Report from the Methodology Working Group

CLSI

June 30, 2014

Methodology WG Members

Steve Jenkins – chairperson

Seth Housman

Laura Koeth

Darcie Roe-Carpenter

Susan Sharp

John Turnidge

Brandi Limbago – chairperson

Romney Humphries

Sandra Richter

Katherine Sei

Ribhi Shawar

Presentation to Sub-committee

- Informational reports/ guidance:
  - Ceftriaxone-Resistant/Oxacillin Susceptible Strains of *Staphylococcus aureus* – Discussion
  - CarbaNP Ad Hoc WG Report
  - Broth Microdilution Methods Ad Hoc WG Report
  - Colistin/ Polymyxin Ad Hoc WG Report
  - Oritavancin - Informational presentation on testing issues and potential use of vancomycin as a surrogate test agent
- Items for a vote:
  - Table 1 Ad Hoc WG Report (several issues)
  - Anaerobic AST Ad Hoc WG Report
  - Intrinsic Resistance Ad Hoc Working Group Report

Presentation to Sub-committee

- Call for isolates & potential new projects
  - Atypical *S. aureus* – Romney Humphries
  - Should we develop guidance as it relates to molecular detection of resistance (e.g., issue of mecA-positive *Staphylococcus aureus* that test cefoxitin (and/or oxacillin) susceptible)?
  - Should we address lack of standards for “direct” AST from blood culture bottles, etc.?

Tables 1 and 2
Ad Hoc Working Group Report

Dr. Steve Jenkins for Dr. Mary York

Tables 1 and 2 Ad Hoc Working Group

Charges

1. To delete FDA-discontinued drugs from Tables 1
2. To delete or retain older drugs in Tables 1 & 2
3. Review Table 1's suggested testing/reporting based on current guidelines

Members

- Mary York-chair
- Dwight Hardy
- Tony Mazzulli
- Susan Munro-recording secretary
- Barth Reller
- Tom Thomson
- Steve Jenkins; co-chair, Methodology Working Group

Task 1: Deletion of Drugs - Algorithms

- For retention in Tables 1, a drug must be (at a minimum) FDA-cleared and available in the United States.
- For retention in Tables 2, a drug must be manufactured for use to treat non-topical patient infections somewhere in the world.
- Being cleared by the FDA is not a requirement for retention in Tables 2.

What if breakpoints are needed after removal from Tables 2?

- The breakpoints will be in the archives.
- Some companies in India and China will manufacture compounds upon order, but they may be for research or veterinary use only.
- If a representative from any country wishes to come forward to report a compound's use in a country, the applicable information can be added back in the document.

Summary of approaches taken:

- The FDA, Wikipedia, and several Medical web sites were the among the sources used to determine availability.
- Some pharmaceutical and chemical web sites were also checked as well as web sites in China and India.
- If we doubted a drug's availability, we deleted it.

Drugs Discontinued in the USA but not Internationally

Unanimous WG vote to delete the following from Table 1 Only; <u>Request vote from SAST</u>

- Azlocillin
- Mezlocillin
- Ticarcillin
- Cloxacillin
- Mecillinam
- Cephradine
- Cefamandole
- Cefoperazone
- Cephradine
- Enoxacin
- Lomefloxacin
- Sparfloxacin

Drugs no longer thought to be available worldwide
Ad Hoc WG Vote: Delete from Tables 1 & 2

- Carbenicillin
- Methicillin
- Cephalothin
- Cephapirin
- Cefonicid
- Ceftizoxime
- Cefmetazole
- Moxalactam
- Loracarbef
- Spectinomycin
- Dirithromycin
- Cinoxacin
- Grepafloxacin
- Trovafloxacin

Methodology WG Votes

- Unanimous: Revisit this list of drugs and determine more completely which compounds are definitively available and used outside of the US (for Table 2), and to delete those applicable compounds from the Table (and all other relevant Tables) as part of the clean-up process. (Martindale)
- Unanimous: Clean up glossary to remove obsolete agents AND remove drug names from Table 1 (refer to Glossary) (Text and Tables?)

