Leveraging the Lab and Microbiology Department to Optimize Stewardship

Presented by:
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Objectives

• Identify, explain, and analyze the recommendations made by Clinical Laboratory Standards Institute (CLSI) for the preparation of a Cumulative Antimicrobial Susceptibility Report (CASR).

• Discuss how the clinical microbiology laboratory can be leveraged to optimize antimicrobial stewardship.
Definition of Antibiogram

• CLSI Guideline: M39-A4 definition: “The report generated by analysis of results on isolates from a particular institution(s) in a defined period of time that reflects the percentage of first isolates (per patient) of a given species that is susceptible to each of the antimicrobial agents routinely tested.”
Purpose of the M39-A4 Guidelines

• Guide the preparation of cumulative antimicrobial susceptibility test data reports that will prove useful to clinicians in the selection of the most appropriate agents for initial empirical antimicrobial therapy.

• Other analysis of antimicrobial susceptibility test data may also be of significant value to clinicians, infection control personnel, epidemiologists, pharmacists, and others.

• These reports are often used to support antibiotic stewardship efforts.

Used with permission from CLSI
MIC.21946 Cumulative Susceptibility Data

- For hospital based microbiology laboratories, cumulative antimicrobial susceptibility test data are maintained and reported to the medical staff at least yearly.
- Phase I deficiency if not done.
Question: What is the purpose of an antibiogram (who should use it)?

**Primary aim:**
- Preparing a report to guide clinicians in the selection of empirical antimicrobial therapy for initial infections.

**Secondary aims:**
- Provide Microbiology techs with “typical” susceptibility patterns, in order to determine if particular patient results are reasonable (e.g. repeat, accept, reject, send out)
- Share patterns with other facilities/epidemiologists.
- Individuals who “use clinical antimicrobial susceptibility data to make clinical decisions and/or participate in antibiotic stewardship programs (ASPs)” (e.g., clinical microbiologists, infectious disease specialists and other clinicians, infection control practitioners, pharmacists, epidemiologists, other health care personnel, and public health officials).
CLSI Recommendations (total 10)

1. Analyze and present a cumulative antibiogram report at least annually.
2. Include only final, verified test results.
3. Include only species with testing data for ≥ 30 isolates.
4. Include only diagnostic (not surveillance) isolates.
5. Eliminate duplicates by including only the first isolate of a species/patient/analysis period, irrespective of body site or antimicrobial susceptibility profile.
6. Include only antimicrobial agents routinely tested and calculated, the percent susceptible (%S) from results reported, as well as those that might be suppressed on patient reports using selective reporting rules; do not report supplemental agents selectively tested on resistant isolates only.
7. Report the %S and do not include the percent intermediate (%I) in the statistic.
8. *Streptococcus pneumoniae* and cefotaxime/ceftriaxone/penicillin: list the %S using both meningitis and nonmeningitis breakpoints; for penicillin, also consider including the %S using oral breakpoints.
9. Viridans group streptococci and penicillin: list both the %I and the %S.
10. *Staphylococcus aureus*: list the %S for all isolates and the methicillin-resistant S. aureus (MRSA) subset.
1. Prepare a report annually.
   • Could be prepared more frequently if:
     – Large number of isolates are tested
     – When new antimicrobial agents are tested
   • Presentation of data on a more frequent basis may be complicated by seasonal variations in resistance rates and imprecise measures due to small numbers of isolates.
Data Verification

2. Include only final, verified test results.
   • Confirm all antimicrobial susceptibility test results on every patient before reporting results as final and before including these dataset into the cumulative antibiogram report.
   • Many LIS and commercial susceptibility testing instrument data management systems include software (eg, expert systems) that automatically checks all results to ensure they appear reasonable, and also caution the user to confirm unusual results.

Examples include:
Meropenem resistance in *Escherichia coli*, which is uncommon in many facilities.
Vancomycin resistance in *S. pneumoniae*, which (to date) has not been confirmed in a clinical isolate.
3. Include only species with results for \( \geq 30 \) isolates.

