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Summary Minutes
Subcommittee on Antimicrobial Susceptibility Testing
Hilton Ft. Lauderdale Marina
Ft. Lauderdale, Florida
11-13 January 2015

A meeting of the CLSI Subcommittee on Antimicrobial Susceptibility Testing was held on 12-13 January 2015, at the Hilton Ft. Lauderdale Marina, Ft. Lauderdale, Florida. 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**	
Richard B. Thomson, Jr., PhD, D(ABMM), FAAM **Consensus Committee on Microbiology** **Chairholder**	**Evanston Hospital, NorthShore University HealthSystem**

Members Present

George M. Eliopoulos, MD	Beth Israel Deaconess Medical Center
Stephen G. Jenkins, PhD, D(ABMM),F(AAM)	New York Presbyterian Hospital
James S. Lewis, II, PharmD	Oregon Health & Science University
Brandi Limbago, PhD	Centers for Disease Control and Prevention
David P. Nicolau, PharmD, FCCP, FIDSA	Hartford Hospital
Robin Patel, MD	Mayo Clinic
Mair Powell, MD, FRCP, FRCPath	MHRA
Sandra S. Richter, MD, D(ABMM)	Cleveland Clinic
John D. Turnidge, MD	SA Pathology at Women's and Children's Hospital
Melvin P. Weinstein, MD	Robert Wood Johnson Medical School
Barbara L. Zimmer, PhD	Siemens Healthcare Diagnostics Inc.

Advisors Present

Patricia A. Bradford, PhD	AstraZeneca Pharmaceuticals
William B. Brasso	BD Diagnostic Systems
Rafael Canton	Hospital Universitario Ramon Y Cajal
Michael N. Dudley, PharmD,FIDSA	The Medicines Company
Dwight J. Hardy, PhD	University of Rochester Medical Center
Janet A. Hindler, MCLS, MT(ASCP)	UCLA Medical Center
Romney M. Humphries, Ph.D., D(ABMM)	UCLA David Geffen School of Medicine

Amy J. Mathers, MD	University of Virginia Medical Center
Tony Mazzulli, MD, FRCPC, FACP	Mt. Sinai Hospital
Sumathi Nambiar, MD, MPH	FDA/CDER
Helio S. Sader, MD, PhD	JMI Laboratories
Michael Satlin, MD, MS	Weill Cornell Medical College
Paul C. Schreckenberger, PhD, D(ABMM), F(AAM)	Loyola University Medical Center
Susan Sharp, PhD, D(ABMM) Representative	Kaiser Permanente-NW/ASM
Ribhi M. Shawar, PhD, D(ABMM)	FDA Ctr. for Devices/Rad. Health (CDRH)
Pranita D. Tamma, MD, MHS	Johns Hopkins University School of Medicine
Maria M. Traczewski, BS, MT(ASCP)	The Clinical Microbiology Institute

Reviewers Present

April Abbott	Deaconnes Health System
Paul G. Ambrose, PharmD, FIDSA	Ordway Research Institute
Sujata M. Bhavnani, PharmD	Ordway Research Institute
Lynn Boyer	Siemens Healthcare Diagnostics Inc.
Steven D. Brown, PhD, ABMM	Consultant
Karen Bush, PhD	Indiana University
Laurent Chesnel	Cubist Pharmaceuticals, Inc.
Diane M. Citron, M(ASCP), BS	R.M., Alden Research Laboratory
Patricia S. Conville, MS, MT(ASCP)	FDA/Center for Devices and Radiological Health (CDRH)
Katie Coyle	Becton Dickinson
Sharon K. Cullen, BS, RAC	Siemens Healthcare Diagnostics Inc.
Christopher Doern, PhD	Virginia Commonwealth University Medical Center
Michael J. Dowzicky	Pfizer Inc
German Esparza, BSc	Hospital Santa Clara
Robert Eusebio, MSHA, MT(ASCP)	Siemens Healthcare Diagnostics Inc.
Gina L. Ewald-Saldana, CLS(CA), MT(ASCP)	Siemens Healthcare Diagnostics Inc.
Robert K. Flamm, PhD	JMI Laboratories
Lawrence V. Friedrich, PharmD	Cubist Pharmaceuticals, Inc.
Barb Gancarz	bioMerieux, Inc.
Beth P. Goldstein, PhD	Beth Goldstein Consultant
Meredith Hackel	IHMA, Inc.
Patricia Hogan, MT(ASCP), MBA	Pfizer Inc
Michael D. Huband	AstraZeneca Pharmaceuticals
James H Jorgenson, PhD	University of Texas Health Science Center
Jack L. Johnson	IHMA, Inc.
Scott B. Killian	Thermo Fisher Scientific
Thomas J. Kirn, MD, PhD	North Shore University Health
Cythia C. Knapp, MS	Thermo Fisher Scientific
Laura M. Koeth, MT(ASCP)	Laboratory Specialists, Inc.

