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Summary Minutes
Subcommittee on Antimicrobial Susceptibility Testing
Hyatt Regency Baltimore
Baltimore, Maryland
23-25 June 2013

A meeting of the CLSI Subcommittee on Antimicrobial Susceptibility Testing was held on 23-25 June 2013, at the Hyatt Regency Baltimore, Baltimore, Maryland. The following were in attendance:

Jean B. Patel, PhD, D(ABMM) **Chairholder**	**Centers for Disease Control and Prevention**
Franklin R. Cockerill, III, MD **Vice-Chairholder**	**Mayo Clinic**
Richard B. Thomson, Jr., PhD **Consensus Committee on Microbiology** **Chairholder**	**Evanston Hospital, NorthShore University HealthSystem**
John H. Rex **Consensus Committee on Microbiology** **Vice-Chairholder**	**AstraZeneca**

Members Present

Jeff Alder, PhD	Bayer HealthCare
Patricia A. Bradford, PhD	AstraZeneca Pharmaceuticals
George M. Eliopoulos, MD	Beth Israel Deaconess Medical Center
Dwight J. Hardy, PhD	University of Rochester Medical Center
Janet A. Hindler, MCLS, MT(ASCP)	UCLA Medical Center
Stephen G. Jenkins, PhD, D(ABMM),F(AAM)	Weill Cornell Medical College of Medicine
James S. Lewis, II, PharmD	University of Texas Health Science Center
Linda A. Miller, PhD	GlaxoSmithKline
Mair Powell, MD, FRCP, FRCPath	MHRA
John Turnidge	SA Pathology
Melvin P. Weinstein, MD*	Robert Wood Johnson Medical School
Barbara L. Zimmer, PhD	Siemens Healthcare Diagnostics Inc.

* Attended 23 June only

Advisors Present

Steven D. Brown, PhD, ABMM	
Karen Bush, PhD	Indiana University
William A. Craig, MD	University of Wisconsin School of Medicine
John Farley, MD*	FDA/CDER
Cynthia L. Fowler, MD	MF Health and Sciences Consulting
Howard Gold, MD	Beth Israel Deaconess Medical Center
Romney M. Humphries, PhD, D(ABMM)	UCLA David Geffen School of Medicine
Brandi Limbago, PhD	Centers for Disease Control and Prevention
Melissa B. Miller, Ph.D., D(ABMM)	UNC School of Medicine
Sumathi Nambiar, MD, MPH	FDA/CDER
David P. Nicolau, PharmD, FCCP, FIDSA	Hartford Hospital
Robin Patel, MD	Mayo Clinic
Sandra S. Richter, MD, D(ABMM)	Cleveland Clinic
Flavia Rossi, MD	University of Sao Paulo
Jeff Schapiro, MD	Kaiser Permanente
Audrey N. Schuetz, MD, MPH, D(ABMM)*	Weill Cornell Medical College/ NewYork-Presbyterian Hospital
Susan Sharp, PhD, D(ABMM)	ASM Representative from Kaiser Permanente-NW
Ribhi M. Shawar, PhD, D(ABMM)	FDA Ctr. for Devices/Rad. Health (CDRH)
Kerry Snow, MS, MT(ASCP)	FDA/CDER
Jana M. Swenson, MMSc	

* Substitution in place of Ed Cox

<u>Reviewers Present</u>

Vanessa Allen	Public Health Ontario
Paul G. Ambrose, PharmD, FIDSA	ICPD/Ordway Research
Francis Arhin	The Medicines Company
Robert E. Badal	International Health Management Assoc Inc.
Johanne Blais	Novartis Institutes for Biomedical Research
Sujata M. Bhavnani, PharmD	ICPD/Ordway Research Institute
Donald Biek, PhD	Cerexa, Inc.
Paul Bien	Trius Therapeutics
April Bobenchik	UCLA
Lynn Boyer	Siemens Healthcare Diagnostics
William B. Brasso	BD Diagnostic Systems
Linda C. Bruno, MA, MT(ASCP)	ACL Laboratories
Carey-Ann Burnham, PhD, D(ABMM)	Washington University School of Medicine
Kathy Burtner	Siemens Healthcare Diagnostics
Deborah Butler	GlaxoSmithKline
Laurent Chesnel	Cubist Pharmaceuticals, Inc.
Diane M. Citron, M(ASCP)	R.M. Alden Research Laboratory
Patricia S. Conville, MS, MT(ASCP)	FDA/Center for Devices and Radiological Health (CDRH)

Katie Coyle	BD Diagnostic Systems
Rob Crink	Merck and Co., Inc.
Ian A. Critchley, PhD	Cerexa, Inc.
Sharon K. Cullen, BS, RAC	Siemens Healthcare Diagnostics Inc.
Brian J. Currier	BD Diagnostic Systems
Jeanna Difranco-Fisher	Laboratory Specialists, Inc.
Christopher Doern	UT Southwestern Medical Center
Michael J. Dowzicky	Pfizer, Inc.
Evelyn Ellis-Grosse, PhD	E2g Consulting
German Esparza, BSc	Hospital Santa Clara
Robert Eusebio, MSHA, MT(ASCP)	Siemens Healthcare Diagnostics
Michelle Evans	Siemens Healthcare Diagnostics
Gina L. Ewald-Saldana, CLS(CA), MT(ASCP)	Siemens Healthcare Diagnostics Inc.
John Farley	U.S. Food and Drug Administration
Mary Jane Ferraro, PhD, MPH	Massachusetts General Hospital
Diane Flayhart	BD Diagnostic Systems
Robert K. Flamm, PhD	JMI Laboratories
Jody Fox	MIT
Lawrence V. Friedrich, PharmD	Cubist Pharmaceuticals, Inc.
Marcelo Galas	National Institute of Infections Diseases, Ministry of Health, Argentina
Barb Gancar	BioMerieux, Inc.
Monica Giguere	BD Diagnostic Systems
Tracy Gill	BD Diagnostic Systems
Carmen Giltner	UCLA
Beth P. Goldstein, PhD	Beth Goldstein Consultant
Meredith Hackel	International Health Management Assoc, Inc.
Henry S. Heine, PhD	Institute of Therapeutic Innovation
Patricia Hogan, MT(ASCP), MBA	Pfizer Inc
Denise Holliday, MT(ASCP)	BD Diagnostic Systems
Yang He	FDA/CDER
Akinobu Ito	Shionogi
Scott B. Killian	Thermo Fisher Scientific
Aryun (Eileen) Kim	AstraZeneca R&D, Infection Imed
Susan M. Kircher, MS, MT (ASCP)	BD Diagnostics
Cynthia C. Knapp, MS	Thermo Fisher Scientific
Laura M. Koeth, MT(ASCP)	Laboratory Specialists, Inc.
Kevin Krause	Cerexa, Inc.
Katherine Laessig	FDA
Brigitte Lefebvre	Laboratoire de santé publique du Québec
Blaine Leppanen	Blaine Healthcare Associates, Inc.
Dyan Luper, BS, MT(ASCP)SM	BD Diagnostic Systems
Linda M. Mann, PhD, D(ABMM)	Consultant
Maureen Mansfield	Thermo Fisher Scientific
Ronald Master, MS, SM(AAM)	Quest Diagnostics Nichols Institute

Amy J. Mathers, MD	Univ. of Virginia School of Medicine
Jorge Matheu	PAHO
Sandra McCurdy	Cubist
Hiroshige Mikamo, MD, PhD	Aichi Medical Univ Graduate School of Medicine
Dr. Greg Moeck	The Medicines Company
Ian Morrissey, MBA, PhD, FRSM	IHMA Europe Sàr
Ross Mulder, MT(ASCP)	BioMerieux, Inc.
Susan D. Munro	Independent Consultant
Jennifer O'Connor	Siemens Healthcare Diagnostics Inc.
Susan O'Rourke	BD Diagnostic Systems
Ryan Owen	FDA/CDER
Elizabeth Palavecino, MD	Wake Forest Univ Baptist Medical Center
Samir Patel, PhD, FCCM	Public Health Ontario
Armando Perez-Cardona	Jackson Memorial Hospital
Chris Pillar	Micromyx
Dionne Price	FDA/CDER
Kerian Grande Roche	FDA/CDER
Darcie E. Roe-Carpenter, PhD, CIC, CEM	Siemens Healthcare Diagnostics Inc.
Helio S. Sader, MD, PhD	JMI Laboratories
Nicole Scangarella-Oman	GlaxoSmithKline
Paul C. Schreckenberger,PhD,D(ABMM),F(AAM)	Loyola University Medical Center
Dale A. Schwab, PhD, D(ABMM)	Quest Diagnostics, Nichols Institute
Katherine Sei	Siemens Healthcare Diagnostics
Alisa Serio	Achaogen
Sharon Shinn	Siemens Healthcare Diagnostics Inc.
Dee Shortridge	BioMerieux, Inc.
Carole Shubert	BioMerieux, Inc.
Simone Shurland	FDA/CDER
Jennifer Singelyn	BD Diagnostic Systems
Jennifer Smart	Theravance Inc.
Janine Spafford	BD Diagnostic Systems
Brad Spring	BD Diagnostic Systems
Gregory G. Stone	AstraZeneca Pharmaceuticals
Debora A. Sweeney	Micromyx, LLC
Kim Sweeney	Rempex Pharmaceuticals
Kazuhiro Tateda, MD, PhD	Toho University School of Medicine
Susan Thomson	Mast International
Laurie D. Thrupp	Univ. of California Irvine Medical Ctr.
Yun F (Wayne) Wang	Emory University School of Medicine/Grady Memorial Hospital
Nancy Watz	Stanford Hospital and Clinics
Frank O. Wegerhoff, PhD	Covance Central Laboratory Svcs., Inc.
Matthew A. Wikler, MD, MBA, FIDSA	The Medicines Company
Anne Windau	Laboratory Specialists, Inc.
Gregory Williams, PhD	Cerexa, Inc.
Teresa Wong	Siemens Healthcare Diagnostics Inc.