   • If fewer than 30 isolates available consider:
     • Adding a note to include less statistical validity of the estimates of %S
     • Combine data on the organism from data collected over more than 12 consecutive months
     • Combine data, when applicable, for more than one species within a genus.
     • Combine data from several comparable institutions in a geographical area (e.g., acute care hospitals)
       • Be aware of combining data from different types of care institutions (e.g., acute care hospitals plus long-term care facilities). Combining data is only appropriate if the %S data among the institutions are similar.
     • Providing data from published summaries and guides.
4. Include only diagnostic (not surveillance) isolates.

• Do not include data on isolates recovered from surveillance cultures (eg, vancomycin-resistant enterococci [VRE], MRSA), environmental cultures, or other nonpatient sources.
Only the First Isolate

5. Include only results from the first isolate of a given species encountered for a patient, and ignore multiple isolates of the same species irrespective of their source or overall susceptibility profile.

- Inclusion of multiple isolates from an individual patient in analysis of cumulative susceptibility rates for a specific time period can significantly bias estimates in favor of the isolates recovered from patients who are cultured most frequently. The risk of acquiring a resistant strain for a typical patient may thus be significantly overstated.

- Therefore, when preparing a cumulative antibiogram to guide clinical decisions about empirical antimicrobial therapy of initial infections, only the first isolate of a given species per patient, per analysis period (e.g., one year) should be included, irrespective of body site, antimicrobial susceptibility profile, or other phenotypical characteristics (e.g., biotype).

- For purposes of infection control, QA, detection of rare phenotypes, assessing resistance profiles among isolates encountered in a facility, and monitoring the development of resistant isolates in a patient over time, inclusion of the results of all isolates in the analysis database is of great value and recommended.
Estimate S & R Rates

There is no single “correct” way to estimate susceptibility and resistance rates.

- Isolate-based
- Patient-based
- Episode based
- Phenotype-based

<table>
<thead>
<tr>
<th>Calculation Method</th>
<th>N</th>
<th>%S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolate-based estimate</td>
<td>1892</td>
<td>54</td>
</tr>
<tr>
<td>All isolates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient-based estimates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most susceptible</td>
<td>1019</td>
<td>69</td>
</tr>
<tr>
<td>First Isolate</td>
<td>1019</td>
<td>67</td>
</tr>
<tr>
<td>Weighted average</td>
<td>1019</td>
<td>66</td>
</tr>
<tr>
<td>Most resistant</td>
<td>1019</td>
<td>64</td>
</tr>
</tbody>
</table>
6. Include only antimicrobial agents routinely tested and calculated, the percent susceptible (%S) from results reported, as well as those that might be suppressed on patient reports using **selective reporting rules**; do not report **supplemental agents** selectively tested on resistant isolates only.

- make certain each antimicrobial agent reported is appropriate for the species.
  - Refer to CLSI M100 Performance Standards for Antimicrobial Susceptibility Testing.

Perform calculations using the interpretative breakpoints and rules current at the time of analysis. The effect of MIC breakpoint changes on susceptibility trend reports can vary depending on the magnitude of the breakpoint change, its relation to the wild-type MIC distribution for the organism/antimicrobial agent combination, and the magnitude of changes in MICs produced by acquisition of resistance mechanisms.
Supplemental agents

**Observation:** Lower % S for cefotaxime at ANMC in comparison to institutions in the geographical area.

**Investigation:**
Gram negative organisms isolated from non-urine sites are tested for susceptibility using a panel that includes cefotaxime. The only time a urine isolate is tested for cefotaxime, is when an atypical resistance pattern is observed (12 DISK).