Kevin Krause	
Dyan Luper, BS, MT(ASCP)SM	BD Diagnostic Systems
Linda M. Mann, PhD, D(ABMM)	Consultant
Maureen Mansfield	Thermo Fisher Scientific
Mary R. Motyl, PhD, D(ABMM)	Merck & Company, Inc.
Susan D. Munro, MT(ASCP)	Consultant
Margaret Ord onex Smith de Danies, PhD	Microbiology Institute of Colombia
Elizabeth Palavecino, MD	Wake Forest University Baptist Medical Center
Samir Patel, PhD, FCCM	Public Health Ontario
James A. Poupard, PhD	Pharma Institute of Philadephia
L. Barth Reller, MD	Duke University Medical Center
Robert P. Rennie, PhD	Provincial Laboratory for Public Health
Darcie E. Roe-Carpenter, PhD, CIC, CEM	Siemens Healthcare Diagnostics Inc.
Flavia Rossi, MD	University of Sao Paulo
Daniel F. Sahm, PhD	IHMA, Inc.
Dale A. Schwab, PhD, D(ABMM)	Quest Diagnostics, Nichols Institute
Katherine Sei	Siemens Healthcare Diagnostics
Sharon Shinn	Siemens Healthcare Diagnostics Inc.
Dee Shortridge, PhD	bioMerieux, Inc.
Judith N. Steenbergen, PhD	Cubis Pharmaceuticals, Inc.
Gregory G. Stone	AstraZeneca Pharmaceuticals
Lauri D. Thrupp, MD	University of California Irvine Medical Center
Karla M. Tomfohrde	Eurofins Medinet
Ben Turng	Accelerate Diagnostics Inc.
Wayne F. Wang, MD, PhD	Emory University Hospital
Nancy Watz	Stanford Hospital and Clinics
Lars F. Westblade, PhD, D(ABMM)	Children's Healthcare of Atlanta
Matthew A. Wikler, MD, MBA, FIDSA	The Medicines Company
Mary K. York, PhD, ABMM	MKY Microbiology Consulting

<u>Observers Present</u>

Vanessa Allen	Public Health Ontario
Jane E. Ambler, PhD	Cubist Pharmaceuticals Inc.
Karen (Kitty) Anderson	Centers for Disease Control and Prevention
Stella Antonara	Nationwide Children's Hospital
Francis Arhin	The Medicines Company
Mari Ariyasu	Shionogi Co., Ltd
Mary Arndt	Siemens Healthcare Dx MicroScan
Ashley Austerman	MicroScan
Lynette Y. Berkeley, PhD	Food & Drug Administration
Malcolm Boswell	Accelerate Diagnostics
Linda C. Bruno, MA, MT(ASCP)	ACL Laboratories
Susan Bulter-Wu	University of Washington
Carey-Ann Burnham,PhD, D(ABMM)	Washington University School of Medicine

Mariana Castanheira, PhD	JMI Laboratories
Lynn Connelly, MD, PhD	Achaogen
Dana Dressel	IHMA, Inc.
Roger Echols	Shionogi
Paul Edelstein	University of Pennsylvania
Sheila Farnham, MT(ASCP)	bioMerieux
Mary Jane Ferraro, PhD, MPH	Massachuesetts General Hospital
Jeff Fuller, PhD, FCMM, ABMM	University of Alberta
Andrea Gough	Thermofisher Scientific
Alice Gray	bioMerieux
Nicole Holliday	Thermo Fisher Scientific
Seong Jang, PhD	Food and Drug Administration
Jocelyn Jennings	bioMerieux, Inc.
Ron Jones, MD	JMI
Nachum Kaplan	Nobelex Biotech
Blaine Keppanen	BHAI
Aryun (Eileen) Kim, PharmD	AztraZenica Pharmaceuticals
Susan Kircher, MS, MT(ASCP)	BD Diagnostic Systems
Roberta E. Knefel	bioMerieux. Inc.
Melinda Lacy	TheraVance BioPharma
Olga Lamovskay	The Medicines Company
Xian-Zhi Li, PhD	Health Canada Veterinary Drugs
Beth Lingenfelter	Accelerate Diagnostics
Jennifer Marcenelle	Auclerate Diagnostics, Inc.
Sally Maysent	Thermo Fisher Scientific Sensititre
Sandra McCurdy	Durata Therapeutics
Maureen Mende	Accelerate Diagnostics Inc.
Greg Moeck	The Medicines Company
Timothy Morris	Actelion Clinical Research
Ian Morrissey	IHMA, Inc.
Ross Mulder, MT(ASCP)	bioMerieux, Inc.
Jennifer O'Connor	Siemens Healthcare Microscan
Kiyofumi Ohkusu	Tokyo Medical University
Pritty Patel	Covance Labs
Chris Pillar	Microruyx
Janet Raddatz	Cubist
Nilia M. Robles Hernandez	bioMerieux, Inc.
Denis Robichon	Debiopharm
James Ross	JMI Labortories
Nicole Scangarella-Oman	GlaxoSmithKline
Alisa Serio,PhD	Achaogen
Albert T. Sheldon, PhD	Antibiotic & Antiseptic Consultants
Carole Shubert	bioMerieux, Inc.
Simone Shurland	FDA, CDER
Jennifer Smart	Theravance BioPharma
Kazuhiro Tateda, MD, PhD	Toho University

Susan Thomson	MAST Group
Masakatsu Tsui	Shiongi & Co. Ltd
Simon Walker	Thermofisher Scientific
Collette Wehr	Siemens MicroScan
Teresa Wong	Siemens Microscan
Sarah Wood	Siemens Healthcare Microscan
Yoshinori Yamano	Shionogi & Co. Ltd

CLSI Staff

Tracy A. Dooley, BS, MLT (ASCP)
Erica Belanger
Glen Fine, MS, MBA, CAE
Marcy Hackenbrack, MCM, M(ASCP)
Luann Ochs, MS

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I. MEETING/OPENING REMARKS

Dr. Jean Patel called the meeting to order at 1:00 p.m. on Monday, 12 January 2015. This meeting has a different schedule with less time needed for the plenary session due to all the on-going work being done outside these meetings by the standing working groups (WGs) and various ad hoc WGs. All of the WGs have been busy over the past few months, accomplishing much of the work thru conference calls and e-mail, making this meeting more efficient. She asked for any feedback on how this new schedule worked and any additional suggestions or input meeting participants may have.

