(Management Case Study) Exploring the Use of Rapid Diagnostic Tests to Ensure Timely Treatment of Infections

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Disclosure

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.
Learning Objectives

- Describe types of rapid diagnostic tests
- Describe the rapid diagnostic test algorithm
- Describe pharmacist’s impact on improving time to effective therapy
Self-Assessment Questions

- Question 1: Rapid diagnostic tests identify organisms and resistance markers faster than conventional culture and susceptibility method (True/False)

- Question 2: The rapid diagnostic test algorithm can minimize costs associated with laboratory tests (True/False)

- Question 3: Rapid diagnostic tests without concurrent pharmacist’s intervention can reduce time to effective therapy (True/False)
Cedars-Sinai Medical Center

Leading the quest for health...

- Non-profit, acute, tertiary, teaching hospital
- 886 licensed beds
  - 120 intensive care unit beds
- Level I trauma center
- Department of Pharmacy Services:
  - Decentralized clinical pharmacy services
  - Emergency department and operating room services
  - Solid organ transplant services
  - Bone marrow transplant services
  - Transitions of care services
  - Outpatient pharmacy services including ambulatory care clinics
  - 2 Outpatient cancer centers
Rapid Diagnostic Tests (RDTs)

- At least two million illnesses and 23,000 deaths are caused by drug-resistant bacteria in the United States annually
- Up to 50% of antibiotics prescribed in hospitals are unnecessary or inappropriate
- Delayed effective antimicrobial therapy is associated with increased mortality, prolonged hospitalizations, and increased institutional
  - Mortality increased by 7.6% for every hour delay in initiating appropriate antibiotics
- RDT is one of five goals from the National Action Plan for Combating Antibiotic-Resistant Bacteria
- Infectious Diseases Society of America (IDSA) recommends the use of RDT with antimicrobial stewardship program (ASP) support and intervention

https://www.cdc.gov/getsmart/healthcare/
https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf
Rapid Diagnostic Tests (RDTs)

- RDTs provide accurate & timely organism ID and resistance markers
  - Optimize patient care and improve patient outcomes
  - Increase the effectiveness of antimicrobial stewardship programs

- Systemic Review & Meta-Analysis (Timbrook et al)
  - Risk of mortality was significantly lower with molecular RDTs
    - Compared to conventional methods – NNT 20
      (OR 0.66, 95% CI 0.54-0.80)
    - RDTs with ASP (OR 0.64; 95% CI 0.51-0.79)
      o RDTs without ASP failed to significantly decrease in risk of mortality
  - Reduce time to effective therapy: 5.03 hrs (95% CI -8.60 to -1.45)
  - Reduce length of stay: 2.48 days (95% CI -3.90 to -1.06)


https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf
Rapid Diagnostic Tests (RDTs)
Cedars-Sinai Medical Center

- Current RDTs for bloodstream infections
  - Identification of organisms
    - PNAFISH®: C. albicans, C. glabrata
    - QuickFISH®: S. aureus and coagulase negative staphylococci (CoNS)
  - Nanosphere® (Luminex) for Gram Positive & Gram Negative
    - Identifies genus, species, and genetic resistance
Evolution of RDTs at CSMC

- **2005**: Inception
- **2010**: Introduction of QuickFISH® for *S. aureus*
  - **Nanosphere® GP**
- **2011**: AS Rx intervention
- **Dec 2013**: Expansion to Enterococcus
- **Oct 2014**: GNR
  - **Nanosphere® GN**
- **2015**: Candida
  - **PNAFISH®**

**Timeline:**
- Oct 2014: PNAFISH® for Candida
- Dec 2013: Nanosphere® GP for Enterococcus
Candida PNAFISH®
Peptide nucleic acid (PNA) fluorescent in situ hybridization (FISH)

- ~7% of all *Candida* bloodstream isolates are resistant to fluconazole (mostly *C. glabrata*)
- Provides rapid identification directly from blood cultures
  - *C. albicans*
  - *C. glabrata*
- Sensitivity & specificity: 100%
- Results are available within 90 minutes
  - 2-5 days earlier than conventional methods
- Cost per test: ~$42

http://www.advandx.com/products/quickfish/candida/
Staphylococcus QuickFISH®
Rapid peptide nucleic acid fluorescence in situ hybridization (FISH)

- Provides rapid identification directly from GPC in positive blood culture
  - *S. aureus*
  - Coagulase-negative staphylococci
- Sensitivity & specificity: 100%
- Results are available within 20 minutes
  - 1-3 days earlier than conventional methods
- Identify potential CoNS contaminants
- Less costly and faster than Nanosphere®
- Cost per test: ~$45

https://www.luminexcorp.com/clinical/infectious-disease/verigene-bloodstream-infection-tests/
Automated nucleic acid test
Identifies genus, species, and genetic resistance
Need to perform Gram stain first to confirm GP or GN organisms
Determine antibiotic resistance up to 48H faster than conventional methods
Cost per test: ~$70