Sarah Wood	Siemens Healthcare Diagnostics Inc.
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Mary K. York, PhD, ABMM	MKY Microbiology Consulting

CLSI Staff

Tracy A. Dooley, BS, MLT (ASCP)
Erica Berlanger
Glen Fine, MS, MBA, CAE
Luann Ochs, MS
Jenny Sarkisian, MLS(ASCP)^{CM}

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I. MEETING/OPENING REMARKS

Dr. Jean Patel called the meeting to order at 8:00 a.m. on Monday, 24 June 2013. With this meeting being the 1st one operating under the new structure, she gave an overview of the activities of the various Ad Hoc Working Groups (WGs). All WGs have been active since the January meeting with several bringing breakpoint recommendations to the subcommittee at this meeting. Currently the new structure has four standing WGs:

- Text and Tables
- Quality Control
- Methodology
- Breakpoint (this WG will be forming soon)

The Methodology WG led by Drs. Brandi Limbago and Steve Jenkins held their 1st meeting yesterday, addressing various topics and issues of the Ad Hoc WGs that report to the Methodology WG such as:

- M100 Clean-up Ad Hoc WG lead by Drs. Susie Sharp and Mary Jane Ferraro presented recommendations on items in M100 that need further review (eg, extrapolation comments, drugs that can be deleted due to non- or decreased-usage, and outdated supplemental/screening tests).

  These recommendations will be considered and prioritized by the Methodology WG and additional Ad Hoc WGs to address specific items will be formed as needed.

- Joint CLSI/EUCAST Polymyxins Ad Hoc Working Group led by Dr. John Turnidge as the CLSI Ad Hoc WG Chair discussed the various testing challenges the WG is trying to address.

Dr. Patel also discussed the Ad Hoc WGs charged with the task of document revision and/or development that report directly to the subcommittee including:

- M45 Ad Hoc WG led by Dr. Sandy Richter, Chairholder and Ms. Janet Hindler, Vice-Chairholder. This WG will revise and update the M45 document.
- M23 Ad Hoc WG led by Dr. Mair Powell, Chairholder and Mr. Kerry Snow, Vice-Chairholder. This WG will revise and update the M23 document.
- PK/PD Ad Hoc WG led by Drs. Linda Miller and Paul Ambrose, Co-Chairholders. This WG will be developing a new document with their 1st priority being to generate PK/PD content for the M23 document and then generating a larger PK/PD guidance document for CLSI and global use.

Dr. Patel then noted the impact of all the recent work this subcommittee has done including updates from FDA on drug labels that are now consistent with CLSI breakpoints (eg, meropenem and most recently ceftaroline).

Lastly, Dr. Patel reviewed the purpose of the subcommittee's mission statement that is provided in electronic file folder 4 - References for Use on the meeting CD, noting that the ultimate purpose of the

subcommittee's mission is to provide useful information to enable laboratories to assist the clinician in the selection of appropriate antimicrobial therapy for patient care.

II. CLSI UPDATE

Ms. Luann Ochs, Senior Vice President of Operations with CLSI welcomed everyone to the meeting and gave an overview of some of the change happening at CLSI including:

- The launch of the new electronic eM100 in March which includes M100, M02, M07, M11, and M45 with all content of M100 being in an interactive and searchable format.

  CLSI is planning training webinars in the fall to show all the user features of the eM100 software including customizing for hospital specific formulary.

- Development CLSI Communities of Interest – microbiology is one of the 5 communities that will be on the CLSI website and will include articles, case studies, blogs, chat rooms, and links to other microbiology related websites.

Ms. Ochs then introduced CLSI staff present at the meeting as follows:

- Mr. Glen Fine, Executive Vice President;
- Tracy Dooley – Senior Project Manager and Staff Liaison to the Consensus Committee on Microbiology and Consensus Committee on Molecular Methods;
- Jenny Sarkisian – Project Manager for various projects under Microbiology as well as Quality Systems and Laboratory Practices and Hematology; and
- Erica Berlanger – Meeting Manager who coordinates all the logistics for these meetings.

III. UPDATES TO THE CURRENT AST DISCLOSURE SUMMARY

Dr. Patel asked the members and advisors for any updates to the current disclosure summary provided on the CD of meeting materials – no updates were provided so the summary in folder 2 of the materials is current.

IV. APPROVAL OF THE JANUARY 2013 MEETING MINUTES

Summary minutes of the 13-15 January 2013 subcommittee meeting were approved: **(11-0; 1 absent)**

V. CEFEPIME AD HOC WORKING GROUP PROPOSAL (Electronic Tab A)

The Cefepime Ad Hoc Working Group led by Dr. Paul Schreckenberger was charged with:

- Establishing a plan of action to conduct a full data review for cefepime for purposes of revaluating the cefepime breakpoints.

- Determining whether there are data for organism populations with known resistance mechanisms eg. ESBL, CTX-M, KPC etc.
- Examining patient outcome data (published and/or from clinical trials).
- Evaluating PK/PD at various dosing regimens taking into consideration recent findings on possible increased toxicity at higher doses and FDA response to same.

Dr. Schreckenberger presented various data including:

- Microbiological data
- Pharmacological data
- Pharmacokinetic data and results from patients
- Clinical data

Cefepime Breakpoint Conclusions:

- Epidemiologic Cutoff
  - Supports Susceptible BP of 1 µg/mL
- PK/PD
  - 2g/day – Support Susceptible BP of 1 or 2 µg/mL
  - 3-4 g/day – Support Susceptible BP of 2or 4 µg/mL
  - 6g/day – Support Susceptible BP of 8 µg/mL
- Clinical Data
  - Inconclusive – tendency for improved outcome when MIC's 1-4, Poorer outcome with MICs 8-16

Working Group Proposal:

Cefepime	S	I	R	Dosage
Current CLSI/FDA	≤8	16	≥32	1 g every 8 h or 2 g every 12 h (3-4 g/day)
Proposal	≤2	4	≥8	Covers all dosage ranges outside the urinary tract
WG #1	≤4	8	≥16	S-Does not cover 1-2g/day S-Does not capture all KPCs
WG#2	2	4-8	≥16	Intermediate range allows treatment with high dose

Subcommittee vote:

Motion – A motion was made and seconded to have S ≤2, S-DD 4-8, R ≥16 Approved 8-1; 2 abstain, 1 absent. Some of the discussion points to have an S-DD category:

- Part of definition of S-DD from Antifungal Document M27 - *implies clinical efficacy when higher than normal dosage of a drug can be used*. This term (S-DD) has been used in Antifungals for over 10 years.
- Would be a re-branding of I (intermediate) since it seems to be misunderstood although it says isolates treated with a higher dose of drug could be used to treat. Using S-DD helps define what I category really means. The term S-DD and its use is known in the Infectious Disease community.
- If isolate has a higher MIC, a higher dose could work
- S-DD communicates a clear message that the breakpoint is dose dependent and gets patients to the right dose.

Data for the disk correlates will be circulated after the meeting for a separate electronic vote.

Post Meeting: The below disk correlates for cefepime vs *Enterobacteriaceae* were approved with the following comment:

S	≥ 25 mm
S-DD	19-24 mm
R	≤ 18 mm

Cefepime comment:

(12) The interpretive criterion for susceptible is based on a dosage regimen of 1 g every 12 h. The interpretive criterion for SDD is based on dosing regimens that result in higher cefepime exposure, either higher doses or more frequent doses or both, up to approved maximum dosing regimens. See Appendix F for more information about interpretive criteria and dosing regimens. Also see the definition of SDD in the Instructions for Use of Tables section.

The following definition for SDD was approved and will appear in the Instructions for Use of Tables section:

Susceptible-Dose Dependent (SDD) definition.

The "susceptible-dose dependent" category implies that susceptibility of an isolate is dependent on the dosing regimen that is used in the patient. In order to achieve levels that are likely to be clinically effective against isolates with MICs or disk zone diameters in this category, it is necessary to use a dosing regimen (i.e., higher doses, more frequent doses, or both) that results in higher drug exposure than the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum approved dosage regimen, since higher exposure gives the highest probability of adequate coverage of an SDD isolate. The dosing regimens used to set the SDD interpretive criterion are provided in Appendix E. The drug label should be consulted for recommended doses and adjustment for organ function.

Note: The SDD interpretation is a new category for antibacterial susceptibility testing, although it has been previously applied for interpretation of antifungal susceptibility test results (M27). The concept of SDD has been included within the Intermediate category definition for antibacterials. However, this is often overlooked or not understood by clinicians and microbiologists when an Intermediate result is

reported. The SDD category may be assigned when doses well above those used to calculate the susceptible breakpoint are approved and used clinically, and where sufficient data to justify the designation exist and have been reviewed. When the Intermediate category is used, its definition remains unchanged.

Also approved was a new appendix that provides dosing regimens used to establish susceptible or susceptible-dose dependent interpretive criteria (see Appendix E at end of these minutes).

VI. REPORT OF THE METHODOLOGY WORKING GROUP (Electronic Tab B)

Co-Chairholder - Brandi Limbago
Co-Chairholder - Stephen Jenkins

Members Present: Seth Housman, Romney Humphries, Laura Koeth, Sandra Richter, Darcie Roe-Carpenter, Katherine Sei, Susan Sharp, Ribhi Shawar, John Turnidge, Melvin Weinstein

1. Oral cephalosporins/UTI Ad Hoc Working Group (WG) report – Dr. Audrey Schuetz (Ad Hoc WG Chair)

   Dr. Schuetz presented previously submitted data supporting replacement of cephalothin with cefazolin as a predictor of oral cephalosporins for treatment of uncomplicated urinary tract infections (uUTI).