Dr. Patel discussed the recent changes to the subcommittee including the addition of 2 new voting members: Robin Patel from Mayo Clinic and Sandy Richter from Cleveland Clinic. New advisors include:

- Dr. Rafael Canton - representing EUCAST.
- Amy Mathers, MD – from University of Virginia Medical Center
- Pranita Tamma, MD, MHS – from John Hopkins Medical Institutions
- Graeme Forrest, MBBS – from Oregon Health Sciences University

Other rotations/changes:

Members who rotated to advisors, each of whom have done a lot of work over the years for CLSI and this subcommittee (SC) include:

- Patricia Bradford
- Janet Hindler
- Linda Miller

Advisors who rotated to reviewers:

- Karen Bush –has a long distinguished history on the SC as a voting member, as an advisor and she has also chaired various WGs. Karen continues to serve as a member of the Breakpoint WG.
- Gunnar Kahlmeter – has served since 2003 as an advisor and representative for EUCAST.
- Jeff Schapiro – served since 2013 as an advisor.

II. CLSI UPDATE

Mr. Glen Fine, CEO with CLSI welcomed everyone to the meeting, introduced CLSI staff, and then provided updates within CLSI.

Mr. Fine then introduced CLSI staff present at the meeting as follows:

- Luann Ochs – Senior Vice President of Operations;
- Tracy Dooley – Senior Project Manager and Staff Liaison to the Consensus Committee on Microbiology and;

- Marcy Hackenbrack – Senior Project Manager and Staff Liaison to the Consensus Committee on Molecular Methods who also assists with various projects under; and
- Erica Berlanger – Meeting Manager who coordinates all the logistics for these meetings.

He noted that people may have noticed additional CLSI meetings have been taking place during the week as well. In an effort to consolidate in-person meetings and optimize volunteer and staff time as well as save on meeting costs, CLSI is holding joint meetings for various committees four times per year during 'Committee Weeks'. Two of these weeks will be held in conjunction with the January and June meetings of the AST SC. Mr Fine noted were are nine committees that met during the week in Ft. Lauderdale.

Mr. Fine than gave an overview of the CLSI Board of Directors recent policy change that impacts the three standing susceptibility testing subcommittees and their working groups whereby representatives from pharmaceutical companies and allied stakeholders whose business model significantly depends on selling services to pharmaceutical companies, will no longer be voting members of these subcommittees/working groups.

He stressed that representatives from pharmaceutical companies and allied stakeholders and their active participation in the consensus process is highly valued and strongly encouraged in all capacities as advisors and reviewers. The only intended and practical impact of this change is for the subcommittees' and working groups' formal votes.

The Board's rationale for this decision:

- This issue of Pharma as voting members has been a long standing debate at CLSI as it relates to its disclosure and conflict of interests' policy, alignment with US FDA Advisory Committee and other guidelines, and CLSI's perceived reputational image of bias concerns for our related standards, guidelines and supplements from various outside interests.
- The AST/breakpoint-setting groups are the only groups within the CLSI consensus process umbrella that make decisions on specifically named manufacturers' products published in CLSI documents.
- Besides the concern of perceived conflict of interest not adequately addressed within the existing disclosure/conflict of interest process, it at times, places Pharma voting members in a position of abstaining on various votes or potentially be perceived as biased, even though none may actually exist in the decision processes.
- This approach is more closely aligned with the US FDA's invitation of industry representatives for its advisory committees.
- Representatives from the industry constituency who do not benefit from the sales of anti-infective products are encouraged to continue participation as voting members.
  The implementation of this change was effective on January 1, 2015 for the AST Subcommittee, and is scheduled to go into effect on January 1, 2016 for the Veterinary and Antifungal subcommittees.

III. CLSI'S EP23 AND IQCP (Electronic Folder 1) (Also refer to Attachment 1 provided separately)

Ms. Luann Ochs, Senior Vice President of Operations with CLSI provided some background and an overview of the new CLIA requirements for an Individualized Quality Control Plan (IQCP). Around 2004, CMS came out with some new guidelines called Equivalent QC but they were not very scientifically

based. AdvaMed then asked CMS, CDC, and FDA to come together and worked with CLSI to develop a document to explain how to base QC on actual risk. CLSI then developed EP23, *Laboratory Quality Control Based on Risk Management; Approved Guideline.* EP23 outlines how to identify potential failures for test including considering what the risks might be, what the errors could be and what can mitigate those errors and then include those actions in your QC plan.

Laboratories have two options:

- Can revert back to traditional QC according to CLIA guidelines; or
- Develop an IQCP

As of January 2016 these will be the only options laboratories will have.

Laboratories can develop a QC plan by doing a risk assessment:

- Identify potential failures and their causes (from time sample is acquired to specimen reporting)
- Assess each potential failure
- Where a failure could occur and then determine if there is an action that will reduce the possibly of that failure. For each possible failure, assess:
  - the likelihood of that failure occurring
  - the severity of the consequences if it occurs
  - whether the test system is likely to detect the failure
- Repeat this for each identified failure. In the end you will have a list of actions to control the quality of a test. This then becomes your IQCP.

