetics

- Rises 3-6 hours after bacterial infection
- Peak occurs 12-24 hours
- Half life of PCT is 24 hours
- Can take 24 hours of appropriate antibiotic therapy to see reduction in serum PCT
- PCT production and serum concentrations will decrease by up to 50% per day with appropriate antibiotic treatment
- If antibiotic therapy is inadequate, PCT levels will remain high

PCT in Antimicrobial Stewardship

<table>
<thead>
<tr>
<th>PCT &lt; 0.1 ng/ml</th>
<th>Bacterial Infection</th>
<th>NO ANTIMICROBIALS</th>
<th>Consider repeat 6-24hrs based on clinical status</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT 0.1-0.25 ng/ml</td>
<td>Bacterial infection UNLIKELY</td>
<td>NO ANTIMICROBIALS</td>
<td>Use of ABX based on clinical status (‘unstable’) &amp; judgment</td>
</tr>
<tr>
<td>PCT &gt; 0.25-0.5 ng/ml</td>
<td>Bacterial infection LIKELY</td>
<td>YES ANTIMICROBIALS</td>
<td>Repeat PCT day 3, 5, 7 (for Duration)</td>
</tr>
<tr>
<td>PCT &gt; 0.5 ng/ml</td>
<td>Bacterial infection VERY LIKELY</td>
<td>YES ANTIMICROBIALS</td>
<td>CONSIDER STOP ABX when 80=90% decrease; if PCT remains high consider treatment failure</td>
</tr>
</tbody>
</table>

Modified Clin Chest Med. 2011
Chest 2012; 141: 1063.
Real-world impact of PCT-guided antibiotic management

![Graph showing days on therapy and % patients for Pre-PCT and Post-PCT](image)

![Graph showing all-cause 30-day readmission, ADEs from antimicrobials, all-cause hospital mortality, and C difficile infection for Pre-PCT and Post-PCT](image)

Rapid Diagnostic Tests (RDT)
Roles of diagnostic and antimicrobial stewardship in the implementation of rapid molecular infectious disease diagnostics

• Should ASPs Advocate for Use of Rapid Viral Testing for Respiratory Pathogens to Reduce the Use of Inappropriate Antibiotics?
We suggest the use of rapid viral testing for respiratory pathogens to reduce the use of inappropriate antibiotics

• Should ASPs Advocate for Rapid Diagnostic Testing on Blood Specimens to Optimize Antibiotic Therapy and Improve Clinical Outcomes?
We suggest rapid diagnostic testing in addition to conventional culture and routine reporting on blood specimens if combined with active ASP support and interpretation
Rapid Diagnostic Tests

• Biomarkers of infection/inflammation
  • WBC
  • ESR
  • CRP
  • Lactate
  • PCT

• Gram stain

• Molecular
Organism Identification and Initiation of Targeted Antimicrobial Therapy

Traditional versus Rapid Molecular

Traditional Identification & Testing Methods:
- Blood drawn
- Gram stain
- Empiric and broad-spectrum antimicrobial therapy
- Standard organism identification and susceptibility

Rapid Molecular Identification Methods:
- Blood drawn
- Rapid molecular identification
- Empiric antimicrobial therapy
- Targeted antimicrobial therapy
## FDA-Approved RDTs