Drugs not FDA discontinued but not thought to be in use
Table 1 Ad Hoc WG Vote: Delete from Tables 1 & 2
(Tabled by Methodology WG)

- **Telithromycin**
  - black box warning
  - banned in a number of countries

- **Gatifloxacin**
  - common ophthalmic use in US
  - discontinued by manufacturer because of significant side effects
  - banned in India for systemic use in 2011 due to side effects
  - still sold as tablets and IV in China

  Recommended to delete because of side effects and due to the fact that our published drug breakpoints do not apply to ophthalmics (the most common use)

Direction from SAST?

FQ Decisions in January

- Deleted in 2F (*Neisseria gonorrhoeae* Table): **Enoxacin**, Gatifloxacin, Grepafloxacin, **Lomefloxacin**, **Ofloxacin**, Trovafloxacin, and **Fleroxacin**
- Deleted in 2G (*Streptococcus pneumoniae* Table): Grepafloxacin, **Ofloxacin**, **Sparfloxacin**, Trovafloxacin.
- Removal of following drugs is not consistent with our algorithm and recommendations:

  Table 2G **Sparfloxacin, Ofloxacin**

  Table 2F: **Enoxacin**, **Lomefloxacin**, **Fleroxacin, Ofloxacin**

Fluroquinolones Use in China: IV, PO, drops (From IMS data)

Drugs	Sum of Value (RMB) in 2013	Sum of Volume (Box) in 2013
ENOXACIN	74,627,668	2,390,737
GATIFLOXACIN	42,834,562	1,648,837
LOMEFLOXACIN	13,227,509	904,258
SPARFLOXACIN	11,091,943	333,558
OFLOXACIN	11,024,428	491,176
FLEROXACIN	1,972,989	89,146

FQs voted for removal from Table 2
Removal not recommended by
Table 1 & 2 Ad Hoc Group
For review by SAST

- ENOXACIN
- LOMEFLOXACIN
- SPARFLOXACIN
- FLEROXACIN
- OFLOXACIN

Footnotes Issues

There are many notes that list drugs in the same class whose results can be inferred from testing another drug.

- These lists predated the glossary and now one can refer the user to the glossary
- Recommend referring user to the glossary because it makes the communication easier to understand
- Not all drugs are equally effective and listing implies they are.
- Vote on note changes as follows:

Footnote Table 1A k

Reads: "*If a penicillinase-stable penicillin is tested, oxacillin is the preferred agent, and results can be applied to the other penicillinase-stable penicillins, ~~cloxacillin, dicloxacillin, flucloxacillin. Methicillin and nafcillin~~*"

Proposed Revison: *"If a penicillinase-stable penicillin is tested, oxacillin is the preferred agent, and results can be applied to the other penicillinase-stable penicillins.* ***Please refer to glossary 1****."*

Footnote Issues

- WG voted unanimously to approve concept (including elimination of a redundant comment) and defer a number of similar comments to Text and Tables WG to address final verbiage

- **Request vote from SAST to move forward with process**

WG unanimously to following Changes to Table 1

- Enterobacteriaceae:
  - Add fosfomycin with note “for urinary isolates of *E. coli”* only. Change to “U” in Table 2
- *Enterococcus*:
  - Add fosfomycin with note “for urinary isolates of *E. faecalis* only”; change to “U” in Table 2

Request vote by SAST

Delete the following from Tables 1 for Vancomycin and Daptomycin:

*MIC testing only; disk diffusion test unreliable.

- Comment does not relate to the purpose of Tables 1 and is self-evident in the Tables 2 because there are no disk breakpoints.
- Also consider deleting cefoxitin in the *Staphylococcus* spp. table and the footnote with it, for same reason:

Table 1 Ad Hoc WG: No consensus on following issue

Proposed note on drug: "Doripenem should not be reported for isolates from the respiratory tract."

- Safety warning by the FDA for VAP and drug is not approved for treatment of pneumonia, although it is effective and not a problem if not VAP.
- Cannot restrict only for VAP because the laboratory does not know disease, but drug generally only used for hospitalized very ill patients that are on ventilators.