   Primary concerns:

   - Many laboratories do not test cephalothin and it overcalls resistance. Cefazolin is much more widely tested and it does a better job of predicting susceptibility and resistance to these other agents.

   - Automated systems issues: 1) many automated systems are not aligned with current CLSI breakpoints (may not have low enough dilutions); 2) most panels do not have antibiotics and/or applicable dilutions to address breakpoints applicable to treatment of uUTI.

   - Agents were originally selected based upon available data meeting a 95% agreement AND an FDA indication for treatment of UTI. (these criteria would have excluded cefdinir and cefprozil).

Discussion:

- Dr. James Lewis indicated that not including cefdinir may represent a problem for pediatrics and that the compound is very commonly used for this purpose at his institution.
- Dr. Jeff Schapiro stated that we should also attempt to target cefprozil because the AAP recommends its use for treatment of UTI.

- Dr. Audrey Schuetz clarified that these agents were excluded due to lack of an FDA indication and/or low urinary recovery of the drug.
- It was discussed that cefdinir and cefprozil should be included due to their use and to the high potency of these drugs in the urine.
- Concerns were raised re: providing uUTI breakpoints when laboratories won't know what type of infection the patient actually has.
- Dr. Mel Weinstein pointed out that we frequently allow for this if there is data re: efficacy and clinical utility.
- Dr. Lauri Thrupp opined that the "I" category is already meant to denote that such isolates could be used to treat uUTI.
- Concerns were raised that laboratories would only report results based upon the proposed uUTI breakpoints.
- Dr. Romney Humphries discouraged such granular guidance; e.g., instructing clinical laboratories how to report results.
- Dr. Laura Koeth stated that: cefpodoxime doesn't really fit the criteria outlined because cefazolin under-calls susceptibility by 10.7%.
- It was decided to include cefpodoxime in the second sentence of the comment stating that testing can be performed individually for this drug if cefazolin tests resistant.
- Dr. John Turnidge expressed concern that the cefazolin breakpoint MIC = 16 µg/mL lacks clinical data.
- Cefazolin also undercalls susceptibility to cefuroxime (6.3%) and cefdinir (8.8%).

Working Group Vote:

A motion was made and seconded to accept the proposal as outlined by Dr. Schuetz (cefazolin MIC ≤16 µg/mL Susceptible; ≥ 32 µg/mL Resistant) can be used to predict susceptibility to the following oral agents: cefaclor, cefpodoxime, cefuroxime axetil, cephalexin and loracarbef for *E. coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis.*

WG vote - 7 voted in favor; 3 were opposed; 1 member abstained
Opposed: Dr. John Turnidge: Wants clinical data to support a cefazolin breakpoint of 16 µg/mL.
Laura Koeth & Dr. Romney Humphries: Concerned about cefpodoxime; want to include cefdinir and cefprozil.

A follow-up motion was made and seconded: If cefazolin is adopted as a surrogate agent for other oral cephalosporins, remove the recommendation for cephalothin as a surrogate agent from the M100 document (in Table 1 and in Table 2)
WG vote – approved 10 to 0 with 1 abstention

Subcommittee Vote:

Motion – A motion was made and seconded to accept the proposal as outlined by Dr. Schuetz (shown below) with a new comment (11) stating that cefazolin can be used to predict susceptibility to the following oral agents: cefaclor, cefpodoxime, cefuroxime axetil, cephalexin and loracarbef for *E. coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis.*

Test/ Report group		Disk Content	Zone Diameter			MIC Interp Criteria		
			S	I	R	S	I	R
A	Cefazolin (systemic infections)	30µg	≥23	20-22	≤19	≤2	4	≥8
U	Cefazolin (for uUTI only)	30µg	≥15	-	≤14	≤16	-	≥32

Subcommittee vote - **Approved 7-3; 1 abstain; 1 absent**. Dr. Schuetz will work with the Text and Tables WG to finalize the wording and recommendations in M100. See post meeting update below.

Another motion was made and seconded to add an additional sentence to new comment (11) stating that cepodoxime, cefuroxime, and cefdiner may be tested individually because some isolates may be susceptible to these agents when resistant to cefazolin.

Subcommittee vote - **Approved 9-1; 1 abstain; 1 absent.**

Post meeting: The Oral cephalosporins/UTI Ad Hoc Working Group and Text and Tables Working Group decided on the following verbiage for comments 19 and 20 for Cefazolin (surrogate test for uncomplicated UTI) listed under Oral Cephems with a "U" indication:

"(19) Rx: Cefazolin results predict results for the oral agents cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime axetil, cephalexin and loracarbef when used for therapy of uncomplicated UTIs due to *E. coli*, *K. pneumoniae*, and *P. mirabilis*. Cefpodoxime, cefdinir, and cefuroxime axetil may be tested individually because some isolates may be susceptible to these agents while testing resistant to cefazolin.

(20) To predict results for oral cephalosporins when used for therapy of uncomplicated UTIs, testing cefazolin is preferred to testing cephalothin."

For cephalothin under the parenteral cephems section the following sentence was added to the box to emphasize preference of use of cefazolin for prediction: "To predict results for oral cephalosporins when used for therapy of uncomplicated UTIs, testing cefazolin is preferred to testing cephalothin."

Additionally, the comment for cephalothin was changed to emphasize that it predicts susceptibility and not resistance to the listed drugs: "Cephalothin interpretive criteria can be used only to predict ~~results~~ **susceptibility…"**

For Table 1A, cephalothin was replaced with cefazolin under Group U, and the phrase "surrogate test for uncomplicated UTI" was added to cefazolin.

2. M100 Cleanup Ad Hoc Working Group Report – Dr. Susan Sharp (Ad Hoc WG Co-Chair)

The below recommendations were presented as guidance. It is perceived that the Methodology WG will review the suggestions below, prioritize the work and then another Ad Hoc WG would be formed to work on the task. The suggestions from the M100 Ad Hoc WG include:

- Extrapolation comments (eg, using the results from one drug to infer the results of other drugs): Review to ensure that they are supported by sufficient data, and that they are similarly formatted throughout the document. (No specific examples of poor comments were given).
- Remove drugs that are no longer used or no longer available. Strong recommendation that this would go into an archival section in case the information were needed at some future date. Furthermore, drugs widely used in other countries should be added and included. It would be important to have representation from other countries where different drugs are used.
- Review documents for outdated supplemental/ screening tests.

  Dr. Richard Thomson indicated that we should remember that we have agreed previously that these will have a large role, but that the question continues to be *where* these tests belong in the document (or as a separate document).

- Consider developing an 'expert rules' guideline, to include the 'chart comments' which are recommendations for reporting to clinicians.
  This could be a large undertaking.

- Review for Rx and Rx-like comments, some of which are misleading and may even be dangerous. A list of these has been compiled by the Ad Hoc WG.

3. Intrinsic Resistance Ad Hoc Working Group Report – Dr. Barbara Zimmer (Ad Hoc WG Chair)

This was mainly an informational presentation; single item proposed for a vote.

When the intrinsic resistance table was created for the non-fermenters, aminopenicillins were inadvertently omitted. The WG had proposed adding it back to the comment at the bottom of the Appendix 2B.2 table, either as a class (aminopenicillins) or an agent (ampicillin), in the comment that starts "Nonfermentative gram-negative bacteria are universally resistant to…"

During discussion, several people pointed out the several species of non-fermenters are NOT intrinsically resistant to ampicillin. Also, as new species are identified in laboratories, the question was asked whether we will know if this statement is actually true. Therefore, it was proposed to make the change in the table, to only apply to the four non-fermenters listed therein.

Discussion pointed out that the comment at the bottom should also be modified to make it consistent.

Working Group Vote:

Motion #1: Add ampicillin to Table in appendix B.2, replacing ticarcillin-clavulanic acid.
10 in favor, 0 opposed, 1 abstain

Motion #2: Modify existing comment to replace beginning verbiage with "These nonfermentative…" 10 in favor, 0 opposed, 1 abstain

Subcommittee vote: The subcommittee approved these recommendations from the WG – **Approved 11-0; 1 absent.**

4. Data Analysis Ad Hoc Working Group Report – Dr. John Turnidge (Ad Hoc WG Chair)

This group should be absorbed into the routine function of the Methodology Working Group such that consistent data analysis becomes part of our Methodology.

Very nice presentation, raised questions about inter-laboratory reproducibility and testing variation. There is considerable data to suggest that this is a significant issue, but CLSI guidance only really addresses it for QC studies. Suggested that we might consider this for other data requirements in support of breakpoints, zone diameters, etc.

5. Joint CLSI/EUCAST Polymyxins Ad Hoc Working Group – Dr. John Turnidge (CLSI Ad Hoc WG Chair)

This is a collaborative WG between CLSI and EUCAST, charged with setting colistin/polymyxin B breakpoints for the *Enterobacteriaceae*.

Large number of challenges associated with polymyxins as a class, including the fact that they are a mixture of molecules (unknown whether the different molecules result in different MICs), they are large, and very highly charged (positive charges).

The charge issue is a major hurdle; it is well established that polymyxins stick to plastic in MIC trays (and in beakers, flasks, tubing, etc.).

Polymyxins are a mixture of compounds (this is true of both polymyxin B and Colistin). Not clear if the components have the similar/same potency.

Addition of Tween 80 lowers MICs ranges, but does not impact the inter-laboratory variation.

Discussion:

- Dr. Turnidge's recommendation: Do not add Polysorbate 80 to the test systems. 1) Its addition only changes the metric; it doesn't change the outcome; 2) most of the *extensive* literature is based on data without Polysorbate 80.