<table>
<thead>
<tr>
<th></th>
<th>Gram-positive BC</th>
<th>Gram-negative BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turn around time</td>
<td>2.5 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>Resistance markers</td>
<td><em>meca, vanA, vanB</em></td>
<td>CTX-M (ESBL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IMP, KPC, NDM, OXA, VIM (carbapenemase)</td>
</tr>
</tbody>
</table>

https://www.luminexcorp.com/clinical/infectious-disease/verigene-bloodstream-infection-tests/
## Nanosphere® Gram Positive Blood Culture Panel

<table>
<thead>
<tr>
<th>Organism</th>
<th>Genus Marker</th>
<th>RESISTANCE Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em>, <em>S. epidermidis</em>, <em>S. lugdunensis</em></td>
<td><em>Staphylococcus</em> spp.</td>
<td><em>mecA</em>, <em>vanA</em>, <em>vanB</em></td>
</tr>
<tr>
<td><em>S. pneumoniae</em>, <em>S. pyogenes</em>, <em>S. pneumoniae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus anginosus</em> group, <em>S. agalactiae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. faecalis</em>, <em>E. faecium</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sensitivity & Specificity:**

>95%
### Nanosphere® Gram Negative Blood Culture Panel

<table>
<thead>
<tr>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
</tr>
<tr>
<td><em>K. pneumoniae, K. oxytoca</em></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genus marker</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acinetobacter</em> spp.</td>
</tr>
<tr>
<td><em>Proteus</em> spp.</td>
</tr>
<tr>
<td><em>Citrobacter</em> spp.</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
</tr>
</tbody>
</table>

### RESISTANCE Targets
- KPC, NDM, CTX-M
- IMP
- OXA

Sensitivity ≥95%
Specificity ≥97%

RDTs Algorithm for Gram-Positive

- Gram stain positive
  - Clusters
    - QuickFish®
      - CoNS
    - S. aureus
      - Nanosphere®
        - MSSA
        - MRSA
  - Positive BCx
    - Pairs and chains
      - Nanosphere®
        - Enterococcus sp.
      - Streptococcus sp.
Time to Effective Therapy
RDT to Initiation of Therapy

- Gram-Positive and *Candida*: 12/6/13-1/8/15

<table>
<thead>
<tr>
<th>With AMS Intervention</th>
<th>N= 136</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial-Related Opportunity</td>
<td>42/136 (31%)</td>
</tr>
<tr>
<td>- Escalation</td>
<td>17/42 (41%)</td>
</tr>
<tr>
<td>- De-escalation</td>
<td>21/42 (50%)</td>
</tr>
<tr>
<td>- Dose Optimization</td>
<td>4/42 (19%)</td>
</tr>
</tbody>
</table>

Acceptance Rate  
37/42 (88%)

Average time from RDT to initiation of effective therapy  
1.4 hr
RDTs and Antimicrobial Stewardship

- Notify antimicrobial stewardship (AMS) pharmacists of positive blood culture and RDT results via pager
  - 7 days per week (previously Monday to Friday)
  - 7am to 10pm (previously 7am – 5pm)

- AMS pharmacists evaluate antimicrobial regimen and contact prescribers if opportunity is identified

- Unsuccessful interventions are reviewed at the Antimicrobial Stewardship Task Force to identify opportunities to improve acceptance of recommendations
Blood cultures: 4/4 at 24H *S. aureus* without *mecA* resistance marker

- Current therapy: vancomycin
- Intervention: Change to oxacillin
- Rationale:
  - *mecA* gene is responsible for resistance to methicillin and other beta-lactams
  - Oxacillin is the preferred agent for *S. aureus*
Blood culture: 1/2 at 24H *Enterococcus* with resistance markers for VRE (*vanA*)

- Current therapy: vancomycin
- Intervention: Change vancomycin to linezolid
- Rationale: Vancomycin is not active against VRE
Blood culture: 2/2 *E. Coli* at 24H. CTX-M Class A Extended Spectrum β-lactamase resistance marker (ESBL) detected

- Current therapy: ciprofloxacin, metronidazole
- Intervention: Recommend change to imipenem
- Rationale:
  - Carbapenem is the drug of choice
  - Ciprofloxacin is not active against ESBL

**Escalation: example 3**
## CSMC RDT Results

<table>
<thead>
<tr>
<th></th>
<th>2015 (n=310)</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jan (n=55)</td>
<td>Feb (n=46)</td>
</tr>
<tr>
<td>Antimicrobial-Related Opportunity</td>
<td>29%</td>
<td>38%</td>
</tr>
<tr>
<td>Acceptance Rate (%)</td>
<td>88.9%</td>
<td>95.2%</td>
</tr>
</tbody>
</table>
# Type of Antimicrobial-Related Opportunity