Enterococcus issue for vote:

- Delete *Erythromycin* from Table 2D (*Enterococcus*) and its breakpoints
  - No evidence drug works and
  - In some developing countries and rural areas, desire to report all drugs since there are so few available
  - Delete tetracycline from *Enterococcus* urinary treatment in Table 1. - No evidence that it is effective.

Additional Issues

Recommendation from Table 1 Ad Hoc WG:

In the future, if an organism group is found intrinsically resistant to a drug, the breakpoints for that drug should be removed from Tables 1 and 2 for that organism group. Individual species should be handled in footnotes in Appendix B (e.g., ceftazidime and *Stenotrophomonas maltophilia*)

Ad Hoc WG Voted Changes to Table 1
(Tabled by Methodology WG due to lack of time)

Acinetobacter

Delete: Piperacillin-tazobactam, ticarcillin-clavulanate, cefotaxime, ceftriaxone, doxycycline, tetracycline, and piperacillin

Add: Colistin and polymyxin B to Group B.

Move: Ciprofloxacin and levofloxacin From Group A to Group B

Move: Gentamicin and tobramycin from Group A to Group B

Move: Cefepime and minocycline from Group B to Group A

Ad Hoc Table 1 Voted Changes to Table 1
(Tabled by Methodology WG due to lack of time)

Burkholderia

- Levofloxacin and meropenem moved to Group A
- Ticarcillin-clavulanate moved to Group C

Stenotrophomonas

- Ticarcillin-clavulanate and levofloxacin moved to Group A
- Chloramphenicol moved to Group C

Ad Hoc WG Voted Changes to Table 1

(Tabled by Methodology WG due to lack of time)

Haemophilus influenzae/parainfluenzae:

Move: amoxicillin-clavulanate, ciprofloxacin, levofloxacin, and moxifloxacin to group B from group C

Move: ampicillin-sulbactam, chloramphenicol, cefuroxime (parenteral), and meropenem to from group B to group C

Also voted to change footnotes for *Haemophilus*
(Tabled by Methodology WG due to lack of time)

- For isolates of *H. influenzae* from CSF, only results of testing with ampicillin, one of the third-generation cephalosporins**, ~~chloramphenicol, and meropenem~~** are appropriate to report routinely.
- ~~**Amoxicillin-clavulanate**~~**,** azithromycin, cefaclor, cefdinir, cefixime, cefpodoxime, cefprozil, cefuroxime, clarithromycin, and loracarbef, ~~telithromycin~~ are oral agents that may be used as empiric therapy …..

Vote on Changes to Table 1

- *Enterococcus*:
  - Add **BOLDED Sentence** to tetracycline footnote:

Organisms that are susceptible to tetracycline are also considered susceptible to doxycycline and minocycline. However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline, minocycline, or both. "**Doxycycline and minocycline are not routinely reported on organisms isolated from the urinary tract because of low urine concentrations**."

Urine Culture Isolate Reporting: Doxycycline (Enterococci and Staphylococci)

- WG questioned listing doxycycline in these comments, and voted unanimously to garner more information on urine concentrations for both minocycline and doxycycline before proceeding

There will be time, there will be time….
And time yet for a hundred indecisions,
And for a hundred visions and revisions…
And indeed there will be time
To wonder, "Do I dare?" and, "Do I dare?"…
In a minute there is time
For decisions and revisions which a minute will reverse.

- T. S. Elliot
- Love Song of J. Alfred Prufrock

From Mary York-sorry I could not be here…

Use of Vancomycin Susceptibility Testing Results as a Surrogate for Oritavancin Activity

Ronald N. Jones, MD,
Rodrigo E. Mendes, PhD,
and
John D. Turnidge, MD

JMI Laboratories
North Liberty, Iowa
and
University of Adelaide
Australia

Oritavancin

- Broad-spectrum Gram-positive active lipoglycopeptide with an extended serum $T_{1/2}$
- PK/PD investigations suggested a single 1,200 mg dose for treatment of ABSSSI
- In two ABSSSI clinical trials oritavancin was demonstrated to be non-inferior to a regimen of vancomycin given twice daily for 7-10 days
- Registrations in the USA and Europe are pending