  Additional question: Does CLSI need to mandate the features/ characteristics of trays for BMD panels?

- Dr. William Craig stated that serum ultrafiltrate is a more biologically relevant molecule. In his opinion, it should be included with testing so we have a sense of how it would impact AUC/ MIC.

- Dr. Katherine Sei suggested that as an interim effort changing the QC organism from *E. coli* to another with MICs closer to the breakpoints would be helpful. An organism as *Pseudomonas aeruginosa* for which the MICS are higher might be considered. Then, we'll see more reproducible data because we are nearer the available range after plastic saturation.

- Dr. James Lewis pointed out that in data presented previously by Dr. Helio Sader, use of Polysorbate 80 in the panels helped to separate populations of susceptible organisms from resistant ones.

  PROs for adding Polysorbate 80: The sticking issue will be reduced substantially and this may improve variation between plastics from various manufacturers. This may also result in better differentiation of susceptible from resistant strains.

  CONs: We would lose all historic data; re the polymyxins; it doesn't improve assay variance.

Working Group Vote:

Motion: Maintain a reference method that does NOT include Polysorbate 80, but encourage further development with its inclusion in test systems.

9 in favor; 1 opposed; 1 abstain

Opposed vote - Dr. Romney Humphries: In the range we're discussing, the ability to separate susceptibility from resistance is compromised

Subcommittee vote:

Motion – A motion was made and seconded to proceed with testing using polysorbate 80 – **Approved 10-0; 1 abstain, 1 absent.**

6. Fluoroquinolone Disk Diffusion Ad Hoc Working Group Report – Dr. Cynthia Fowler (Ad Hoc WG Chair)

A study is currently being conducted to assess validity and utility of nalidixic acid (NA) disk test for *Salmonellae*:

- Investigation by Dr. Robert Skov (Pilot study data presented Jan 2013): Detection of reduced susceptibility to fluoroquinolones for salmonellae spp using alternative fluoroquinolone disks.

- Materials and methods

  – 126 isolates
  – Examined by PCR for qnr, QRDR and aac6
  – 43 isolates with no identified resistance mechanisms
  – 37 isolates with qnr genes
  – 45 isolates with QRDR mutations
  – 1 isolate with an aac6-Ib-cr gene
  – Possible also an additional resistance mechanism – not identified

  Disks (µg)
  – Ciprofloxacin 5
  – Ofloxacin 5
  – Levofloxacin 5
  – Nalidixic acid 30
  – Ciprofloxacin 1
  – Enoxacin 10
  – Norfloxacin 2
  – Pefloxacin 5

  MIC
  – BMD, Frozen panels, Trek ML1FNFQ, lot 12494
    - Ciprofloxacin 0.016 – 16 mg/L
    - Levofloxacin 0.016 – 32 mg/L
    - Ofloxacin 0.016 – 32 mg/L
    - Nalidixic acid 0.016 – 32 mg/L

  QC

  E.coli ATCC 25922 and *P. aeruginosa* ATCC 27853

• Summary/Conclusion:

- By MIC using current CLSI break points, all three FQ (CIP, LVX, OFX) distinguished between isolates with and without resistance mechanisms.
- By DD neither CIP 5µg, LVX 5, OFX 5 or NA 30 were able to reliably distinguish isolates with resistance mechanisms from WT.
- Alternative disks were identified
- Pefloxacin 5 was able to reliably distinguish between isolates with and without resistance mechanisms on all tested batches of MH agar
- Pooling all results (readers, media etc) a breakpoint of

  S≥ 25 mm
  R< 25 mm

  yielded a sensitivity of 100%
  specificity of 99,6%

- Subsequent testing demonstrated that pefloxacin disks from different manufacturers did not provide reproducible results. Efforts are underway to identify an alternative disk.

• Next Steps:

Goal is to have a reliable, robust, low cost screen test available for publication in the next edition of M100 (M100-S25).

• Anticipate presentation of data package to SC in Jan 2014

7. List of Susceptibility Testing Issues Identified to Date Requiring Possible Action by Methodology Working Group

The WG reviewed the list provided in the agenda materials (file 2 in Tab B). Issues that appeared to have most support included:

- *There is a need for guidance on how to test staphylococci that don't grow well in broth - alternate methods may be required.
- There is a need for data such that vancomycin MIC interpretive criteria might be developed for gram-positive anaerobes.

- Standardized criteria for what constitutes a good surrogate agent for antimicrobial susceptibility testing are needed.

- An accuracy assessment for vancomycin susceptibility testing, establishment of recommendations should be considered for interpretation of the testing results (in light of IDSA treatment guidance).

8. A request was made by Rempex Pharmaceuticals that minocycline be placed in its own box in Tables 1 and 2B-2 when testing *Acinetobacter* spp.

   Dr. Kim Sweeney (representing Rempex Pharmaceuticals) reported that laboratories are using resistance to tetracycline to predict resistance to minocycline, although the data do not support this. The comment that accompanies that drug class is misleading to laboratories resulting in widespread over-calling of minocycline resistance.

   The WG reviewed the comment on pg. 25 of M100 explaining criteria for inclusion of drugs in a single box, which states that such agents should have similar interpretive results (S, I, R) and clinical efficacy…. When no 'or' connects drugs in the same box, testing of one agent cannot be used to predict results for the other.

   During the discussion, it was mentioned several times that tetracycline probably shouldn't be in the table at all, and that its inclusion was almost certainly intended to be as a surrogate.

Working Group Vote:

Motion: Place minocycline in its own box in Table 1 and Table 2B-2 of M00, separate from tetracycline and doxycycline. 8 in favor; 0 opposed; 3 abstentions

Subcommittee vote:

Motion – A motion was made and seconded to put doxycycline, minocycline, and tetracycline all in their own boxes in Table 1 and Table 2B-2 **- Not Approved – 6-4; 1 abstain; 1 absent.** Reasoning – work needs to be done on the tetracycline class for *Staphylococcus* and *Acinetobacter*.

Another motion was made and seconded to put minocycline in its own box for Acinetobacter in Table 1 and Table 2B-2 – **Approved 10-0; 1 abstain, 1 absent.**

VII. CEFTRIAXONE/*ENTEROBACTERIACEAE* BREAKPOINT CONSIDERATIONS (Electronic Tab C)

Dr. Pranita Tamma from John Hopkins University School of Medicine provided an informational discussion on a paper for which she was an author titled Outcomes of Children with *Enterobacteriaceae* Bacteremia with Reduced Susceptibility to Ceftriaxone: Do the Revised Breakpoints Translate to Improved Patient Outcomes?

She gave an overview of a retrospective study they conducted to compare clinical outcomes between children treated with ceftriaxone and those treated with broader-spectrum β-lactams for Enterobacteriaceae bacteremia with reduced susceptibility (MICs 4-8 μg/mL) to ceftriaxone according to the new CLSI interpretive criteria. Mortality and microbiological relapse were also evaluated using a multivariable logistic regression model. Results of the study having a total of 783 unique children during the study period with *Enterobacteriaceae* bacteremia showed that using the CLSI breakpoints prior to 2010, 76 children would have had clinical isolates resistant to ceftriaxone. With the revised breakpoints, 229 *Enterobacteriaceae* isolates would no longer be susceptible to ceftriaxone (>300% increase). Of the 136 children who met eligibility criteria, 63 children received ceftriaxone and 73 children received broader spectrum β-lactams. There was no difference in 30-day mortality (Odds ratio [OR] 0.81; 95% CI 0.31-2.59) or microbiological relapse (OR 0.97, 95% CI 0.36-2.66) between the groups. The conclusion was that more clinical data from a larger, multicenter study, are needed before the ceftriaxone breakpoints would be re-evaluated for children.

VIII. MALDI-TOF MS (Electronic Tab B)

Dr. Carey-Ann Burnham submitted an agenda item requesting the subcommittee consider some issues related to MALDI-TOF and the impact on susceptibility testing of newly described isolates identified using this method.

Dr. Patel outlined the need to collect data initially to see if there is a need to do additional susceptibility testing of the new isolates that emerge. This would be an ongoing activity and she proposed that Dr. Burnham enlist the assistance of other clinical microbiologists currently using MALDI-TOF to collect data. Dr. Patel asked that anyone willing to assist and provide data for this, to contact Dr. Burnham.

IX. REPORT OF THE QUALITY CONTROL WORKING GROUP (Electronic Tab D)

Co-Chairholder - Steven Brown
Co-Chairholder - Sharon Cullen

Members Present: Bill Brasso, Patti Conville, Janet Hindler, Ron Jones, Ross Mulder, Susan Munro, Frank Wegerhoff

Members Absent: Stephen Hawser, Michael Huband, Erika Matuschek, Bob Rennie

1. User QC Subgroup:

To clarify recommendations for routine QC for *Enterobacteriaceae* and non-fermenting gram-negative rods in Tables 2A, 2B-1 to 2B-5, M100-S24.

Background:

Questions from users have been received by members of the group regarding the necessity to test multiple QC strains when performing daily QC (includes "with each use") or weekly QC. If 2 or more QC strains have QC ranges in QC Tables 3 and 4 do all have to be tested? Also when a physician requests a single drug for additional susceptibility testing, is more than one QC strain necessary?

Proposal:

- Identify *E. coli* ATCC® 25922 for *Enterobacteriaceae and Pseudomonas aeruginosa ATCC®* 27853 for non-fermenters as the routine QC strain for most antimicrobial agents.
- List the exceptions where a different QC strain should be tested

Rationale:

- Prefer to test QC strains with similar growth requirements for the clinical isolates tested (e.g. *E. coli ATCC® for Enterobacteriaceae and Pseudomonas aeruginosa* ATCC® 27853 for non-fermenters).
- If this QC strain has no QC range for an antimicrobial agent or does not provide optimum QC for the antimicrobial agent (e.g. MIC QC range very high or very low), recommend other QC strains for that antimicrobial agent.
- Minimize need for multiple QC strains when testing single agents
- Note: no change in recommendation to use *Escherichia coli* ATCC® 35218 for inhibitor combination agents.