Once a QC plan is developed, then laboratories need to assess this at regular intervals to determine if improvement is needed.

After Ms. Ochs presentation, Dr. Patel noted that the subcommittee has formed an IQCP Ad Hoc WG to help assist laboratories with implementing a QC plan for susceptibility testing.

IV. UPDATES TO THE CURRENT AST DISCLOSURE SUMMARY (Electronic Folder 2)

Dr. Patel asked the members and advisors for any updates to the current disclosure summary provided on the CD of meeting materials –Dr. George Eliopoulos, Dr. Barb Zimmer, Dr. Sandy Richter, Dr. David Nicolau, and Dr. Amy Mathers provided updates that will be added to the summary.

V. APPROVAL OF JUNE 2014 MINUTES (Electronic Folder 4)

Summary minutes of the June 2014 subcommittee meeting were approved: **(11-0)**

VI. REPORT OF BREAKPOINT WORKING GROUP (Electronic Folder 5)

Co - Chairholder – George Eliopoulos
Co - Chairholder – Jim Lewis
Recording Secretary – Karen Bush

Members Present: Amy Mathers, David Nicolau, Mair Powell, Michael Satlin, Paul Schreckenberger, Audrey Schuetz, Simone Shurland, Melvin Weinstein, Barbara Zimmer

Technical Advisors Present: Matt Wikler

Oritavancin Breakpoint Presentation (See Briefing documents 6.1.0, 6.1.1, 6.1.2, 6.1.3)
Presenters Greg Moeck and Matt Wikler

Oritavancin (ORI) was approved by FDA in August 2014 for treatment of acute bacterial skin and skin structure infections (ABSSSI) caused or suspected to be caused by susceptible isolates of designated Gram-positive bacteria. Dr. Moeck presented the basic microbiological properties and the pharmacological characteristics supporting a single dose of 1200 mg. Dr. Wikler reviewed the clinical studies conducted with oritavancin.

The following breakpoints were approved by the FDA.

	MIC (µg/mL)		
Microorganism	S	I	R
Staphylococcus aureus (including methicillin-resistant isolates)	≤0.12	-	-
Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus, Streptococcus constellatus, and *Streptococcus intermedius*	≤0.25	-	-
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤0.12	-	-

The sponsor requested that CLSI accept the FDA-approved breakpoints.

Discussion

- No disagreements were voiced concerning the proposal.

WG Motion: A motion was made and seconded to accept the FDA breakpoints.

- The motion passed with a vote of Yes= 10; No = 0; Abstain = 2.

This motion was presented to the AST Subcommittee.

AST Subcommittee Motion: A motion was made and seconded to accept the FDA breakpoints.
Discussion:

- *E. faecalis* may not be involved in ABSSSI, but it's good to have a breakpoint included.
- Text and Tables can clean up any comments.
- The motion passed with a vote of Yes= 9; No = 0; Abstain = 2. **Approved by Subcommittee**
-

Vancomycin surrogate testing request

The sponsor also requested that surrogate testing with vancomycin (VAN) be acceptable as a means of predicting oritavancin (ORI) susceptibility prior to the FDA approval of automated testing panels containing oritavancin. An Ad Hoc Working Group that met prior to the CLSI meeting (members: Jim Lewis, chairholder; Mary Jane Ferraro, Robin Patel, Jim Jorgensen and Mike Satlin) recommended that CLSI include a comment to accompany oritavancin breakpoints in the next CLSI update.

"Isolates of designated organisms that are susceptible to vancomycin can be considered and reported to be susceptible to oritavancin. Susceptibility to oritavancin should be tested directly in vancomycin non-susceptible isolates."

Discussions with the WG and the AST Subcommittee involved the following considerations.

- All ORI-NS *S. aureus* isolates tested as VAN-S (approx. 2% of the total of 17,717 strains). However, all but one of these strains had ORI MICs only one dilution higher than the breakpoint (0.25 µg/mL), within the error of the test. Dr. Moeck showed that in a study of 70 VISA/VRSA strains, all but one strain was NS to oritavancin.
- Depending on the dataset, it was noted that many hVISA test as susceptible to ORI. All hVISA from the clinical trials (n=21) were ORI-S (MICs $\leq$0.12 µg/mL) with approximately 90% clinical cures. In surveillance strains of hVISA, elevated MICs for both ORI and VAN were reported, with approximately half ORI-NS.
- It was suggested that since three different mechanisms of action for oritavancin were possible, VAN-S isolates may not include ORI-resistant strains that are due to mutations at sites other than the common cell wall synthetic step.
- Some clinical microbiologists were hesitant to call all VAN-S isolates ORI-S. It was clarified by Dr. Ferraro that the intention of the Ad Hoc WG was to provide guidance for the use of oritavancin but not to call isolates ORI-S based on vancomycin testing.

Motion from WG:

A motion was made and seconded that a comment should be added to the CLSI documents stating: "Isolates of designated organisms that are susceptible to vancomycin can be considered ~~and reported~~ to be susceptible to oritavancin. Susceptibility to oritavancin should be tested directly in vancomycin non-susceptible isolates."

