Value of Diagnostics to Enhance Antimicrobial Stewardship
A Case Based Approach

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Learning Objectives

1. State the primary goals of an antimicrobial stewardship program (ASP).
2. List the basic principles of diagnostic antimicrobial stewardship.
3. Describe the role of procalcitonin (PCT) in supporting antimicrobial stewardship.
4. Explain the uses, advantages and disadvantages of different types of Rapid Diagnostic Tests (RDTs).
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

courtesy Dr Rita Olins
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.
GLOBAL DIMENSIONS

Estimate: By 2050, 10 Million Deaths Attributed to AMR Every Year Costing World Economy $100 Trillion
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.
Antimicrobial Stewardship: Goals

- Improve patient outcomes
- Optimize selection, dose and duration of Rx
- Reduce adverse drug events including secondary infection (e.g. *C. difficile* infection)
- Reduce morbidity and mortality
- Prevent or slow the emergence of antimicrobial resistance
- Reduce length of stay
- Reduce health care expenditures

Ohl CA. *J. Hosp Med*. In press.
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?

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?

RDTs offer opportunities to inform antimicrobial use with diagnostic information quickly

Roles of diagnostic and antimicrobial stewardship in the implementation of rapid molecular infectious disease diagnostics

- **Diagnostic Stewardship**
  - Right test
  - Right patient
  - Right time

- **Antimicrobial Stewardship**
  - Right interpretation
  - Right antimicrobial
  - Right time

- Clinical evaluation
- Rapid diagnostic test ordered
- Rapid diagnostic test performed
- Microbiology laboratory
- Diagnosis & treatment
- Health Care Provider
- Patient
- Rapid diagnostic result reported

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
Traditional Method of Infectious Disease Diagnosis

• Clinical history/exam
• Is the patient infected?
• Is the infection viral or bacterial?
• Gram stain?
• Which virus or bacterium?
• Local antibiogram
• Treatment decision
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 Microbiology


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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.
Case Study #1

• MS is a healthy 34 year-old female who presents with dysuria, fever, and left-sided flank pain
• T-101.2° BP 80/50 P-120 lungs clear, no murmur, has left-sided abdominal and flank pain
• WBC 14,100 15B, creatinine is 1.7, lactate 2.4, Procalcitonin(PCT) is 3.4, urinalysis pyuria and bacteriuria nitrite +

What is the most common organism?

What antibiotic would you start empirically?

a. Cefazolin
b. Ceftriaxone
c. Levofloxacin
d. TMP/SMX
e. Gentamicin
Case study #1 continued

• The most common organism would be *Escherichia coli* (*E coli*)

• What antibiotic would you start?
  • Depends of local antibiogram:
    • Hospital A (% susceptible)
      • Cefazolin  82%
      • Ceftriaxone  92%
      • Levofloxacin  78%
      • TMP/SMX  75%
      • Gentamicin  96%
    • Hospital B (% susceptible)
      • Cefazolin  91%
      • Ceftriaxone  96%
      • Levofloxacin  82%
      • TMP/SMX  80%
      • Gentamicin  98%
Point of Care (POC) NAAT
Original POC Test

• Rapid Antigen Tests
  • Group A Streptococcus
    • Sensitivity/Specificity
      86%/92% in children, 91%/93% in adults
  • Influenza EIA
    • Sensitivity/Specificity 50-70%/90-95%

2www.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

• Normally produced in the C cells of the thyroid
  • Converted to calcitonin
  • Normal levels are undetectable to <.05 ng/mL
• Bacterial infection stimulates PCT production
  • Endotoxins and cytokines cause PCT to be produced in many tissues of the body
  • Concentrations >.25 ng/mL may indicate a bacterial infection
  • Levels >2 ng/mL can indicate high risk of severe sepsis or septic shock
PCT continued

- Increased in bacterial infection
- More specific for bacterial infection than Sed Rate or CRP
- Inhibited by TNF-\(\gamma\) in response to variety viral infections
- Levels change rapidly in response to bacterial infection
- Rapid response to treatment of bacterial infection

Guideline Recommendations:
- Sepsis, Stewardship, HAP/VAP
- Assist in both starting and discontinuation of empiric antibiotics


PCT continued.