<table>
<thead>
<tr>
<th>Technology</th>
<th>Manufacturer, Trade Name</th>
<th>Syndrome Testing</th>
<th>Targets</th>
<th>Need Pure Colony</th>
<th>Resistance gene</th>
<th>Time to result (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNA-FISH</td>
<td>AdvanDx, PNA-FISH</td>
<td>Blood</td>
<td>1-15</td>
<td>No</td>
<td>mecA</td>
<td>0.3-1.5 for ID; 7 for AST</td>
</tr>
<tr>
<td></td>
<td>Accelerate PhenoTest; PNA-FISH with morphokinetic cellular analysis</td>
<td>Blood</td>
<td>1-15</td>
<td>No</td>
<td>NA</td>
<td>Ph (M)</td>
</tr>
<tr>
<td>PCR or LAMP</td>
<td>GeneOhm, StaphSR</td>
<td>Blood</td>
<td>1</td>
<td>mecA</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cepheid, Xpert MRSA/SA BC</td>
<td>Blood</td>
<td>1</td>
<td>mecA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BD MAX</td>
<td>GI</td>
<td>4</td>
<td>mecA</td>
<td>0.5-2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gen-Probe Prodesse</td>
<td>GI, Respiratory</td>
<td>3-4</td>
<td>mecA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meridian Bioscience, Illumigene</td>
<td>GI (Clostridium difficile only)</td>
<td>1</td>
<td>mecA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BD GeneOhm, Cdiff Assay</td>
<td>GI</td>
<td>1-2</td>
<td>mecA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALDI-TOF MS</td>
<td>bioMerieux, MALDI-TOF</td>
<td>Any</td>
<td>Database of bacterial and fungal organisms</td>
<td>Yes</td>
<td>None</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Brucker, MALDI-TOF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiplex array</td>
<td>BioFire, FilmArray</td>
<td>Blood, GI, respiratory</td>
<td>14-27</td>
<td>meca, vanA/B, KPC</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>panel</td>
<td>Verigene, Luminex</td>
<td></td>
<td></td>
<td></td>
<td>meca, vanA/B, CTX-M, IMI, KPC, VIM, KPC, NDM, OXA</td>
<td>2</td>
</tr>
<tr>
<td>Nuclear Magnetic Resonance</td>
<td>T2 Biosystems, T2 Candida, T2Bacteria</td>
<td>Whole Blood</td>
<td>3-5</td>
<td>No</td>
<td></td>
<td>3-5</td>
</tr>
</tbody>
</table>

PNA-FISH: Peptide Nucleic Acid Fluorescence in situ Hybridization; PCR: Polymerase Chain Reaction; LAMP: Loop-Mediated Isothermal Amplification; MALDI–TOF MS: Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry; Table is not all inclusive of available products and technologies.
Multiple studies have shown shorter time to optimal therapy along with reduced mortality, LOS, and lower costs when RDTs are combined with effective ASPs.
Molecular RDTs: Culture Dependent

- Rapid biochemical identification \(^a\)
- Proteomic identification (MALDI-TOF MS) \(^a\)
- Rapid identification of pathogens in blood cultures \(^a\)
  - BCID microarrays
  - PNA-FISH
- Rapid phenotypic AST \(^b\)
- NAAT detection of selected resistance
  - \textit{mecA}
  - \textit{vanA/vanB}
  - \textit{KCP}

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MALDI TOF Performance

- Correctly identified 93.2% of organisms to the species level and 5.3% to the genus level (1.5% unidentified)\(^1\)
- Study of 501 pts with bacteremia/candidemia\(^2\)
  - With antibiotic stewardship
  - Improved time to effective therapy from 30.1 to 20.4h
  - Decreased length of stay by 2.8 days
  - Reduced mortality from 20.3% to 14.5%

\(^1\) *J Clin Micro* 48(5):1549-54, 2010

\(^2\) *Clin Infect Dis* 57(9):1237-45, 2013
# Rapid Identification of Positive Blood Cultures

<table>
<thead>
<tr>
<th>Panel</th>
<th>Targets</th>
<th>Accuracy Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>FilmArray BCID Panel, Biofire Diagnostics, Salt Lake City, Utah</td>
<td>• Detects 19 bacterial targets, 3 resistance genes, and 5 yeast targets</td>
<td>91-92</td>
</tr>
<tr>
<td>Verigene BC-GP and BC-GN-RUO, Nanosphere, Inc., Northbrook, IL</td>
<td>• BC-GP test has 12 bacterial targets and 3 resistance markers</td>
<td>90-96</td>
</tr>
<tr>
<td></td>
<td>• BC-GN-RUO test has 9 bacterial targets and 6 resistance markers</td>
<td>94-98</td>
</tr>
</tbody>
</table>

81% of organisms isolated were detected by FilmArray

Time to de-escalate was improved when linked to stewardship

 Clin Infect Dis 2015; 61:1071-80

For BSIs, mRDT was associated with significant decreases in mortality risk in the presence of a ASP, but not in its absence. mRDT also decreased the time to effective therapy and the length of stay. mRDT should be considered as part of the standard of care in patients with BSIs.

