Educating Clinical and Public Health Laboratories About Antimicrobial Resistance Challenges

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As related to clinical and public health laboratories and antimicrobial resistance challenges, at the conclusion of this program, you will be able to:

♦ Describe the primary challenges for antimicrobial susceptibility testing and reporting (AST/R).
♦ Discuss the primary educational resources currently available for AST/R.
♦ List measures that can be taken to enhance knowledge about antimicrobial resistance and improve the quality of AST results reported.

Timeline: Some Major Antimicrobial Resistance Events

- Penicillin-R S. aureus
- Penicillin-R S. pneumoniae
- ESBL
- VRE
- KPC
- VRSA

ESBL, extended-spectrum β-lactamase (Enterobacteriaceae)
KPC, Klebsiella pneumoniae carbapenemase
MRSA, methicillin-resistant Staphylococcus aureus
VRE, vancomycin-resistant Enterococcus
VRSA, vancomycin-resistant S. aureus

Most of current lab workforce trained here!
What is required of USA labs and what information is available for AST/R?

Please note: AST/R = antimicrobial susceptibility testing and reporting

“Specific” mandates by accrediting / certifying agencies for clinical and public health laboratories regarding AST/R:

<table>
<thead>
<tr>
<th>It is mandatory for laboratory to:</th>
<th>As related to AST/R,...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Document competency of staff</td>
<td>Does not specifically address AST/R</td>
</tr>
<tr>
<td>Participate in proficiency testing surveys</td>
<td>Include organisms with specific resistance mechanisms (3 - 8/year)</td>
</tr>
<tr>
<td>Perform adequate quality control</td>
<td>Very specific requirements for AST/R</td>
</tr>
<tr>
<td>Perform appropriate testing / reporting of patient specimens</td>
<td>Very few specific requirements for AST/R</td>
</tr>
</tbody>
</table>

In terms of information for effective AST/R, what is readily available to clinical and public health laboratories?

Information readily available for:

- Selecting organisms to test: +++
- Selecting drugs to test: ++++
- Testing methods: +++++
- Reporting results: ++

+, little information available; ++++, much information available
Sources of Information for AST/R

♦ Text books / manuals
  – CLSI (Clinical and Laboratory Standards Institute) documents (primary resource)
    http://www.clsi.org/

Sources of Information for AST/R (con’t)

♦ Continuing education programs sponsored by:
  – Professional organizations
  – Commercial companies
  – Public health organizations
♦ Various websites, listserves

Primary Challenges for AST/R
What are the primary challenges for AST/R in clinical and public health laboratories?

- Performing susceptibility tests when appropriate (limit over or under reporting)
- Getting access to the most recent CLSI AST/R recommendations and keeping up with the recommendations
- Applying all of the “special” testing/reporting rules (need artificial intelligence!)

What are the primary challenges for AST/R in clinical and public health laboratories? (con’t)

- Dealing with conflicting recommendations (e.g., CLSI vs. FDA breakpoints)
- Having confidence in performance of commercial testing systems
- Deciding how far a smaller lab should go with AST/R
- Defining the role of public health laboratories
- Communicating results effectively

Specimen: Leg wound
Diagnosis: Hypertension

GS:
- Many GPC clusters
- Many pleomorphic GPR
- No WBCs

Culture:
- Many coag-neg staphylococcus
- Many diphtheroids
- Few E. coli-like colonies
- Few Proteus-like colonies

Should AST be performed?
CLSI (Clinical and Laboratory Standards Institute, formerly NCCLS) Documents

- *M100-S17: Tables with breakpoints, QC ranges, drugs to test (2007)

*updated yearly; others updated every 3-5 years

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### Staphylococcus aureus

#### AST/R Rules

<table>
<thead>
<tr>
<th>Agent</th>
<th>Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>Report &quot;R&quot; for MRSA even if test result is &quot;S&quot;</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Perform D zone test for inducible resistance if erythromycin-R and clindamycin-S Do not report on urine isolates</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Only “S” breakpoint; send isolate to reference lab if not “S”</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Erythromycin results predict those for azithromycin and clarithromycin Do not report on urine isolates</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Only “S” breakpoint; send isolate to reference lab if not “S”</td>
</tr>
</tbody>
</table>

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### Staphylococcus aureus (con’t)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxacillin</td>
<td>Cefoxitin detects mecA-mediated resistance better than oxacillin</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Perform β-lactamase test if MIC ≤0.12 µg/ml</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Add report note &quot;rifampin should not be used alone for antimicrobial therapy&quot;</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>If S, consider doxycycline and minocycline “S”; if R, doxycycline and/or minocycline may be “S”</td>
</tr>
<tr>
<td>Trimeth–sulfa</td>
<td>Ignore 20% growth when determining endpoint</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Verify any result with MIC &gt;2 µg/ml</td>
</tr>
</tbody>
</table>

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How can we ensure AST/R rules and recommendations are followed consistently?

**AST/R Rules**

- Need “Artificial Intelligence”
  - Flag organisms needing further testing
  - Report appropriate drugs
  - Edit “S” or “I” results to “R”
  - Flag atypical / inconsistent results
  - Add comments to report

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**Examples of FDA vs. CLSI Breakpoints**

<table>
<thead>
<tr>
<th>Drug / bug</th>
<th>S, I, R Breakpoints (μg/ml)</th>
<th>FDA</th>
<th>CLSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxacillin</td>
<td>≤2, ≥4</td>
<td>≤2, ≥4</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>none</td>
<td>≤2, ≥4</td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>≤2, 4, ≥28</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Vancomycin       | ≤4-16, ≥2≤32               | ≤2, 4-8, ≥16 |}

Currently, diagnostic manufacturers must use FDA breakpoints. Clinical laboratories can use CLSI or FDA breakpoints. Need “harmonization” of breakpoints.