Working Group Vote: Approved 7-0; 4 absent

Subcommittee vote:

Motion – A motion was made and seconded to accept the QC WG recommendations as shown below – **Approved 10-0; 2 absent.**

Table 2A:

Routine Quality Control (QC) Recommendations (See Tables 3A and 4A for acceptable QC ranges.)
***Escherichia coli* ATCC®* 25922**
***Pseudomonas aeruginosa* ATCC® 27853 (for carbapenems)**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**

Table 2B-1:

Routine QC Recommendations (See Tables 3A and 4A for acceptable QC ranges.)
***Pseudomonas aeruginosa* ATCC® 27853**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**
NOTE: DELETED FROM BOX: *Escherichia coli* ATCC® 25922

Table 2B-2:

Routine QC Recommendations (See Tables 3A and 4A for acceptable QC ranges.)
***Pseudomonas aeruginosa* ATCC® 27853**
***Escherichia coli* ATCC® 25922 (for tetracyclines and trimethoprim-sulfamethoxazole)**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**

Table 2B-3:

Routine QC Recommendations (See Tables 3A and 4A for acceptable QC ranges.)
***Pseudomonas aeruginosa* ATCC® 27853**
***Escherichia coli* ATCC® 25922 (for chloramphenicol, minocycline, and trimethoprim-sulfamethoxazole)**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**

Table 2B-4:

Routine QC Recommendations (See Tables 3A and 4A for acceptable QC ranges.)
***Pseudomonas aeruginosa* ATCC® 27853**
***Escherichia coli* ATCC® 25922 (for chloramphenicol, minocycline, and trimethoprim-sulfamethoxazole)**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**

Table 2B-5:

Routine QC Recommendations (See Table 4A for acceptable QC ranges.)
***Pseudomonas aeruginosa* ATCC® 27853**
***Escherichia coli* ATCC® 25922 (for chloramphenicol, tetracyclines, sulfonamide, and trimethoprim-sulfamethoxazole)**
***Escherichia coli* ATCC® 35218 (for β-lactam/β-lactamase inhibitor combinations)**

2. Q&A:

– Topic: Using retrospective QC data to convert from daily (with each use) to weekly QC testing.

Question submitted from user and publish as Q & A

Previously, Antibiotic A was not on our routine test panel. When we were asked to test Antibiotic A on a patient's isolate, we tested the patient's isolate and performed QC testing for Antibiotic A on the same day. Now we want to begin testing Antibiotic A routinely. Can we use the last 20 consecutive

QC results (obtained over the past year) to justify conversion from daily to weekly QC testing of Antibiotic A? Only one QC result for antibiotic A was out of control during the past 20 days on which we tested Antibiotic A and this corrected upon repeat testing.

Response:

Yes, you have demonstrated satisfactory performance of "daily QC" by obtaining acceptable results from at least 20 consecutive test days and you can now implement weekly QC testing. Consecutive test days", "or Testing with each use" refers to the actual number of days when a QC test is performed; it is not meant to indicate consecutive calendar days. Don't forget to maintain the records for conversion from daily to weekly QC testing indefinitely. The Subcommittee will clarify wording to address this situation in the next editions of the M02 and M07 standards.

Rationale:

When an antimicrobial agent not previously tested is added to a laboratory's AST battery, it is important to document that the laboratory can obtain accurate and reproducible results for that drug. This is typically done by testing QC strain(s) each day patient's isolates are tested initially and then converting to a weekly QC testing schedule once satisfactory performance with daily testing is documented. The 20-30 day plan or 15 replicate plan is generally used to convert from daily to weekly QC.

If a patient's isolates are tested with the drug infrequently, the number of QC results needed to convert from daily to weekly QC can span many days or weeks. Reproducibility can be assessed prospectively or retrospectively. This scenario represents a robust test of QC strain performance since it is likely that more staff and a greater variety of lots of materials are used for QC testing.

Working Group Vote to include this Q&A in M100-S24: Approved 7-0; 4 absent

Subcommittee vote: **Approved 10-0; 2 absent**

– Topic: One QC result out-of-range when performing weekly QC and no obvious error;

  Proposal: Ability to use previous weekly QC data from the same lot instead of testing 5 additional replicates (in accordance with statistical 95% random error).

Question based on message received by CLSI:

I am seeking assistance regarding the following; our laboratory was recently cited during a CAP inspection for not following the CLSI guidelines regarding an unacceptable MIC value for one drug per one QC organism per one instance with weekly QC done for the month of March. Repeat testing on said organism was okay the following day. (Please keep in mind that this was only one instance for one drug on one QC organism; aside from this exception, our weekly controls are typically within expected ranges).

Response:

QC ranges are established based on multi-lab, multi-lot M23 QC Studies. Ranges are established to include ≥ 95% of the results. Therefore a small number of (random) out-of-range QC results may be obtained even when the test method is performed correctly and materials are maintained adequately. If the cause of the error can be reasonably determined, corrective action can be taken and satisfactory performance confirmed with a single QC repeat. However, if the cause of the error can't be reasonably determined, additional testing is needed to determine if the cause of the out-of-range result is due to random error, test conditions, or materials.

The Subcommittee will work on clarifying the wording in "Troubleshooting Out-of-Control Results" to Table 3C (or 4F) and modify M02 and M07 standards to provide additional guidance on troubleshooting and corrective action with the next publication. In addition, we will describe 2 alternatives to satisfy the requirement to have 5 QC results to evaluate by allowing use of retrospective QC (if the previous 4 QC results from the same lot of materials was acceptable) and the ability to test up to 3 QC replicates in a single day. These alternatives may detect problems faster and minimize cost while providing the same level of confidence in confirming acceptable performance.
(Note: rationale is given in text)

The below two examples will be published with the Q & A, and included in subsequent M2 and M7 QC sections:

Scenario #1
Ampicillin *E.coli* ATCC® 25922 Acceptable Range: 2-8 µg/mL

Week	Day	Lot #	Result	Action
1	1	3564	4	
2	1	3564	8	
3	1	3564	8	
4	1	3564	4	
5	1	3564	16	Out of Range. Repeat QC same day.
5	2	3564	8	In range. 5 acceptable in range QC tests for *E.coli* ATCC® 25922 and ampicillin with lot 3564. Resume weekly QC testing.

Conclusion: Random QC error

Scenario #2
Ampicillin *E.coli* ATCC® 25922 Acceptable Range: 2-8 µg/mL

Week	Day	Lot #	Result	Action
1	1	9661	4	
2	1	9661	8	
3	1	9661	16	Out of Range. Repeat QC same day.
3	2	9661	8	In range. 3 acceptable in range QC tests for *E.coli*

				ATCC® 25922 and ampicillin with lot 9661. Repeat WC 2 more consecutive days.
3	3	9661	8	In range.
3	4	9661	8	In range. 5 acceptable in range QC tests for *E.coli* ATCC® 25922 and ampicillin with lot 9661. Resume weekly QC testing.

Conclusion: Random QC error

Working Group Vote to include this Q&A in M100-S24: Approved 7-0; 4 absent

Subcommittee vote: **Approved 10-0; 2 absent**

3. Other Items – Preliminary Recommendations that the WG plans to bring back in January

a) QC testing recommendations for β lactam and carbapenem inhibitor combinations

- For avibactam combinations - *K. pneumoniae* 700603 (ESβL organism) is needed for adequate QC.
  - Compound active against TEM1 which is contained by *E. coli* 35218
  - Will propose *E. coli* 35218 as supplemental and *K. pneumoniae* as routine QC in 2015 publications (projected timing for avibactam combination availability). WG approved 7/0/4.

- For other β lactamase/β lactamase inhibitor combinations both QC strains adequate

  - Will revise recommendations (e.g., both acceptable, replace *E. coli* 35218 with *K. pneumoniae* 700603)
  - Request inclusion of disks with *K. pneumoniae* 700603 in future studies?

- Plan text/table cleanup to in 2014

  - Revise/combine statement about testing QC org with single drug to ensure org hasn't lost plasmid (footnotes b-e in Table 3A;b-f in Table 4A)
  - Revise Appendix for QC orgs
  - Update Troubleshooting Guide with all QC strain/antimicrobial agents

b) Evaluate the need for 20-30 day QC testing prior to implementing a new drug for susceptibility testing – proposed to WG by Christopher Doern, PhD, D(ABMM) on behalf of the Clinical Laboratory Practices Committee

Background - The CLSI M2/M7/M100 documents state that 20-30 day QC (or 15 replicate plan) must be performed prior to implementing a new drug for patient testing.

Objective – Collect a 20-30 day dataset for disk diffusion validations from multiple institutions and assess QC errors during those studies.

Hypothesis – Most meaningful QC failures will happen in the early phases of testing and further testing is unnecessary.

Preliminary Data/Future Plans:

- Solicited disk diffusion validation data for any bug/drug combination.
- Data collection is ongoing but suggest low failure rate.
  - 6 total QC failures occurred over a total of >1,800 data points (2 institutions).
- QCWG suggestions for additional information
  - Experience when adding new drug (frequency of problems/success, cause of issues, # of replicates that would have detected problem)
  - Data may also be helpful for Tier 3 monitoring/reassessment

4. QC Text/Table Review

- Comprehensive review for Jan 2014 (2015 publication)
  - Request for volunteers
- Table 2:
  - Routine vs Supplemental
- Table 3A and 4A (QC acceptable ranges)
  - Routine vs Supplemental
  - Revise/combine footnotes
  - Consider separate sections for those with no breakpoints
- Appendix C
  - Routine vs Supplemental
  - Revise/combine footnotes
- Troubleshooting Guide
  - Add other drugs with ranges to *E. coli* 35218 and *K. pneumoniae* 700603 to statement about loss of plasmid
  - Add *K. pneumoniae* ATCC BAA1705 with similar comments for carbapenem inhibitor combinations
  - Other revisions for Jan 2014?