- 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

How long does it take PCT to rise in response to a bacterial infection?

a. 0-2 hours
b. 3-6 hours
c. 6-12 hours
d. 12-24 hours
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 Level</th>
<th>Bacterial Infection</th>
<th>PCT Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT &lt; 0.1 ng/ml</td>
<td>Bacterial Infection</td>
<td>NO ANTIMICROBIALS</td>
</tr>
<tr>
<td></td>
<td>VERY UNLIKELY</td>
<td>Consider repeat 6-24hrs based on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clinical status</td>
</tr>
<tr>
<td>PCT 0.1-0.25 ng/ml</td>
<td>Bacterial Infection</td>
<td>NO ANTIMICROBIALS</td>
</tr>
<tr>
<td></td>
<td>UNLIKELY</td>
<td>Use of ABX based on clinical status</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(‘unstable’) &amp; judgment</td>
</tr>
<tr>
<td>PCT &gt; 0.25-0.5 ng/ml</td>
<td>Bacterial Infection</td>
<td>YES ANTIMICROBIALS</td>
</tr>
<tr>
<td></td>
<td>LIKELY</td>
<td>Repeat PCT day 3, 5, 7 (for Duration)</td>
</tr>
<tr>
<td>PCT &gt; 0.5 ng/ml</td>
<td>Bacterial Infection</td>
<td>YES ANTIMICROBIALS</td>
</tr>
<tr>
<td></td>
<td>VERY LIKELY</td>
<td>CONSIDER STOP ABX when 80 = 90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>decrease; if PCT remains high</td>
</tr>
<tr>
<td></td>
<td></td>
<td>consider treatment failure</td>
</tr>
</tbody>
</table>

Case Study #2 Comparison of two UTI presentations (Case 2 courtesy Dr. Broyles)

<table>
<thead>
<tr>
<th>CC/Hx/Presentation</th>
<th>CC: dysuria, fever, nausea/vomiting</th>
<th>CC: dysuria, fever, nausea/vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temp</td>
<td>103.4</td>
<td>102.8</td>
</tr>
<tr>
<td>RR</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>BP</td>
<td>142/84</td>
<td>156/86</td>
</tr>
<tr>
<td>HR</td>
<td>95</td>
<td>91</td>
</tr>
<tr>
<td>WBC</td>
<td>28.4 w/12 bands</td>
<td>26.4 w/14 bands</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.9 mmol/L</td>
<td>1.8 mmol/L</td>
</tr>
<tr>
<td>SrCr</td>
<td>1.6 mg/dl w/ BUN 38</td>
<td>1.8 mg/dl w/ BUN 34</td>
</tr>
<tr>
<td>Mini-cath UA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrite positive</td>
<td></td>
<td>Nitrite positive</td>
</tr>
<tr>
<td>Leukocyte esterase positive</td>
<td></td>
<td>Leukocyte esterase positive</td>
</tr>
<tr>
<td>4+ bacteria</td>
<td></td>
<td>4+ bacteria</td>
</tr>
</tbody>
</table>

Mini-cath UA

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1. CC/Hx/Presentation

2. CC/Hx/Presentation
Case Study #2 continued

1

PCT 4.3

Ceftriaxone 1gm every 24 hours

2

PCT 5.9

Levofloxacin 500mg every 24 hours
Replace levofloxacin with meropenem
Repeat PCT in 12 to 24 hours
Real-world impact of PCT-guided antibiotic management

Low PCT and Infection

• Early course of infections
• Localized infections pharyngitis, maxillary sinusitis, cystitis
• Subacute infectious endocarditis, osteomyelitis
• Mycoplasma pneumonia (higher than viral but lower than pneumococcus)
Non Bacterial Causes of Elevated PCT

• **Severe physiologic stress:** burns, trauma, surgery, bowel ischemia, pancreatitis, intracerebral hemorrhage, ischemic stroke, shock of any kind (septic, anaphylactic, hemorrhagic, or cardiogenic)

• **Malignancies:** Medullary thyroid cancer, lung cancers with neuroendocrine components

• **Medications:** Alemtuzumab (CD52 antibody), Granulocyte transfusions, Interleukin 2, Rituximab (anti-CD20 antibody), T-cell antibodies

• **Nonbacterial pathogens:** malaria, invasive *Candida* infections

• **Renal Failure**
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
- Positive blood culture
- Targeted antimicrobial therapy
- Standard organism identification and susceptibility

**Rapid Molecular Identification Methods:**
- Blood drawn
- Gram stain
- 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><strong>PNA-FISH</strong></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 Phenotypic AST</td>
<td></td>
</tr>
<tr>
<td><strong>PCR or LAMP</strong></td>
<td>GeneOhm, StaphSR</td>
<td>Blood</td>
<td>1</td>
<td></td>
<td>mecA</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Cepheid, Xpert MRSA/SA BC</td>
<td>Blood</td>
<td>1</td>
<td></td>
<td>mecA</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>BD MAX</td>
<td>Gi</td>
<td>4</td>
<td>No</td>
<td></td>
<td>0.5-2</td>
</tr>
<tr>
<td></td>
<td>Gen-Probe Prodesse</td>
<td>Gi, Respiratory</td>
<td>3-4</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meridian Bioscience, Illumigene</td>
<td>Gi (Clostridium difficile only)</td>
<td>1</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BD GeneOhm, Cdiff Assay</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cepheid, Xpert C difficile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MALDI-TOF MS</strong></td>
<td>bioMerieux, MALDI-TOF</td>
<td>Any</td>
<td></td>
<td>Database of bacterial and fungal organisms</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Brucker, MALDI-TOF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Multiplex array panel</strong></td>
<td>BioFire, FilmArray</td>
<td>Blood, Gi, respiratory</td>
<td>14-27</td>
<td>No</td>
<td>mecA, vanA/B, KPC</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Verigene, Luminex</td>
<td></td>
<td></td>
<td></td>
<td>mecA, vanA/B, CTX-M, IMI, VIM, KPC, NDM, OXA</td>
<td>2</td>
</tr>
<tr>
<td><strong>Nuclear Magnetic Resonance</strong></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>
Multiple studies have shown shorter time to optimal therapy along with reduced mortality, LOS, and lower costs when RDTs are combined with effective ASPs