Background

- **Lipoglycopeptides have physicochemical features that challenge accuracy/reproducibility of *in vitro* susceptibility testing**
  - **Reference broth microdilution**
  - **Agar disk diffusion**
- **Application of polysorbate-80 (P-80) increases accuracy of reference MIC testing**
- **Newly approved drugs, regardless of testing problems, may not be tested in commercial devices for years**

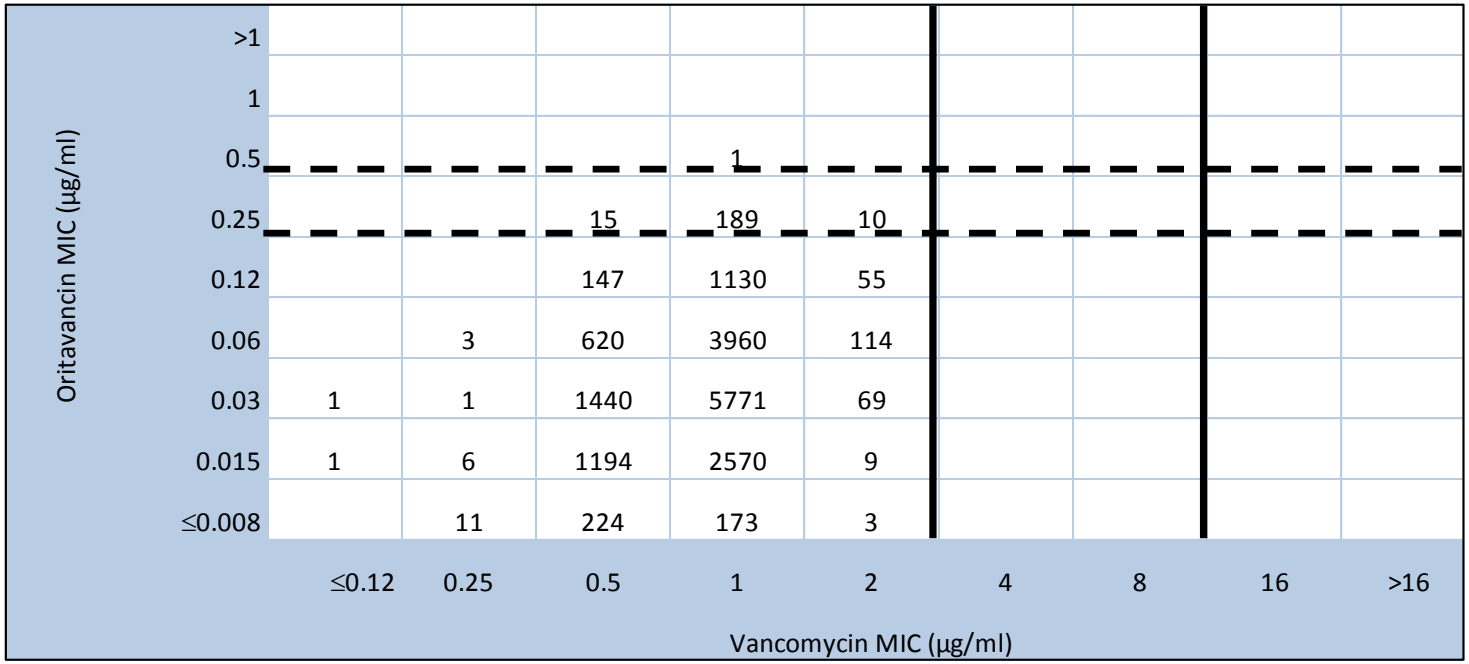
Solutions

- Clinical microbiology laboratories to facilitate use of potent new products, selectively test pathogens with agar diffusion reagents (disks, stable gradient devices)
  - "Not a currently-available option with this class"
- Surrogate marker strategies are used in numerous antimicrobial classes
  - Latest application for uUTI and orally administered cephalosporins by the CLSI
- "Could vancomycin predict susceptibility to ORITAVANCIN across possible indicated species?"