5. Tier 3 QC Review and Plans

- Reviewed data available to determine if signal warranted further action.
  - Signal <5% out of range: monitor

- Signal >5% out of range: get Tier 2 data, collect data <3 yrs old, reassess
- Signal >5% out of range, Tier 2 available, sufficient data: propose revision

- Will request recent data and review in Jan 2014
- Ad Hoc groups to review data then make recommendations January 2014
- Teicoplanin discussion/plans

  - Draft 3 teicoplanin distributed just prior to meeting with original Tier 2 data.
    - Adds M23 Tier 2 data from 1986 and similar 1991 study (blue)
    - Highlighted data without pluronic (purple).
  - Draft 4 with corrections reviewed in QCWG (errors in data entry in draft 3)
  - Clarified position on use of surfactants
    - Original Tier 2 Study most likely included surfactant in inoculum
    - Previous concerns about use of surfactant with teicoplanin primarily referred to preparation of stock solutions and panels.
    - Teicoplanin not as sticky as colistin and televancin (doesn't need surfactant when making stock solutions and panels)
    - Use of surfactant in inoculum some impact (lower shift).
  - QCWG recommends teicoplanin range change to 0.12 – 1 (current 0.25 -1) to be formally voted on in January 2014 after proper review or data.
    - Separate data with and without surfactant and identify the amount of surfactant in MIC well

Tier 3 QC Data/Action Plans

QC Strain (ATCC)	Antimicrobic	Method	Current Range	Action Recmd	Concern
P. aeruginosa 27853	Cefepime	Disk	24-30	Get original M23, reassess	Out high
H. influenzae 49247	Cefepime	Disk	25-31	Monitor	Out high
S. pneumoniae 49619	Cefepime	Disk	28-35	Monitor	Out high
E. coli 25922	Meropenem	Disk	28-34	Get original M23, reassess	Out high
K. pneumoniae 700603	βlactam/βlactamase inhibitors	Disk	No range	Monitor	Alternative for E. coli 35218
E. coli 25922	Cefixime	Disk	23-27	Get original M23, need addn data	Out low
E. coli 25922	Ampicillin	Disk	16-22	Better troubleshooting or reassess QC range	Out low, some double zones

QC Strain (ATCC)	Antimicrobic	Method	Current Range	Action Recmd	Concern
P. aeruginosa 27853	Etrapenem	MIC	2-8	Monitor	Out low
E. faecalis 29212	Teicoplanin	MIC	0.25-1	Recommend 4 dil range 0.12-1 based on original Tier 2 and current Tier 3 combined. Will pursue in Jan 2014	Mode from Tier 2 0.12, Tier 3 0.5 w/o surfactant. Shift lower with some media. 9% out low with current range.
S. aureus 29213	Minocycline	MIC	0.06–0.5	Request data/feedback	Mode at low end regardless of read time 16-20 hr
E. faecalis 29212	Minocycline	MIC	1–4	Request data/feedback	Mode at low end at 16 hrs, bimodal at 18 hrs, at middle of range at 20 hrs

QC Strain (ATCC)	Antimicrobic	Method	Current Range	Action Recmd	Concern
K. pneumoniae 700603	Ceftazidime	MIC	>16	Monitor/collect data	Verbal reports of some MICs at 16 from one lab
B. fragilis 25285	Pip/tazo	Agar MIC	0.12-1	Monitor	Out low (control M23 study Jan 2010)
H. influenzae 49247	Tigecycline	MIC	0.06-0.5	Monitor	Out high
S. pneumo 49619	Meropenem	MIC	0.06-0.25	Monitor	Bi-modal 0.06 to 0.12.
S. pneumo 49619	Cefuroxine	MIC	0.25-1	Request data/feedback	Mode at 0.25

X. CARBAPENEM/*ACINETOBACTER* AD HOC WORKING GROUP PROPOSAL (Electronic Tab E)

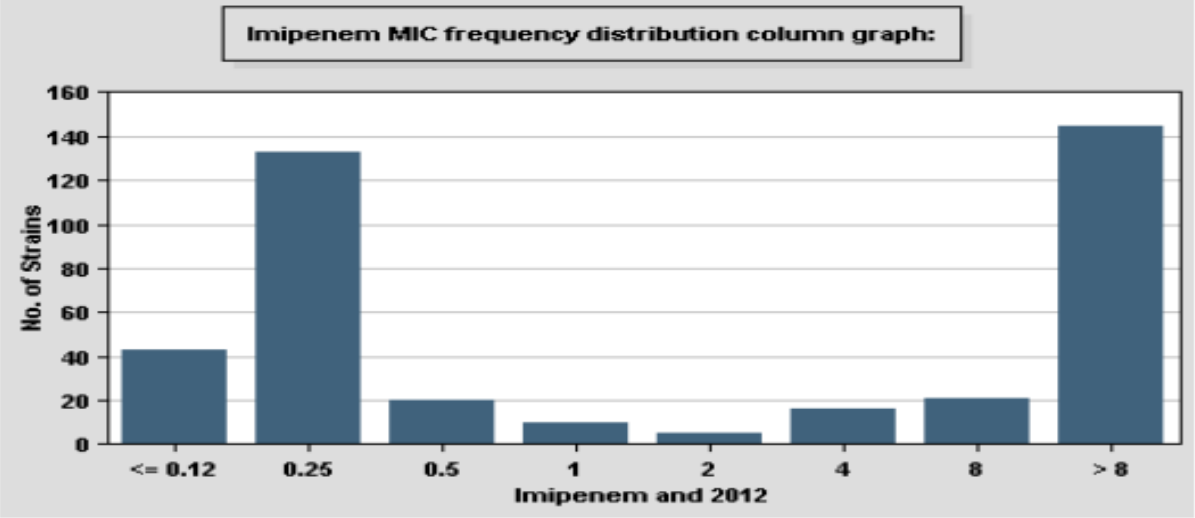
The Carbapenem/*Acinetobacter* Ad Hoc Working Group led by Dr. Jim Lewis was charged with re-examining the data that was presented June 2011 to the AST Subcommittee for doripenem as well as more recent data reflecting current carbapenem resistance issues among *Acinetobacter* spp. to make certain that the breakpoints for doripenem, meropenem, and imipenem are still applicable for *Acinetobacter* spp.

Considerations from June 2011 meeting:

- Historically, *Acinetobacter* MIC breakpoints have generally been the same as *Enterobacteriaceae*
- It is logical to build in a buffer zone to account for testing variation that occurs but generally this is only one MIC dilution
- The exceptions for a wider "I" range eg, have to be well rationalized (it was acknowledged that EUCAST has an intermediate range of 2-4 and this would be different now in the CLSI tables)
- The CLSI decision was based on the 1 hour infusion and not the 4 hour infusion as the 4 hour infusion is not in the US FDA label
- There were no clinical data at MIC = 2 presented for review (except for one complicated UTI) that would fit the subcommittee's definition of "I" where a higher than normal dosage of drug can be used.
- The subcommittee did not see any data on the MICs that would result with carbapenemases in *Acinetobacter*. It is suspected that they could be as low as MIC = 4 with certain carbapenemases.
- The "S" breakpoint selected (MIC = ≤1) covers all doses and mode of administration.
- The subcommittee did not review any data that would allow to conclude that the "I" range should include the different dosage regiments.
- The target attainment rates for *Acinetobacter* are more like *Enterobacteriaceae* but this specific data was not presented.
- No animal model data was presented.

Imipenem: *Acinetobacter* spp.
Validated: sentryMICValidated
North America
2012
Total: 393

MIC	<= 0.12	0.25	0.5	1	2	4	8	> 8	MIC_{50}	MIC_{90}
Count	43	133	20	10	5	16	21	145	1	>
Percent	10.94	33.84	5.09	2.54	1.27	4.07	5.34	36.90		
Cum Pct	10.94	44.78	49.87	52.42	53.69	57.76	63.10	100.00		



Meropenem: *Acinetobacter* spp.