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**How well does an “I” or “R” result predict KPCs?**

(N = 31 KPC producers; 45 non-KPC producers)

<table>
<thead>
<tr>
<th>Method</th>
<th>Carbapenem “I” or “R” result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Meropenem</td>
</tr>
<tr>
<td>Reference BMD</td>
<td>94/98</td>
</tr>
<tr>
<td>Etest</td>
<td>58/96</td>
</tr>
<tr>
<td>Disk diffusion</td>
<td>71/96</td>
</tr>
<tr>
<td>Vitek Legacy</td>
<td>52/98</td>
</tr>
<tr>
<td>Vitek 2</td>
<td>48/96</td>
</tr>
<tr>
<td>MicroScan</td>
<td>84/98</td>
</tr>
<tr>
<td>Phoenix</td>
<td>61/98</td>
</tr>
<tr>
<td>Sensititre</td>
<td>42/98</td>
</tr>
</tbody>
</table>

NA, not applicable (range not low enough or drug not available on panel)

Example: types of labs doing AST/R

- lab in 50-75 bed rural hospital
- lab in >500 bed tertiary care center or reference lab

What testing menu might the small rural hospital laboratory adopt for AST/R?

- **S. aureus**
  - Must all AST/R rules be considered?

- **E. coli / Klebsiella spp.**
  - Should ESBL testing be performed?
  - Should ertapenem be tested to detect KPC (Klebsiella pneumoniae carbapenemase) producers?

- Should other bacteria be tested?

- Should all AST be sent out?
  - Turn around time considerations

Issues for the small rural hospital laboratory re: AST/R

- How can small lab have a limited AST/R menu when any type of resistant organism is possible in any patient?

- How can limited staff be adequately trained to perform all AST/R reliably?
  - Staff often do microbiology “part time”
Specimen: Peritoneal fluid
Diagnosis: Appendicitis

Pseudomonas aeruginosa

MIC (µg/ml)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>8 S</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1 S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2 S</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>16 S</td>
</tr>
</tbody>
</table>

“Combination therapy (e.g. β-lactam + aminoglycoside or β-lactam + fluoroquinolone) should be considered for serious P. aeruginosa infections”

Cumulative Antibiogram 2006

Communicate results effectively

<table>
<thead>
<tr>
<th>% Susceptible</th>
<th>E. coli</th>
<th>E. cloacae</th>
<th>P. aerug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Am</td>
<td>Cfaz</td>
</tr>
<tr>
<td>E. coli</td>
<td>729</td>
<td>61</td>
<td>92</td>
</tr>
<tr>
<td>E. cloacae</td>
<td>144</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P. aerug</td>
<td>221</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

%S data compiled according to CLSI M39-A2.

Public Health Labs and AST/R

PH Labs
How are public health laboratories involved with AST/R?

- Most do no AST and have limited expertise in AST
- If testing is done:
  - Campylobacter jejuni / coli
  - Neisseria gonorrhoeae
  - Salmonella spp.
  - Streptococcus pneumoniae
  - Staphylococcus aureus
- Method primarily disk diffusion and/or Etest

How are public health laboratories involved with AST/R? (con’t)

- Some state PH labs are helping to educate clinical laboratories with AST/R; examples:
  - New Jersey – cumulative antibiogram project
  - New York – proficiency testing program
  - Washington – regional technical workshops

How are public health laboratories involved with AST/R? (con’t)

- Some state PH labs have affiliation with clinical lab (university) and can provide more support for clinical laboratories; examples:
  - Nebraska – clinical lab is resource for problem isolates
  - Iowa – collect, test, provide feedback on specific isolates
- Some state PH labs do limited surveillance for antimicrobial resistance
**Expectations**

**PH Lab expects Clin Lab to provide:**
- Isolates w/ unusual “R” (e.g., VRSA)
- Cumulative antibiogram data

**Clin Lab expects PH Lab to provide:**
- Verification of unusual results (or sends to CDC)
- Technical information from CDC / Others
- Notice of “R” events (e.g., VRSA)
- Notice of training events
- Regional antibiogram data
- CLSI AST standards

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**What 10 steps can we take to educate clinical and public health laboratories about antimicrobial resistance challenges and improve practices to optimize reporting of “quality” results?**

**10 steps**

**What can we do?**

1. Provide the latest CLSI standards to all labs that perform AST/R for patient care.
2. Continue to develop/promote/present educational programs to help labs “interpret” and apply the latest CLSI standards (routine AST/R and cumulative antibiograms).
3. Develop “standards of practice”
   - a) When to perform AST (which organisms to test from various specimen types)
   - b) How to most effectively report results
   - c) Enhanced guidelines for interpreting results
What else can we do?

4. Investigate ways a small rural lab could best handle AST/R.

5. Continue to pursue harmonization of FDA and CLSI breakpoints.

6. Encourage diagnostic manufacturers to reevaluate their systems regularly to determine the system’s abilities to detect resistance in “contemporary” pathogens.

What else can we do?

7. Encourage diagnostic manufacturers and software vendors to improve artificial intelligence for AST/R.

8. Develop/promote/present educational programs to assist PH labs to better serve as a resource (or identify an alternative resource) for AST/R in their community.

9. Interact with accrediting and regulatory agencies to help their surveyors identify inappropriate AST practices that might lead to medical errors.

What else can we do?

10. Provide validated materials (e.g., ppt. presentations and other) that can be used by others to emphasize effective ways to confront emerging resistance; audiences:
   - Clinical lab
   - Public health (lab/epi)
   - MDs
   - Infection Control
   - Pharmacy
Might there be mechanisms
to further educate clinical and public health laboratories
about antimicrobial resistance challenges?

http://www.idsociety.org/STAARAct.htm

Thank you!