The vote was Yes = 8; No = 2; Abstain = 2

Objections from the WG members who voted No were based on the concerns that too many ORI-NS isolates may be called S and that ORI-NS strains will inevitably arise with currently unknown mechanisms, and the CLSI wording will again need revision. The WG was reminded that this footnote was to be only an interim comment that would be removed after ORI was included in FDA-approved automated testing systems. This comment was proposed to the AST Subcommittee for consideration.

Additional Discussion at the AST Subcommittee

- Members asked about the timing of the placement of oritavancin on commercial testing systems. Testing panels for broth dilution assays may be available later this year, but automated systems will not be ready for a longer time.

- It was emphasized that the comment should be applicable for only a fixed time and would be removed after oritavancin was available for general testing.
- Surrogate testing comments are already in the CLSI book for tetracycline and cefazolin, so this would not set a precedent.
- One suggestion was to provide actual susceptibility data in a footnote, with a date (eg, "As of 2014, 98% of VAN-S isolates tested S to oritavancin." The Sponsor objected to this statement unless it was species-specific in each table.
- Some clinicians asked that a comment be included, because ORI could be a useful single-dose antistaphylococcal drug for emergency room use or for drug users. Guidance would provide reassurance to physicians.

Multiple motions were proposed for acceptable wording for surrogate testing, but none generated sufficient votes to pass.

A proposal was made that there could be a mini-rationale document to explain the situation and education on the CLSI site could be provided.

The topic was sent back to the WG for the June meeting.

Table 1 Placement for Oritavancin

Following the WG meeting, the sponsor met with the WG chairholders and requested Table 1 placement for oritavancin as follows:

Group B: *Staphylococcus aureus*
Group C: *Streptococcus* spp. β-hemolytic group, and *Streptococcus* spp., Viridans Group
Group B: *Enterococcus* spp. (*faecalis* only)

The AST Subcommittee noted that this placement is not possible because oritavancin can't be routinely tested. A suggestion was made to "time stamp" this and move oritavancin to Group B when it is freely available.

Motion for Table 1 placement

Oritavancin should be in Group C for all organisms listed. The sponsor should return to the Subcommittee when the drug is freely available for laboratory testing.

The motion passed with a vote of Yes = 9; No = 1; Abstain = 1 **Approved by Subcommittee**

The opposing vote was based on the observation that oritavancin seems to be in line with the other drugs in Group B. Availability of the test shouldn't make a difference.

Telavancin Breakpoint Presentation (See Briefing Documents 6.3.0 and 6.3.1)

A presentation by Jennifer Smart summarized the microbiological and pharmacological properties of telavancin (TLV). Telavancin is approved by the FDA for the treatment of the following infections in adult patients caused by designated susceptible bacteria:

- Complicated skin and skin structure infections (cSSSI) (1.1)
- Hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus*.

Telavancin QC ranges were originally approved by CLSI in 2011. However, changes in methodology involving dilution in DMSO and solution preparation in 0.002% P-80 have resulted in lower telavancin MICs. CLSI QC ranges have been revised based on new dilution methodology. Breakpoint revisions are now requested based on:

- Normal MIC distributions based on new testing methodology
- PK/PD target attainment using new MICs
- Clinical outcome data correlations with MICs tested with new methodology

Using the new testing methodology, the PK/PD target AUC/MIC increased from 219 to 3650, as the MIC of the MRSA test strain decreased from 1 µg/mL to 0.06 µg/mL. With 90% protein binding, free AUC/MIC = 365 (vancomycin approx. 400). A re-calculation of >90% target attainment was reached at MICs $\leq$ 0.12 µg/mL.

All clinical isolates from Phase 3 studies (cSSSI and HABP/VABP; n=2157) were re-tested with the new methodology. All *S. aureus* isolates had TLV MICs $\leq$0.12 µg/mL. Similar lowered MICs were reported for *E. faecalis* and streptococcal isolates (see slides). Clinical cures were aligned with new FDA breakpoints that were approved in Feb. 2014 (see below). Note that EMA approval was only for MRSA Oct. 2014 with a breakpoint of S $\leq$0.12 µg/mL.

A request was made for harmonization of breakpoints. The emphasis should be on MIC breakpoints, as there are some testing issues for disk diffusion data and poor correlations for hVISA and VRSA strains.

Telavancin breakpoints as approved by FDA

Organism	Interpretation	MIC µg/mL)	Zone diameter (mm)
Staphylococcus aureus	Susceptible Intermediate Resistant	$\leq$0.12 - -	$\geq$15 - -
Enterococcus faecalis (vancomycin-susceptible isolates only)	Susceptible Intermediate Resistant	$\leq$0.25 - -	$\geq$15 - -
Streptococcus pyogenes *Streptococcus agalactiae*	Susceptible Intermediate Resistant	$\leq$0.12 - -	$\geq$15 - -
Streptococcus anginosus Group	Susceptible Intermediate Resistant	$\leq$0.06 - -	$\geq$15 - -

WG Motion: A motion was made and seconded: Approve the FDA breakpoints for MICs only.

- The motion passed with a vote of Yes=9; No=0; Abstain = 3

This motion was presented to the AST Subcommittee.