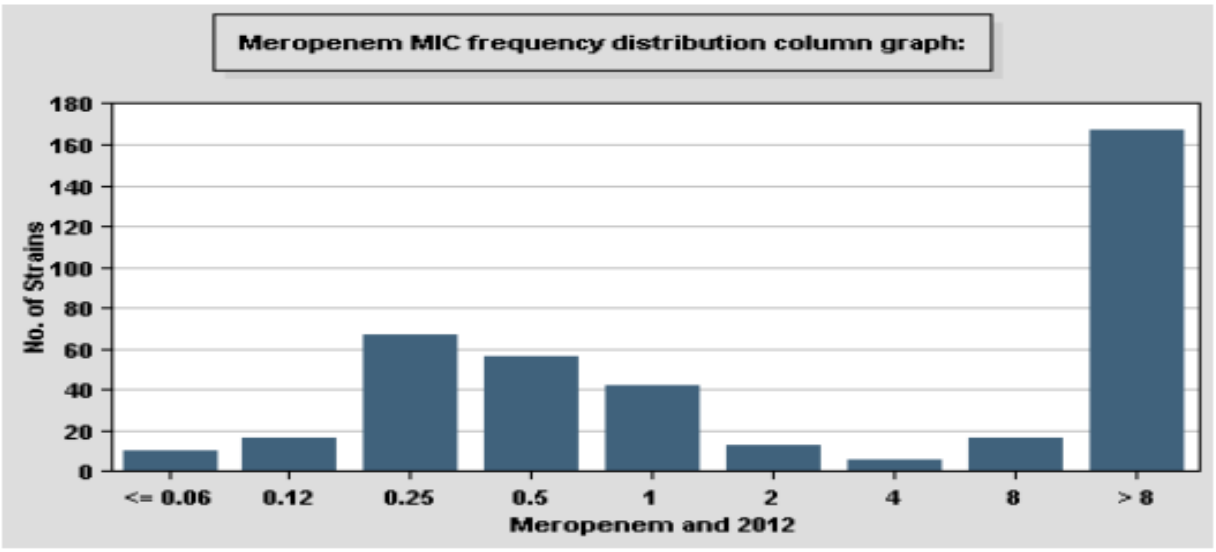
Validated: sentryMICValidated

North America

2012

Total: 393

MIC	<= 0.06	0.12	0.25	0.5	1	2	4	8	> 8	MIC_{50}	MIC_{90}
Count	10	16	67	56	42	13	6	16	167	2	>
Percent	2.54	4.07	17.05	14.25	10.69	3.31	1.53	4.07	42.49		
Cum Pct	2.54	6.62	23.66	37.91	48.60	51.91	53.44	57.51	100.00		



Doripenem: *Acinetobacter* spp.

Validated: sentryMICValidated

North America

2012

Total: 393

MIC	<= 0.06	0.12	0.25	0.5	1	2	4	8	> 8	MIC_{50}	MIC_{90}
Count	13	27	75	60	17	12	5	20	164	2	>
Percent	3.31	6.87	19.08	15.27	4.33	3.05	1.27	5.09	41.73		
Cum Pct	3.31	10.18	29.26	44.53	48.85	51.91	53.18	58.27	100.00		

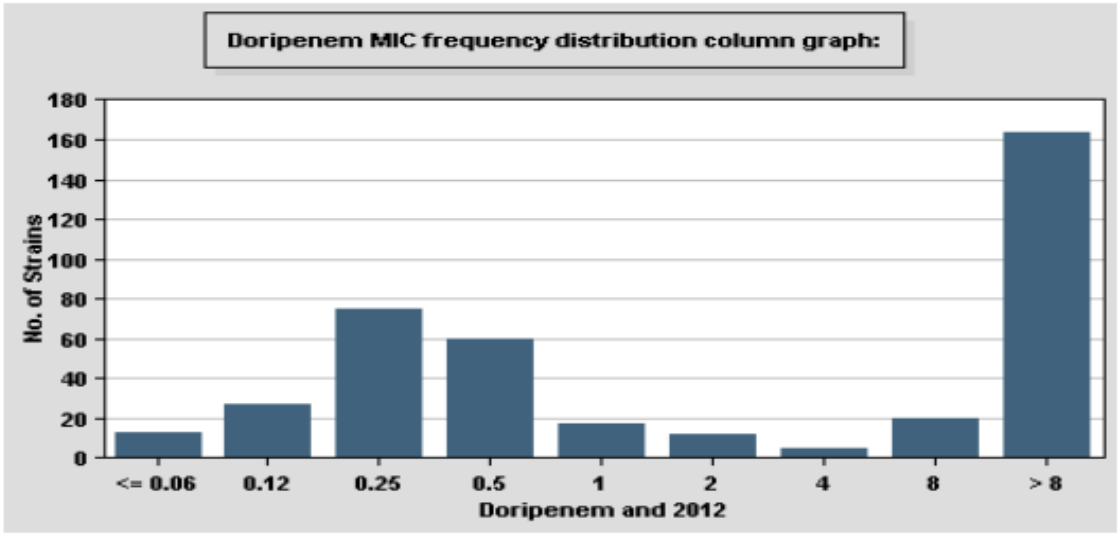
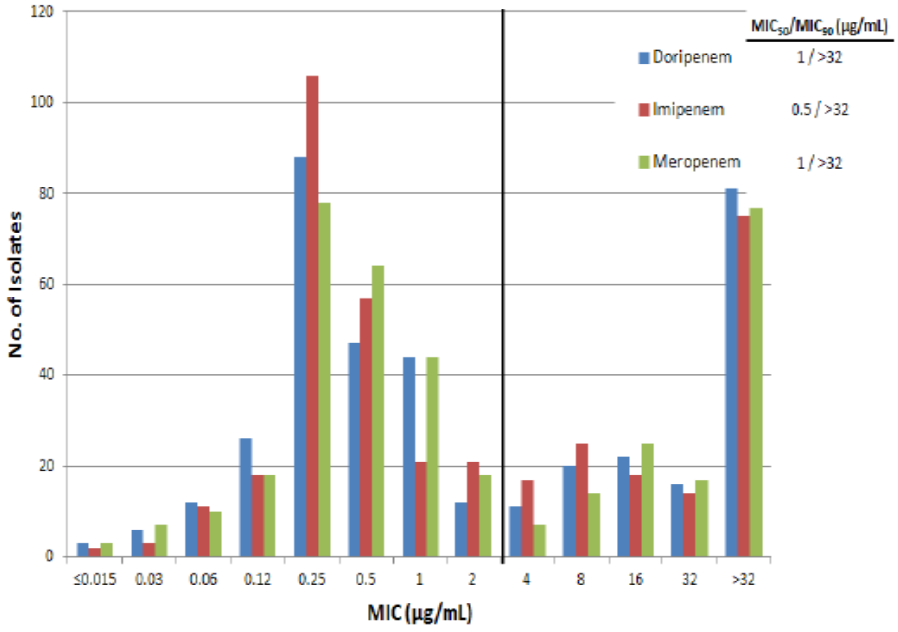


Figure 6. *Acinetobacter spp.* TRUST 13 (2009) Carbapenem MIC Distribution (n=388)



MICs and Resistance Mechanisms:

- 108 isolates of *A. baumanii* from San Antonio Military Medical Center 2006-2008: no isolates with OXA-23 or OXA-24 had mero, imi, or dori MICs ≤4.
- 350 isolates from Walter Reed National Military Medical Center. No carbapenemases at an MIC ≤4µg/mL.

Current FDA Breakpoints:

Imipenem	**Minimum Inhibitory Concentrations (µg/mL)**		
Pathogen	**S**	**I**	**R**
Enterobacteriaceae	≤1	2	≥4
Pseudomonas aeruginosa	≤2	4	≥8
Acinetobacter spp.	≤4	8	≥16

Meropenem	**Minimum Inhibitory Concentrations (µg/mL)**		
Pathogen	**S**	**I**	**R**
Enterobacteriaceae	≤1	2	≥ 4
Pseudomonas aeruginosa	≤ 4	8	≥ 16

*Note – generic meropenem label not updated reflects *Acinetobacter* BP of 4
*Doripenem FDA *Acinetobacter* spp. BP = 1

CLSI 2013 Breakpoints:

P. aeruginosa:

Drug/Dose	S	I	R
Imipenem 500mg q6h	2	4	8
Meropenem 1g Q8h	2	4	8
Doripenem 500mg q8h	2	4	8

Enterobacteriaceae:

Drug/Dose	S	I	R
Imipenem 500mg q6h	1	2	4
Meropenem 1g Q8h	1	2	4
Doripenem 500mg q8h	1	2	4

Thoughts from the Working Group:

- Appears to be clear population break for each drug at an MIC of 1 or 2
- No good animal data
- No good clinical data
- Do no harm – given the paucity of antibiotics for *Acinetobacter* spp. don't go too low
- Emphasize dose used for breakpoint setting and duration of infusion

Working Group Conclusion:

- By a vote of 8-0 the WG proposes a susceptible breakpoint of ≤2µg/mL for all 3 carbapenems at the specified doses. Intermediate = 4µg/mL, Resistant ≥ 8.

Subcommittee vote: The Subcommittee committee approved the below as follows:

Doripenem, Meropenem, Imipenem for *Acinetobacter* spp. S 2, I 4, R 8

Dosing:

Doripenem: 500 mg every 8 h
Meropenem: 1 g every 8 h or 500 mg every 6 h
Imipenem: 500 mg every 6 h

Approved 6-3; 1 abstain, 2 absent

Data for the disk correlates will be circulated after the meeting for a separate electronic vote.

Post meeting: The below disk correlates for doripenem, meropenem, imipenem for *Acinetobacter* spp were approved:

Drug	Zone Diameter (mm)		
	S	I	R
Doripenem	≥18	15-17	≤14
Imipenem	≥22	19-21	≤18
Meropenem	≥18	15-17	≤14

XI. REPORT OF THE TEXT AND TABLES WORKING GROUP (Electronic Tab F)

Co - Chairholder – Jana Swenson

Co - Chairholder – Maria Traczewski

Members Present: Janet Hindler, Dyan Luper, Linda Mann, Susan Munro, Jeffrey Schapiro, Dale Schwab, Tom Thomson, and Mary York

Members Absent: Flavia Rossi

Items presented for a vote by the subcommittee:

1. A suggestion was made by J. Hindler to add ceftaroline to Appendix A for *H. influenzae, S. aureus, S. pneumoniae* and β-hemolytic streptococci.

Working Group: Approved 9-0; 2 absent (see Appendix A at end of these minutes)

Subcommittee vote: **Approved 8-0; 4 absent**

Other M100 Changes (no vote by the subcommittee taken – all changes agreed upon):

1. A suggestion was made by D. Luper after review of M100 to combine Table 2C comments (4) and (13).

   - After discussion and as proposed by Ms. Luper, the WG decided to incorporate comment 13 wording into comment (4) and to then remove comment 13, as follows:

   (4) In most staphylococcal isolates, oxacillin resistance is mediated by *mecA*, encoding the penicillin-binding protein 2a (PBP 2a, also called PBP2'). Isolates that test positive for *mecA* or PBP 2a should be reported as oxacillin resistant.