<table>
<thead>
<tr>
<th></th>
<th>2015 (n=310)</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jan (n=55)</td>
<td>Feb (n=46)</td>
</tr>
<tr>
<td>Escalation</td>
<td>48%</td>
<td>38%</td>
</tr>
<tr>
<td>De-escalation</td>
<td>44%</td>
<td>48%</td>
</tr>
<tr>
<td>Dose</td>
<td>8%</td>
<td>14%</td>
</tr>
<tr>
<td>Optimization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Time to Effective Therapy: RDT to Therapy

<table>
<thead>
<tr>
<th></th>
<th>2015 (n=310)</th>
<th>2016 (Mean time – hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jan (n=55)</td>
<td>Feb (n=46)</td>
</tr>
<tr>
<td>RDT to Initiation of Therapy</td>
<td>0.83</td>
<td>0.92</td>
</tr>
<tr>
<td>RDT to Administration of Therapy</td>
<td>2.2</td>
<td>2.9</td>
</tr>
</tbody>
</table>
# Time to Effective Therapy:
**Blood Culture to Antimicrobial Administration**

<table>
<thead>
<tr>
<th>Escalation of Therapy</th>
<th>Without AMS Intervention (n=91)</th>
<th>With AMS Intervention (n=51)</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>52.4 ± 37.3 hours</td>
<td>24.9 ± 10 hours</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>
Challenges

- Large number of private physicians including Infectious Diseases Specialists
- Clinicians are not familiar with the RDTs
- Delay in MD responses requiring multiple calls/pages
- Unable to reach prescriber requiring multiple calls to multiple MDs
- Limited Resources: Microbiology & Pharmacy
### RDT Reporting Language

<table>
<thead>
<tr>
<th>Report</th>
<th>Mayo Clinic Reporting Comments</th>
<th>CSMC Resulting Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td><em>mecA detected</em></td>
<td>Positive <em>Staphylococcus aureus</em>. <em>mecA</em> gene DETECTED by testing.</td>
</tr>
<tr>
<td><em>S. aureus</em> + <em>mecA</em> +</td>
<td>Probable methicillin-resistant <em>Staphylococcus aureus</em> (MRSA); further testing in progress.</td>
<td>Probable methicillin-resistant <em>Staphylococcus aureus</em> (MRSA). Full susceptibility panel to follow.</td>
</tr>
<tr>
<td></td>
<td>MRSA is predictably resistant to beta-lactam antibiotics (except ceftaroline).</td>
<td>Place patient in CONTACT ISOLATION per infection control.</td>
</tr>
<tr>
<td></td>
<td>Patient requires contact precautions if hospitalized.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Semi-Urgent Result</td>
<td></td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td><em>mecA</em> not detected</td>
<td>Positive <em>Staphylococcus aureus</em>. <em>mecA</em> gene NOT detected by testing. Full susceptibility panel to follow.</td>
</tr>
<tr>
<td><em>S. aureus</em> + <em>mecA</em> -</td>
<td>Methicillin (oxacillin)-susceptible <em>Staphylococcus aureus</em>. Preferred therapy is an anti-staphylococcal beta-lactam antibiotic, unless clinically contraindicated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resistance Markers <strong>NOT</strong> Detected</td>
<td>Resistance Markers <strong>Detected</strong></td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>S. aureus</strong></td>
<td>Staphylococcus aureus. NO resistance to methicillin (<em>mecA</em>) detected. This result predicts sensitivity to oxacillin (&gt;99% accuracy). Preferred therapy is an IV anti-staphylococcal beta-lactam antibiotic. Full susceptibility panel to follow.</td>
<td>Methicillin (oxacillin)-resistant <em>Staphylococcus aureus</em> (MRSA). <em>mecA</em> resistance marker detected. Vancomycin is the drug of choice for MRSA. Full susceptibility panel to follow.</td>
</tr>
<tr>
<td><strong>E. faecium</strong></td>
<td>Enterococcus faecium. No vanA/B resistance marker detected. This result predicts sensitivity to vancomycin (&gt;99% accuracy). Full susceptibility to follow.</td>
<td>Vancomycin-resistant <em>Enterococcus faecium</em> (VRE). <em>vanA/B</em> resistance marker detected. Linezolid is the empiric drug of choice for VRE faecium. Full susceptibility to follow.</td>
</tr>
</tbody>
</table>
### Resistance Markers NOT Detected

*Escherichia coli*. No ESBL or carbapenem resistance markers detected. This result predicts susceptibility to third-generation cephalosporins (>98% accuracy). Full susceptibility panel to follow.