AST Subcommittee Motion. The following motion was made and seconded:

- Approve the FDA breakpoints for telavancin for MICs

- Discussion: No Etests currently available. An RUO Etest may be available in the near future.
- The motion passed with a vote of Yes=8; No=0; Abstain = 3. **Approved by Subcommittee**

Table 1 Placement

Following the WG meeting, the sponsor met with the WG chairholders and requested Table 1 placement for telavancin as follows:

Group B: *Staphylococcus aureus*
Group C: *Streptococcus* spp. β-hemolytic group, and *Streptococcus* spp., Viridans Group
Group B: *Enterococcus* spp. (*faecalis* only)

Discussion

- The AST Subcommittee noted that only one testing system is available, so it would not be possible for most labs to do routine testing. Although powder is available, most labs don't have the ability to make up their own broth dilution plates.
- The wording of Group B requirements was debated. The suggestion was made that if it is going to be necessary for a drug to be "available for routine testing" for Table 1 placement, companies must know what they are required to do to meet this. Group B says that the drug MUST be tested routinely in primary testing. RUO Etests are not FDA approved and can't serve this purpose. The question was raised as to whether any other company has been required to have drug freely available when it was first listed in Group B. Is ceftaroline (Group B) routinely tested by every lab?

AST Subcommittee Motion: The following motion was made and seconded.

- Accept the groupings as proposed**.**
- The motion failed with a vote of: Yes =3; No = 5; Abstain = 2
- Most objectors said it should be treated as oritavancin.

AST Subcommittee Motion: The following motion was made and seconded.

- Place telavancin in Group C for all organisms.
- The motion passed with a vote of : Yes = 8; No = 1; Abstain = 2. **Approved by Subcommittee**

A suggestion was made that both drugs should be mentioned in Appendix A stating that nonsusceptible isolates should be sent to a reference lab for further testing.

Plazomicin informational presentation (Briefing document 6.2)

Presenters: Alisa Serio, microbiology; Lynn Connolly, clinical development

Plazomicin is a novel aminoglycoside focused on Gram-negative bacteria. CLSI QC ranges were published in Jan. 2012. The presentation included the plazomicin mechanism of action; mechanisms of resistance; MIC distributions for key species, including BARDA strains and β-lactamase-producing/carbapenem-resistant/aminoglycoside-resistant *Enterobacteriaceae.*

Preclinical *in vivo* efficacy studies were summarized; AUC/MIC appears to be the driver for efficacy. Five clinical studies have been completed, four Phase 1 and one Phase 2 trial in patients with cUTI where clinical efficacy was determined to be equivalent to levofloxacin. PK properties in human subjects were presented. The Phase 3 study design was shown for presumed or documented CRE (bloodstream infection or pneumonia).

AST Subcommittee and WG comments for future consideration of plazomicin breakpoints by CLSI

- The presentation was reasonably in line with M23 requirements.
- Requests were made for:
  - More extensive AUC/MIC analyses
  - Monte Carlo simulations
  - More ELF data
  - Comparisons to other aminoglycosides
  - Question concerning frequency of methyltransferases in MBL producers other than NDM? Answer – mainly seen in NDM-1-producing strains, at least for now.
- Questions were asked concerning species-specific breakpoints. What does Achaogen want to see in their label? Answer: Clinical trial will include "suspected" CRE (carbapenem-resistant *Enterobacteriaceae*)isolates, so there may be more pathogens than just CRE.
- Plazomicin clinical trials may include other drugs in combination (meropenem, tigecycline). Complex analyses at are expected at the end.

Achaogen requested that CLSI revise all aminoglycoside breakpoints at the same time that plazomicin breakpoints are assigned. They also asked for advice about how breakpoints will be considered for drug combination studies.

VII. REPORT OF THE TEXT AND TABLES WORKING GROUP (Electronic Folder 6)

Co - Chairholder – Ms. Maria Traczewski
Co - Chairholder – Ms. Jana Swenson (absent)

Members Present: Janet Hindler, Dyan Luper, Linda Mann, Susan Munro, Flavia Rossi, Dale Schwab, Tom Thomson, Nancy Watz, and Mary York

Members Absent: Peggy Kohner, Melissa Miller, and Jeff Shapiro

Item for Vote:

I. Instructions for Use of Tables: V. Development of Resistance and Testing of Repeat Isolates. Paragraphs 1 and 2

Based on publication: C. Giltner, T. Kelesidis, J.Hindler, April M. Bobenchik, R. Humphries Frequency of Susceptibility Testing for Patients with Persistent Methicillin-Resistant *Staphylococcus aureus Bacteremia*, JCM Vol. 52 No. 1 pp 357-361, January 2014

Working group proposed expanding paragraph 2 to include wording about MRSA from patients with prolonged bacteremia.

Paragraph 1: No Change proposed

Isolates that are initially susceptible may become intermediate or resistant after initiation of therapy. Therefore, subsequent isolates of the same species from a similar body site should be tested in order to detect resistance that may have developed. This can occur within as little as three to four days and has been noted most frequently in *Enterobacter, Citrobacter,* and *Serratia* spp. with third-generation cephalosporins; in *P. aeruginosa* with all antimicrobial agents; and in staphylococci with quinolones. For *S. aureus,* vancomycin-susceptible isolates may become vancomycin intermediate during the course of prolonged therapy.

Paragraph 2: (original)

In certain circumstances, testing of isolates to detect resistance that may have developed might be necessary earlier than three or four days. The decision to do so requires knowledge of the specific situation (eg, an *E. cloacae* from a blood culture of a premature infant). Laboratory guidelines on when to perform susceptibility testing on repeat isolates should be determined after consultation with medical staff

Paragraph 2 (Proposed revision - red text added):

In certain circumstances, the decision to perform susceptibility tests on subsequent isolates requires knowledge of the specific situation and the severity of the patient's condition (eg, an isolate of *Enterobacter cloacae* from a blood culture on a premature infant or MRSA from a patient with prolonged bacteremia). Laboratory guidelines on when to perform susceptibility testing on subsequent isolates should be determined after consultation with the medical staff.