 Clin Infect Dis 2017; 64:15-23
# MALDI-TOF Vs Multiplex PCR

**Automated mass spectrometry microbial identification system for identification of bacteria, fungi, and mycobacteria isolated directly from clinical samples in clinical microbiology laboratories**

<table>
<thead>
<tr>
<th>System</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALDI-TOF</td>
<td>• Fast&lt;br&gt;• Accurate&lt;br&gt;• Less expensive per test than molecular and immunological-based detection methods&lt;br&gt;• Not technically complex</td>
<td>• High initial cost of the MALDI-TOF equipment&lt;br&gt;• Identification of new isolates possible only if found in available database&lt;br&gt;• Does not identify resistance genes&lt;br&gt;• May require culture of organism</td>
</tr>
<tr>
<td>Multiplex PCR</td>
<td>• Culturing of the organism not required&lt;br&gt;• Specific, sensitive, rapid, and accurate&lt;br&gt;• Closed-tube system reduces risk of contamination&lt;br&gt;• Can detect many pathogens simultaneously&lt;br&gt;• Can identify fastidious and uncultivable microorganisms</td>
<td>• Highly-precise thermal cycler is needed&lt;br&gt;• Highly-trained laboratory personnel may be required to perform the test, depending on the test platform&lt;br&gt;• Initial cost of the equipment is less than MALDI-TOF, but the cost per run is more</td>
</tr>
</tbody>
</table>

Rapid Phenotypic Susceptibility Testing – Accelerate ID/AST (Application + Blood Culture Bottles)
Multicenter study Accelerate

• VITEK® 2 identification, broth microdilution or disk AST
  • Identification sensitivities 94.6-100%

Gram-positive cocci
• Essential agreement 97.6%
• Categorical agreement 97.9%

Gram-negative bacilli
• Essential agreement 95.4%
• Categorical agreement 94.3%

J Clin Microbiol. 2018;56i:e01329-17
Rapid Diagnostic Tests (3)

• Culture independent
  • Direct antigen detection tests
  • Single target or limited multiplex NAATs
    • In lab and now POC
  • Syndromic multiplex panels for BSI, GI, RT, LRT, and CNS infections
  • Direct detection of BSI by PCR/T2 MRI and PCR/ESI/MS
PCR Panels in Current Use

- Respiratory Panel (FDA approved 2008)
- GI panel (FDA approved 2012)
- Blood culture panel (FDA approved 2014)
- Meningitis panel (FDA approved 2015)
- Lower Respiratory panel (FDA approved 2018)
Limitations of PCR

• False Positives
  • Due to contamination (sensitivity)
  • Need for specialized equipment

• False Negatives
  • Due to inhibitors (Blood, Urine, Sputum)

• Colonizer vs. Pathogen

• Cost

• No Antibiotic Susceptibility Testing
PCR Results Management

• Interpretation and clinical judgment remain critical
  • Determine the significance of a positive result
    • e.g. *Clostridioides difficile* colonization versus infection
  • Understand nuances
    • e.g. the mecA gene in *S. aureus* may be present but not expressed
• Knowing what is on the panels and what is not
• Knowing which panel to order and when
• Will the physician understand how to interpret the test?
• T2 can identify organisms directly from whole blood in 3-5 hours

• T2 bacterial panel
  • *Enterococcus faecium*
  • *Staphylococcus aureus*
  • *Klebsiella pneumoniae*
  • *Pseudomonas aeruginosa*
  • *Escherichia coli*

• T2 Candida panel
  • *Candida albicans*
  • *Candida tropicalis*
  • *Candida krucei*
  • *Candida glabrata*
  • *Candida parapsilosis*
New diagnostic tests should be evaluated as to whether they are value added
  • How will detection of a certain resistance mechanisms affect our choice in antibiotic therapy?
  • Important to establish some collaborative guidance for clinicians upfront involving multiple stakeholders with appropriate education

Communication between antimicrobial stewardship, RDT, and improved process & outcomes
  • Who and when gets notified when an organism and a resistance marker is identified by rapid diagnostics

While becoming widely available, RDT remains costly
  • Clinical demand and appropriate infrastructure are necessary for healthcare to realize return on investment to realize the value proposition
As technology advances:
  • Will the clinician know the result is available?
  • Will the clinician understand the test result?
  • Will the clinician act on the test result promptly to modify the treatment plan if appropriate?
  • Did the intervention improve patient outcome?

Partnership between the clinical microbiology laboratory and the ASP is becoming increasingly important as new tests as well as novel diagnostic approaches become available.

Summary RDT continued
Key Takeaways

• Appropriate indication and specimen collection is critical for both basic microbiology and newer diagnostics
• No one rapid diagnostic platform meets all needs: select test(s) based on work flow and patient population
• Rapid diagnostics can decrease diagnostic uncertainty
• To be effective, rapid diagnostics have to actionable and tied to local stewardship program
• Monitor for unintended consequences
• Testing must be correlated with overall clinical condition of the patient