**Result:**
The inclusion of the supplemental agent results caused a shift towards lower %S for cefotaxime.
Urine vs. Nonurine Cefotaxime

<table>
<thead>
<tr>
<th>Organism</th>
<th>N</th>
<th>%S</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli (All)</td>
<td>360</td>
<td>70</td>
</tr>
<tr>
<td>E. coli (Nonurine)</td>
<td>148</td>
<td>83</td>
</tr>
<tr>
<td>E. coli (Urine)</td>
<td>212</td>
<td>57</td>
</tr>
</tbody>
</table>

- The results of testing supplemental agents, or agents tested selectively, should not be included in the routine cumulative antimicrobial susceptibility test report. The supplemental agents would be biased toward lower levels of susceptibility because they were tested only against a less susceptible subgroup of the isolates.
Report %S and exclude %I

7. Report the %S and do not include the percent intermediate (%I) in the statistic.
Meningitis and nonmeningitis breakpoints

8. *Streptococcus pneumoniae:*
   - **Penicillin:** For all isolates tested, regardless of body site, calculate and list the % S using meningitis, nonmeningitis, and penicillin V (oral penicillin) breakpoints.
   - **Cefotaxime and ceftriaxone:** For all isolates tested, regardless of body site, calculate and list the % S using both meningitis and nonmeningitis breakpoints.

<table>
<thead>
<tr>
<th></th>
<th>Total # of Isolates</th>
<th>Cefotaxime</th>
<th>Ceftriaxone</th>
<th>Penicillin (IV)</th>
<th>Penicillin V (Oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumo</em> (CSF)</td>
<td>127</td>
<td>97</td>
<td>96</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td><em>S. pneumo</em> (non-CSF)</td>
<td>127</td>
<td>99</td>
<td>99</td>
<td>100</td>
<td>72</td>
</tr>
</tbody>
</table>
Viridans Group *Streptococcus* spp

9. Report both %S and %I

For penicillin: in addition to the %S to penicillin, calculate and list separately the %S and %I to penicillin.

• The %I can be indicated in a footnote.
• Only include data from organisms isolated from sterile body sites.
10. Report % S for all isolates and MRSA subset

- It may be useful to perform a separate analysis for oxacillin-resistant S. aureus (MRSA) and oxacillin-susceptible S. aureus (e.g., use the selection criterion of oxacillin susceptibility or resistance) to demonstrate that many MRSA have lower %S to other antistaphylococcal agents.

<table>
<thead>
<tr>
<th></th>
<th>Cefazolin##</th>
<th>Clindamycin^</th>
<th>Linezolid</th>
<th>Nitrofurantoin</th>
<th>Oxacillin</th>
<th>Rifampin#</th>
<th>Tetracycline</th>
<th>Trimethoprim/Sulfa</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staph. aureus</strong></td>
<td>1340</td>
<td>57</td>
<td>89</td>
<td>100</td>
<td>100</td>
<td>57</td>
<td>100</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td><strong>MRSA</strong></td>
<td>579</td>
<td>R</td>
<td>88</td>
<td>100</td>
<td>100</td>
<td>R</td>
<td>99</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td><strong>MSSA</strong></td>
<td>772</td>
<td>100</td>
<td>90</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>98</td>
<td>99</td>
<td>100</td>
</tr>
</tbody>
</table>
Data Presentation

1. List the inclusive dates used to create the cumulative antimicrobial susceptibility test data report.
2. Include contact information for those responsible for preparing or interpreting the report, if desired.
3. List organisms alphabetically, by organism group, or by prevalence. Analyze by organism group or genus if species information is not routinely available.
4. Place an “R” in the data box when it is known that the species or organism group is intrinsically resistant to the antimicrobial agent.
5. Place a dash (-) in the data box if an antimicrobial agent is not tested, or is known to be clinically ineffective (eg, the *Salmonella* spp. And narrow-spectrum cephalosporins).
### Appendix E2. Cumulative Antimicrobial Susceptibility Report Example – Antimicrobial Agents Listed by Class (Hypothetical Data)