   Mechanisms of oxacillin resistance other than *mecA* are rare and include a novel *mecA* homologue, *mecC*.[1] MICs for strains with *mecC* are typically in the resistant range for cefoxitin and/or oxacillin; *mecC* resistance cannot be detected by tests directed at *mecA* or PBP 2a.

   Isolates that test resistant by oxacillin MIC or cefoxitin MIC or cefoxitin disk test should also be reported as oxacillin resistant.

   Working Group: Approved: 9-0; 2 absent

2. The WG voted to revise Table 2C comment (11) now that comment (13) had been removed as follows:

   (11) Oxacillin disk testing is not reliable. See cefoxitin and comment (4) for reporting oxacillin when using cefoxitin disk diffusion as a surrogate test.

   Working Group: Approved: 9-0; 2 absent

3. The WG discussed placement of the new resistance mechanism tables and decided that, because they were too important and likely to be used frequently, they did not fit well in the appendix. Consequently, the WG voted to place them in their own section directly after Tables 2. All resistance mechanism tables will now be listed as Table 3A, B, C, etc.

   Working Group: Approved: 9-0; 2 absent

4. The WG discussed the new role of Text and Tables under the new working group structure. Priorities of the WG are now:

   a. Support for other Working groups with implementing of changes into the various documents
   b. Yearly review of M100
   c. Three year revision of M2 and M7 due in January 2015.

5. The WG made a plan for review of documents beginning with review of M100-S24 in September 2013 followed by reviews of M2 and M7 in April 2014 and M100-S25 in September 2014.

XII. SUBCOMMITTEE VOTE ON M100-S24

The subcommittee members voted to accept the M100-S24 supplemental tables with the changes approved at the January and June meetings and recommend the M100-S24 Tables to the Consensus Committee on Microbiology for approval to be published as supplemental tables.

A tally of the votes follows:

Total Subcommittee Members = 12
Votes to Accept = 11 (J. Alder, P. Bradford, G. Eliopoulos, D. Hardy, J. Hindler, S. Jenkins, J. Lewis, L. Miller, M. Powell, J. Turnidge, , B. Zimmer)
Votes to Accept with Comment = 0
Votes to Reject = 0
Votes not Received = 1 (M. Weinstein)

XIII AGENDA BOOK SUBMISSIONS FOR 12-14 JANUARY 2014 MEETING IN SAN ANTONIO

Materials for the January meeting will be distributed to the subcommittee prior to the meeting. The meeting rooms will be equipped with power strips for those who prefer to view the material on their computer instead of printing the material. Please note there will not be internet access in the meeting rooms.

To meet the schedule to have materials available for review a few weeks prior to the meeting, submission due dates and requirements must be met. In order to present at the 12-14 January 2014 meeting please:

1) Submit agenda materials electronically as a PDF file **on or before Wednesday, 11 December 2013.**
Please Note: For QC submissions based on M23 Tier 2 Studies please make sure to include information for the solvent and diluent to include in Table 5, antimicrobial class and subclass, antimicrobial agent abbreviation, and route of administration for inclusion in Glossary I and II.

2) E-mail proposed agenda topics to Jean B. Patel, PhD, D(ABMM) (vzp4@cdc.gov), Franklin R. Cockerill, III, MD (cockerill.franklin@mayo.edu) please copy his Administrative Assistant JoAnn Brunette (Brunette.Joann@mayo.edu) and also to Tracy Dooley (tdooley@clsi.org) for review.

Note: The 12-14 January 2014 meeting will be held in San Antonio, Texas at the Hyatt Regency Riverwalk. Additional meeting details will be provided in late September when the announcement is circulated.

XIV. ADJOURNMENT – The meeting adjourned at 11:25 a.m. on Tuesday, 25 June 2013.

Respectfully submitted,

Tracy A. Dooley, BS, MLT (ASCP),
Senior Standards Project Manager

Appendix A.

Organism or Organism Group	Resistance Phenotype Detected[a]	Occurrence and Significance of Resistance and Actions to Take Following Confirmation of Results[a]		
		Category I	**Category II**	**Category III**
		Not reported or only rarely reported to date	**Uncommon in most institutions**	**May be common, but is generally considered of epidemiological concern**
Haemophilus influenzae	Carbapenem – NS Extended-spectrum cephalosporin[c] – NS Ceftaroline - NS Fluoroquinolone – NS	x		
	Amoxicillin-clavulanic acid – R Ampicillin – R and β-lactamase negative		x	
Staphylococcus aureus	Vancomycin MIC ≥ 8 µg/mL[e]		x[e]	
	Ceftaroline – R Daptomycin – NS Linezolid – R Quinupristin-dalfopristin – I or R Vancomycin MIC = 4 µg/mL		x	
	Oxacillin – R			X

Appendix A. (Continued)

Organism or Organism Group	Resistance Phenotype Detected[a]	Occurrence and Significance of Resistance and Actions to Take Following Confirmation of Results[a]		
		Category I	**Category II**	**Category III**
		Not reported or only rarely reported to date	**Uncommon in most institutions**	**May be common, but is generally considered of epidemiological concern**
Streptococcus pneumoniae	Ceftaroline – R Linezolid – NS Vancomycin – NS	x		
Streptococcus, β-hemolytic group[g]	Ampicillin or penicillin – NS Extended-spectrum cephalosporin[c] – NS Ceftaroline - NS Daptomycin – NS Ertapenem or meropenem – NS Linezolid – NS Vancomycin – NS	x		

Abbreviations: CoNS, coagulase-negative staphylococci; I, intermediate; ID, identification; MIC, minimal inhibitory concentration; NS, nonsusceptible; R, resistant.

Appendix E. Dosing Regimens Used to Establish Susceptible or Susceptible-Dose Dependent Interpretive Criteria

The evolving science of pharmacokinetics-pharmacodynamics has become increasingly important in recent years in determining MIC interpretive criteria. Recently approved susceptible or susceptible-dose dependent (SDD) interpretive criteria for a number of agents have been based on a specific dosing regimen(s); these dosing regimens are listed in the table below. Proper application of the interpretive criteria requires patient drug exposure at the site of infection that corresponds to or exceeds the expected systemic drug exposure at the dose listed in adult patients with normal renal function. This information should be shared with pharmacists, infectious disease staff, and others making dosing recommendations for the institution.

	Interpretive Criterion			
	Susceptible		SDD	
Antimicrobial Agent	MIC (µg/mL)	Dose	MIC (µg/mL)	Dose
Table 2A. *Enterobacteriaceae*				
Aztreonam	4	1 g every 8 h	NA	
Cefazolin	2	2 g every 8 h	NA	
Ceftaroline	0.5	600 mg every 12 h	NA	
Cefepime	2	1 g every 12 h	4 8 Zone Diameter: 19–24 mm	1 g every 8 h or 2 g every 12 h 2 g every 8 h 2 g every 8 h (because it is not possible to correlate specific zone diameters with specific MICs, an isolate with a zone diameter in the SDD range should be treated as if it might be an MIC of 8 µg/mL)
Cefotaxime	1	1 g every 8 h	NA	
Ceftriaxone	1	1 g every 24 h	NA	
Cefoxitin	8	8 g per day (eg, 2 g every 6 h)	NA	
Cefuroxime	8	1.5 g every 8 h	NA	
Ceftazidime	4	1 g every 8 h	NA	
Ceftizoxime	1	1 g every 12 h	NA	
Doripenem	1	500 mg every 8 h	NA	
Ertapenem	0.5	1 g every 24 h	NA	
Imipenem	1	500 mg every 6 h or 1 g every 8 h	NA	
Table 2B-1. *Pseudomonas aeruginosa*				
Aztreonam	8	1 g every 6 h or 2 g every 8 h	NA	
Cefepime	8	1 g every 8 h or 2g every 12 h	NA	
Ceftazidime	8	1 g every 6 h or 2 g every 8 h	NA	
Doripenem	2	500 mg every 8 h	NA	
Imipenem	2	1 g every 8 h or 500 mg every 6 h	NA	
Meropenem	2	1 g every 8 h	NA	
Piperacillin	16	3 g every 6 h	NA	
Piperacillin-tazobactam	16/4	3 g every 6 h	NA	
Ticarcillin	16	3 g every 6 h	NA	
Ticarcillin-clavulanate	16/2	3 g every 6 h	NA	
Table 2B-2. *Acinetobacter* spp.				
Doripenem	2	500 mg every 8 h	NA	
Imipenem	2	500 mg every 6 h	NA	
Meropenem	2	1 g every 8 h or 500 mg every 6 h	NA	
Table 2C. *Staphylococcus* spp.				
Ceftaroline	1	600 mg every 12 h	NA	
Table 2E. *Haemophilus influenzae* and *Haemophilus parainfluenzae*				
Ceftaroline	0.5	600 mg every 12 h	NA	

Appendix E. (Continued)

Antimicrobial Agent	Interpretive Criterion			
	Susceptible		SDD	
	MIC (µg/mL)	Dose	MIC (µg/mL)	Dose
Table 2G. *Streptococcus pneumoniae*				
Ceftaroline (nonmeningitis)	0.5	600 mg every 12 h	NA	
Penicillin (nonmeningitis)	2	2 million units every 4 h (12 million units per day)	NA	
Penicillin parenteral (meningitis)	0.06	3 million units every 4 h	NA	
Table 2H-1. *Streptococcus* spp. β-Hemolytic Group				
Ceftaroline	0.5	600 mg every 12 h	NA	

Abbreviations: MIC, minimal inhibitory concentration; NA, not applicable; SDD, susceptible-dose dependent.