Old
T A T
Turn Around Time

New
T T I
Time To Intervention

Arch Pathol Lab Med 2013; 137:1247-1254
Clin Infect Dis 2013; 57:1237-1245
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 genes\(^a\)
  - meca
  - vanA/vanB
  - KCP

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Cost of machine and software $200,000
Cost of reagents $0.5
Tech time 5 min
Results in ~1 hour
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 an 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><strong>MALDI-TOF</strong></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><strong>Multiplex PCR</strong></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%
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*
A rapid diagnostic test was performed – what was it?

a. PCR  
b. Gram stain  
c. Sed rate  
d. T2 bacterial panel
Case: Test Results

- Immediate results suggested staphylococci
  - MRSA vs MSSA unknown
- Vancomycin started
- At 12 hours, laboratory confirmed *Staphylococcus aureus*
- Patient taken to surgery for sternal debridement
- TEE indicated a vegetation on her AV

Image courtesy of Edward J. Septimus, MD
Time to Determine Optimal Antibiotic Therapy: Traditional vs Rapid Diagnostic Methods

Traditional Diagnostics: 48 to 72 hours
- Fluid or tissue sample obtained
- Results of Gram stain within minutes
- Culture medium incubated: growth seen in ~24 hours
- Biochemical testing for some organisms: minutes to 24 hours
- Susceptibility testing required another 24 hours: revealed MSSA

Rapid Diagnostics: 16 hours
- MALDI-TOF confirmed *S. aureus*
- PCR indicated MSSA within 4 hours of *S. aureus* confirmation

What would you do now?
- a. Continue vancomycin
- b. Switch to a Beta-lactam
- c. Vancomycin plus a Beta-lactam
β-lactam vs Vancomycin for MSSA Bacteremia

![Graph showing 30-Day In Hospital Mortality](image)

- **β-lactam**: 20%
- **Vancomycin + β-lactam**: 15%
- **Vancomycin**: 25%

*Statistically significant*
Case Study #4

• 45 y/o male added for altered mental status. Patient know alcoholic cirrhosis and continues to drink

• Admission afebrile, BP90/60, ascites without abdominal tenderness. Has asterixis and oriented only to name.

• WBC 12,000, Plat 78,000, creat 4.1 (was normal) ALT/AST 50/125, PT INR 2.1, alb 1.6; NH₃ >100; CXR increased vascular markings

• Hospital course:
  • Required intubation and HD
  • Started on lactulose
  • Day 3 fever to 101, WBC 11,000, CXR increased infiltrates and started on cefepime
  • Day 5 a stool was sent for C diff due to diarrhea
  • Day 5 C diff was + by PCR

Does the patient have CDI?
**Clostridioides difficile Diagnostic Testing**

- Molecular tests be used on their own only when the hospitals have established criteria for patients who are most likely to be at risk for CDI.
- When those criteria don't exist, the guidelines recommend that hospitals use a two- to three-step process that includes a toxin immunoassay plus a molecular test and/or an antigen test.
PCR diagnostic strategies may detect patients colonized with CDI but not infected

UK: prospective, multicenter study of suspected CDI patients tested for cytotoxicity assay (CTA), cytotoxigenic culture (CC), or nucleic acid amplification test (NAAT).

Mortality increased significantly in CTA positive patients (OR 1.61, 95% CI 1.12–2.31)

Clinical course of GDH+/EIA+ vs. GDH+/EIA-/PCR+

Retrospective cohort evaluation of 231 patients that tested positive for C. difficile with EIA vs. PCR

- Severe/severe complicated CDI: 33.9% in GDH+/EIA+/PCR+ vs. 19.2% in GDH+/EIA-/PCR+
- CDI recurrence: 25.5% in GDH+/EIA+/PCR+ vs. 19.2% in GDH+/EIA-/PCR+

‘toxin-positive group’ vs. ‘toxin-negative, PCR-positive group’
Summary RDT

• 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.
• 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