Memorial Medical Center

1 January – 31 December 2012 Cumulative Antimicrobial Susceptibility Report

Percent Susceptible

<table>
<thead>
<tr>
<th>Gram-Negative Organisms</th>
<th>No. Strains</th>
<th>Amoxicillin</th>
<th>Cefazolin</th>
<th>Cefotaxime</th>
<th>Ceftriaxone</th>
<th>Meropenem</th>
<th>Piperacillin-Tazobactam</th>
<th>Amikacin</th>
<th>Gentamicin</th>
<th>Tobramycin</th>
<th>Ciprofloxacin</th>
<th>Nitrofurantoin*</th>
<th>Trimethoprim-Sulfamethoxazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumannii</td>
<td>32</td>
<td>R</td>
<td>R</td>
<td>34</td>
<td>52</td>
<td>80</td>
<td>46</td>
<td>80</td>
<td>60</td>
<td>59</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>49</td>
<td>R</td>
<td>R</td>
<td>72</td>
<td>67</td>
<td>99</td>
<td>67</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>90</td>
<td>78</td>
<td>67</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>31</td>
<td>R</td>
<td>R</td>
<td>68</td>
<td>69</td>
<td>99</td>
<td>74</td>
<td>100</td>
<td>91</td>
<td>91</td>
<td>92</td>
<td>85</td>
<td>95</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>76</td>
<td>R</td>
<td>R</td>
<td>61</td>
<td>62</td>
<td>99</td>
<td>77</td>
<td>99</td>
<td>90</td>
<td>90</td>
<td>92</td>
<td>81</td>
<td>84</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1433</td>
<td>36</td>
<td>68</td>
<td>96</td>
<td>94</td>
<td>99</td>
<td>51</td>
<td>99</td>
<td>91</td>
<td>92</td>
<td>72</td>
<td>98</td>
<td>65</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>543</td>
<td>R</td>
<td>72</td>
<td>91</td>
<td>92</td>
<td>99</td>
<td>86</td>
<td>99</td>
<td>94</td>
<td>94</td>
<td>84</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>Morganella morganii</td>
<td>44</td>
<td>R</td>
<td>R</td>
<td>85</td>
<td>81</td>
<td>99</td>
<td>94</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>99</td>
<td>R</td>
<td>75</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>88</td>
<td>87</td>
<td>80</td>
<td>99</td>
<td>99</td>
<td>100</td>
<td>70</td>
<td>100</td>
<td>90</td>
<td>93</td>
<td>89</td>
<td>R</td>
<td>73</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>397</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>76</td>
<td>80</td>
<td>85</td>
<td>97</td>
<td>80</td>
<td>83</td>
<td>75</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>32</td>
<td>88</td>
<td>–</td>
<td>97</td>
<td>97</td>
<td>100</td>
<td>91</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>90</td>
<td>–</td>
<td>86</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>50</td>
<td>R</td>
<td>R</td>
<td>82</td>
<td>94</td>
<td>99</td>
<td>94</td>
<td>100</td>
<td>94</td>
<td>89</td>
<td>95</td>
<td>R</td>
<td>91</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>33</td>
<td>64</td>
<td>–</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>84</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>95</td>
<td>–</td>
<td>69</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>72</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>63</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>6</td>
<td>R</td>
<td>98</td>
</tr>
</tbody>
</table>

* The percent susceptible for each organism antimicrobial combination was generated by including the first isolate of that organism encountered on a given patient.

* Nitrofurantoin data from testing urine isolates only.

* (--) drug not tested or drug not indicated.

Abbreviations: FQ, fluoroquinolone; R, intrinsic resistance.
Isolates for Inclusion

**Gram-negative:**
- *A. baumanii*
- *Citrobacter freundii*
- *Enterobacter aerogenes*
- *Enterobacter cloacae*
- *E. coli*
- *Haemophilus influenzae* (β-lactamase results for this organism [eg, present β-lactamase positive] may be reported as a footnote to the table)
- *K. oxytoca*
- *K. pneumoniae*
- *Morganella morganii*
- *Proteus mirabilis*
- *Providencia spp.*
- *P. aeruginosa*
- *Salmonella spp.*
- *Serratia marcescens*
- *Shigella spp.*
- *S. maltophilia*