### Resistance Markers Detected

- **CTX-M**: CTX-M Class A Extended Spectrum β-lactamase resistance marker (ESBL) detected. A carbapenem is the drug of choice. Full susceptibility panel to follow.
- **KPC**: KPC marker for carbapenem resistance detected. Full susceptibility panel to follow.
- **IMP**: Imipenem-resistant metallo-β-lactamase (IMP) marker for carbapenem resistance detected. Full susceptibility panel to follow.
Antimicrobial Stewardship Recommendations Validation

- Cases with recommendations not accepted by the prescribers
  - Daily report is sent to the AMS Pharmacists
  - AMS Pharmacists review and summarize cases
    - Summary is sent to the Antimicrobial Stewardship Committee Physician Members for validation & recommendations for next step
    - MD members are requested to provide feedback within 1 week
  - Quorum:
    - (1) Infectious Disease MD, (1) Internal Medicine/ Surgical MD
    - OR
    - (2) Infectious Disease MDs

- Report card will be presented at the Antimicrobial Stewardship Committee
Antimicrobial Stewardship Recommendations Validation

- MD members are requested to provide feedback within 1 week
  - Agree with recommendation _____________________________
  - Disagree with recommendation __________________________
  - Recommend to send Education Letter to prescriber
  - Recommend to send to Peer Review
  - Other ________________________________________________

- Peer Review or Education Letter is sent in the case of a prescriber who consistently practices outside the institutional guidelines, egregious cases, or a Code of Conduct violation based on the AS Panel review and recommendation
### Opportunity Identified

**De-escalate**

- **86 yo F with history L TKA, prosthesis placement 1 month ago**
- Admitted with L knee pain, redness, swelling x 4 days
  - Arthrocentesis done in ED
  - Started on vancomycin IV
  - BCx & synovial fluid cx obtained
- **RDT**
  - Blood culture (+) MSSA
  - Fluid culture prelim GPC

### Recommendation/Outcome

**Recommendation:** Change vancomycin to either oxacillin or cefazolin

**Outcome:**
- Multiple calls to MD dt lack of responses
- Recommendation not accepted
  - Per MD, he had already talked to RN re: (+) BCx; he had also spoken to “somebody” about culture results and that person would take of it
  - Contacted ID MD, antibiotics changed to oxacillin
  - Pt was discharged with oxacillin/rifampin x 6 weeks
## Antimicrobial Stewardship Report Card

<table>
<thead>
<tr>
<th>Date</th>
<th>Prescriber</th>
<th>Antimicrobials</th>
<th>Type of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/16</td>
<td>SR0101</td>
<td>Piperacillin/tazobatam</td>
<td>De-escalation</td>
</tr>
<tr>
<td>6/16</td>
<td>ID1609</td>
<td>Daptomycin or ceftaroline</td>
<td>De-escalation</td>
</tr>
<tr>
<td>7/16</td>
<td>ID2618</td>
<td>Micafungin, miconazole vaginal, nystatin susp</td>
<td>De-escalation</td>
</tr>
<tr>
<td>7/16</td>
<td>ID1609</td>
<td>Ceftaroline</td>
<td>De-escalation</td>
</tr>
<tr>
<td>7/16</td>
<td>ID1922</td>
<td>Daptomycin, imipenem</td>
<td>Optimization, de-escalation</td>
</tr>
<tr>
<td>8/16</td>
<td>ID1609</td>
<td>Linezolid/daptomycin, micafungin</td>
<td>De-escalation</td>
</tr>
<tr>
<td>8/16</td>
<td>SO0313</td>
<td>Cephalexin</td>
<td>Discontinuation</td>
</tr>
</tbody>
</table>
Key Takeaways

- Collaboration with the Division of Microbiology

- Support from the Medical Staff Leadership and the Institution
  - Financial commitment to purchase equipment
  - Microbiology & Pharmacy resources

- Communication
  - Continue to share successes
  - Ongoing feedback
  - In-services to clinicians
Acknowledgements

- Gregory Marks, Pharm.D., BCPS
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- Meghan Madhusudhan, Data Analyst
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- Kathlyn Lim, Pharm.D.
- Hali Yang, Pharm.D., BCPS
- Ethan Smith, Pharm.D.
Self-Assessment Question 1

- Rapid diagnostic tests identify organisms and resistance markers faster than conventional culture and susceptibility method (True/False)

**Answer: True**
Self-Assessment Question 2

- The rapid diagnostic test algorithm can minimize costs associated with laboratory tests

Answer: True
Self-Assessment Question 3

- Rapid diagnostic tests **without** concurrent pharmacist’s intervention can reduce time to effective therapy

Answer: False