Subcommittee Approved: 6-0; 5 absent

II. Based on results of recent CAP proficiency test it has become evident that there is much confusion about what to do with pefloxacin and naladixic acid test results for Salmonella.

a. The text has incomplete information on testing/reporting for surrogates and or testing ciprofloxacin alone (if dilutions go low enough). No one disk is perfect, must use at least two disks, i.e. cip and peflox.

b. It was felt that these two disk tests would be considered surrogate tests since they are used to determine susceptibility or resistance to fluroquinolones or quinolones vs. *Salmonella* when an MIC test for ciprofloxacin or levofloxain is unavailable.

c. Comments referring to pefoxacin and naladixic acid disk tests would be revised in Table 2A and refer the reader to the specific table in Section 3 of M100 where performance of the tests and how to interpret and report would be clarified.

Subcommittee agreed that a revision is needed. T& T will bring revisions for review in June. No formal vote taken.

III. Surrogate Tests (also refer to agenda item 6 2 – provided as separate attachment to the minutes)

As part of the discussion over surrogate tests for fluoroquinolones for *Salmonella* the working group reviewed and created a spreadsheet showing:

- all places in M100 where a susceptibility test result can be used to report susceptibility to an alternative antimicrobial agent.
- boxes where "or" is used in a class box in Tables 2.
- all places containing text stating that result for one agent can predict susceptibility for other agents.

Next steps: The WG will draft definitions for surrogate tests (stand alone tests with no further testing required) and screening tests (may require additional testing)for review at the June meeting.

The Methodology WG will review the spread sheet created by Text & Tables WG (see Attachment 2) that shows all comments pulled from M100 that relate to predicting susceptibility and see what is out-of -date and make recommendations for any necessary changes.

IV. Clarification proposed for Cefazolin used as surrogate to report other cephalosporins in Table 1 and 2A. See Appendix A at the end of these minutes for mock-up of changes.

Subcommittee agreed to changes shown in the Appendix but suggested that the WG include examples of how to report and consider rewording "cefazolin can be used to report cefazolin" comment.

Robin Patel indicated that at Mayo Clinic they report as: "Oral Cephalosporins" And add comment:

"The interpretation applies to uncomplicated urinary tract infections only. The oral cephalosporin category includes cefazolin, cefdinir, cefuroxime and cephalexin."

Subcommittee approved (10-0; 1 absent) to add new breakpoint for cefazolin in UTI and bring back example for reporting in June.

V. Recommendations from Table 1 Ad Hoc Working Group led by Mary York to clean up Tables 1 and 2.

Clean up comments 7 and 8 in Table 2C by reorganizing based on what agent to test (comment 7) and then how to test and what can be considered susceptible and or resistant once you have tested (comment 8). Move list of penicillin stable and labile agents to appendix instead of listing all agents in the comments and add "**See Glossary 1"** instead.

1. Table 2C, Comment 7 and 8 **revised**:

   (7) Penicillin should be used to test the susceptibility of staphylococci to all penicillins. Penicillin-susceptible staphylococci are susceptible to other β-lactam agents with established clinical efficacy for staphylococcal infections (including both penicillin-labile and penicillin-stable agents; **see glossary 1**) Penicillin-resistant staphylococci are resistant to penicillinase-labile penicillins.

   (8) Penicillin should be used to test the susceptibility of all staphylococci to all penicillinase-labile penicillins (**refer to glossary 1).** Penicillin-resistant strains of staphylococci produce beta-lactamase. Perform tests to detect……
   the isolate for the *bla*Z β-lactamase gene may be considered. See Tables 3D and 3E.

   Change approved with minor editing– no formal Subcommittee vote taken.

2. Table 2C Comment 10. Ad Hoc and T& T suggested we remove list of agents (in red) and refer to Appendix for lists of agents as shown below:

   (10) Oxacillin (or cefoxitin) results can be applied to the other penicillinase-stable penicillin (cloxacillin, dicloxacillin, flucloxacillin, methicillin, and nafcillin). For agents with established clinical efficacy and considering site of infection and appropriate dosing, oxacillin (cefoxitin)-susceptible staphylococci can be considered susceptible to:

   - β-lactam/β-lactamase inhibitor combinations (amoxicillin-clavulanate, ampicillin sulbactam, piperacillin-tazobactam, ticarcillin-clavulanate)
   - Oral cephems (cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, loracarbef)
   - Parenteral cephems including cephalosporins I, II, III, and IV (cefamandole, cefazolin, cefepime, cefmetazole, cefonicid, cefoperazone, cefotaxime, cefotetan, ceftizoxime, ceftriaxone, cefuroxime, cephalothin, ceftaroline, moxalactam)
   - Carbapenems (doripenem, ertapenem, imipenem, meropenem)

(**Please refer to glossary 1 for listing of drugs in each of these subclasses**).

Subcommittee agreed to leave as is for now - no change.