**Gram-positive:**
- Enterococcus spp. (it is preferable to separate into *E. faecalis* and *E. faecium* when identified to species level)
- *S. aureus*
- Coagulase-negative staphylococci (CoNS) (consider excluding *Staphylococcus lugdunensis* and *Staphylococcus saprophyticus*, which could be listed separately if sufficient numbers or isolates are tested)
- *S. pneumoniae*
- Viridans group streptococci (from usually sterile body sites only)

**Anaerobes:**
- *Bacteroides fragilis*
- *Bacteroides fragilis* group (other than *B. fragilis*)
- *Clostridium perfringens*
The clinical microbiologist is in an excellent position to understand how the CLSI M39-A4 recommendations influence the utility of CASRs and to contribute to antimicrobial stewardship programs on the basis of this expert knowledge.

From the antimicrobial stewardship standpoint, the method by which the microbiology laboratory communicates results and the use of selective reporting and provision of instructions for how to interpret results can have a profound impact on prescribing habits.
Cascade or Selective Reporting

Cascade or selective reporting can be used to promote the judicious use of antimicrobials. Cascades consist of algorithm-driven reports that provide only a limited number of tested antimicrobial susceptibilities based on formulary availability, local cumulative susceptibilities, and cost of isolates with no or low levels of resistance to drugs in the first “cascade.”

• Examples include:
  – releasing only gentamicin results when an organism is susceptible to all aminoglycosides
  – providing only susceptibilities to narrow-spectrum urine agents such as nitrofurantoin and trimethoprim-sulfamethoxazole when organisms isolated from midstream urine cultures are susceptible to these agents and releasing other agents such as quinolones or cephalosporins only when resistance to the former is demonstrated
  – not releasing non-β-lactam susceptibilities for Streptococcus agalactiae screening cultures if no β-lactam allergy is indicated in the patient chart.

The cascade approach is recommended by the Infectious Disease Society of America (IDSA).

• Frequent reevaluation is necessary to ensure continued value and reliability of the cascade and the quality of the reporting.
• Unreleased susceptibility data should be readily available upon request.
• Unfortunately, no guidelines on cascade reporting are currently available.
New Drug Testing and Changes in Interpretation Guidelines

- Microbiology laboratories should stay abreast of new drug development and assess the laboratory’s capacity to test the activity of new agents against appropriate pathogens.
- Interdisciplinary collaboration is essential in analyzing and implementing new breakpoint guidelines, especially in the case of the annual update of the performance standards for antimicrobial susceptibility testing.
- Clinical microbiologists, in conjunction with ID physicians and pharmacists, are in the best position to rapidly identify such situations and to provide timely insights and recommendations to antimicrobial stewardship programs.

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Guidance in the Preanalytical Phase

• Microbiology laboratories can significantly impact diagnostic accuracy and the quality of antimicrobial prescribing by providing guidance in the preanalytical phase, i.e., guidance for selecting the appropriate test or culture according to the patient’s syndrome, obtaining optimal collection of clinical specimens, and interpreting microbiology test results.

Common problems in preanalytical phase:
  – Contamination of blood cultures
  – Urine cultures in asymptomatic patients
  – Failure to use specific testing in specific clinical syndromes (e.g., Legionella urinary antigen in community-acquired pneumonia)

• Because poorly collected specimens may result in the recovery of commensal or colonizing organisms and are often rejected, clinicians and nurses need instruction in the appropriate timing and technique of specimen collection.
Biomarkers and rapid diagnostic and rapid susceptibility testing:

Biomarkers
• Bacterial infection biomarkers, such as PCT.

Rapid Diagnostic Testing
• The key to successful RDT is the twinning of these technologies to an antimicrobial stewardship team that can notify clinicians about test results and guide their use in initiating or modifying antimicrobial therapy, for without this link between clinical microbiologists and antimicrobial stewardship, the rapid results run the risk of floating adrift at sea.
References