Proof/Analysis of Concept

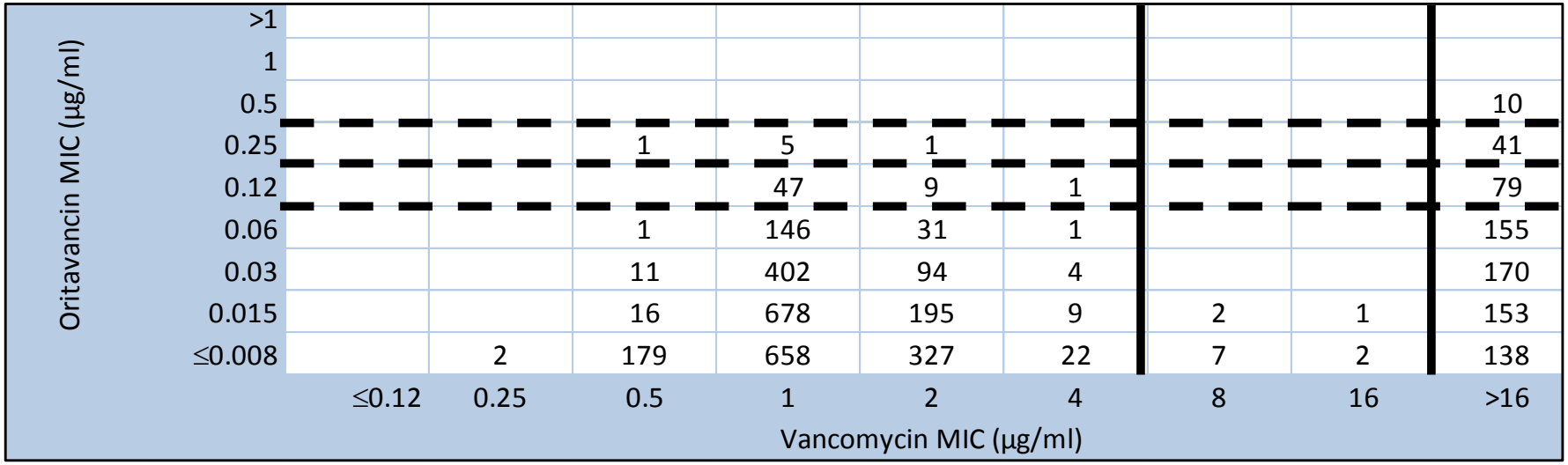
- SENTRY Antimicrobial Surveillance Program (USA and Europe) isolates for 2011-2013, includes 26,994 strains
  - *S. aureus* (17,717) and CoNS (2,073)
  - Enterococci (3,598)
  - Beta-haemolytic (2,357) and viridans group streptococci (1,248)
- Reference broth microdilution methods
- MIC for vancomycin compared directly to oritavancin using three possible breakpoints (≤0.06, ≤0.12, ≤0.25 µg/ml)
  - Target predictive accuracy at ≥95.0%, when minimizing false-susceptible errors
  - ECOFFs were calculated, where appropriate

Figure 1. *S. aureus* (17,717 strains) isolated in 2011-2013 from the USA and Europe[a]



a. Broken horizontal lines show possible breakpoints having acceptable predictive values (≥95.0%)

Figure 6. Enterococci (3,598 strains) isolated in 2011-2013 from the USA and Europe[a]



a. Broken horizontal lines show possible breakpoints having acceptable predictive values (≥95.0%)

Conclusions

- Surrogate use of vancomycin to predict oritavancin susceptibility appears possible with accuracy rates dependent upon the selected susceptible clinical breakpoints by regulatory agencies (USA-FDA, EMA/EUCAST)

- Candidate breakpoints at ≤0.12 µg/ml (ECOFF) for staphylococci results in 99.76-99.79% accuracy

- Candidate breakpoints at ≤0.12 µg/ml for *Enterococcus* spp. and viridans group streptococci were also very acceptable with 99.28-99.74% accuracy

CarbaNP Ad Hoc WG Report

- Dr. Robin Patel

Questions of the Subcommittee

- Should we develop guidance as it relates to molecular detection of resistance (e.g., issue of mecA-positive *Staphylococcus aureus* that test cefoxitin (and/or oxacillin) susceptible)?
- Should we address lack of standards for "direct" AST from blood culture bottles, etc.?

NOTE: Methodology WG voted unanimously on both issues to further pursue these 2 issues