3. Table 2H-1 Comment 5. Revise as follows (remove red text):

(*5*) For the following organism groups, An organism that is susceptible to penicillin can be considered susceptible to the listed antimicrobial agents when used for approved indications and not need to be tested against those agents: for groups A, B, C, and G β-hemolytic ***streptococci,*** penicillin is a surrogate for ampicillin, amoxicillin, amoxicillin-clavulanate, ampicillin-sulbactam, cefazolin, cefepime, ceftaroline, cephradine, cephalothin, cefotaxime, ceftriaxone, ceftizoxime, imipenem, ertapenem, and meropenem, and for **In addition,beta-hemolytic *streptococci*** group ***A*** **only penicillin is a surrogate for cefaclor, cefdinir, cefprozil, ceftibuten, cefuroxime and cefpodoxime and cephapirin.**

Change approved with minor editing– no formal Subcommittee vote taken.

VI. M100-S20 Carbapenem Interpretive Criteria.

Since it has been 5 years since carbapenem breakpoints were lowered, the WG proposed removing all reference to M100-S20 carbapenem breakpoints and remove extra tables in Section 3 that are to be used by labs using M100-S20 breakpoints.

Subcommittee discussion: since there is uncertainty that all AST devices have current breakpoints approved by the FDA implemented on their instruments the subcommittee voted to wait to remove pending verification that most AST devices have FDA approval for current carbapenem breakpoints. **Approved 9-0; 2 absent.**

VII Carba-NP Test

Photographs for Carba-NP test have no labels indicating positive and negative results. Text and Tables will add positive and negative next to current photos and find some better photographs to add, showing actual positive, negative and invalid test results.

No subcommittee vote necessary.

VIII Outreach Ad Hoc WG Update

Janet Hindler co-chair
Audrey Schuetz co-chair

Members: Marcelo Galas, Romney Humphries, Lars Westblade, Beth Prouse, Violeta J. Rekasius, Nicole. E. Scangarella-Oman

The Outreach Ad Hoc WG is a newly formed group charged with developing educational materials/programs to help users navigate CLSI AST documents and CLSI website. This includes:

1. Reviewing meeting minutes and recent versions of CLSI documents M02, M07, M100, and M11 to identify those topics that would benefit from educational or outreach endeavors.
2. Soliciting feedback from users of CLSI documents to determine what additional educational materials would be useful.
3. Determining methods and venues for delivery of various types of educational needs identified in items 1 and 2 above.
4. Develop materials for educational opportunities.

The ad hoc WG's will be working with CLSI's Education Coordinators to find ways to educate users through various multimedia communication as well as look at any potential to partner with other organizations who have delivery systems in place, when appropriate. The ad hoc WG will also review the AST SC page on the CLSI website to see how to better organize/utilize the resources available there.
An update on the progress of this WG will be provided in June.

VIII. M23 WORKING GROUP UPDATE (Electronic Folder 7)

Co – Chairholders – Dr. Mair Powell and Mr. Kerry Snow
Working Group Members: Halsey Boyd, Patricia Bradford, Sharon K. Cullen, Denise Holliday, Seong Jang, Margaret Ordóñez Smith de Danies, Ryan Owen, John Rex, Daniel Rubin, Hala Shamsuddin, Sharon Shinn, John Turnidge, Thamban Valappil, Mel Weinstein, Matt Wikler

Dr. Powell gave an overview of the updates/revisions that the M23 WG have made in the fourth edition of the document including:

- Chapters have been re-arranged to follow the order that usually applies when developing a new antibacterial agent; each chapter also considers revisions

- New arrangement for setting MIC interpretive criteria for new agents depending on time since FDA approval
  - If agreement with FDA then publish
  - If disagreement then delay publication

- New set up for the Working Groups
  - Implications for handling of requests from sponsors for new or revised interpretive criteria
  - New guidance on submitting requests and details of handling, including appointment of ad hoc working groups

- New section on PK-PD covering nonclinical cutoffs and clinical exposure-response cutoffs
  - Drafted by PK-PD Working Group

- Integrated into a single chapter that also considers epidemiologic, clinical exposure-response and clinical cutoffs
  - Drafted by both groups

- New section that considers how interpretive criteria are then arrived at taking into account all available cutoffs
  - This section does not attempt to be definitive but describes the scenarios that may occur in terms of what is available and the relative strength of evidence that may apply

Dr. Powell then requested input regarding a statement in the revised edtion of M23 Appendix A, *Statement of Policy of the AST Standing Subcommittees of the CLSI*. Currently in the policy statement for resolving discrepencies it states:

4. **Resolution of discrepancies:** CLSI will establish a Microbiology Area Committee Working Group to explore a process, with both a U.S. and global perspective, to manage and resolve discrepancies in breakpoints. This process will include drug sponsors, regulatory agencies, device manufacturers, generic drug sponsors, professions, and other interested parties.

Since this has never actually occurred, the WG requested to delete this item from the policy statement. Subcommittee agreed to delete this – **Approved 11-0**.

The revised M23 document is estimated for publication in July.

IX. REPORT OF THE METHODOLOGY WORKING GROUP (Electronic Folder 8)

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

Members Present: Romney Humphries, Sandra Richter, Darcie Roe-Carpenter, Katherine Sei, Susan Sharp, Ribhi Shawar, John Turnidge, and Mel Weinstein

Technical Advisors Present: Laura Koeth

Members Absent: Seth Housman

1. **Report from the Anaerobe Ad Hoc Working Group**: Darcie Roe-Carpenter, Chairperson
   Ad-hoc WG members in attendance at Sunday January 11, 2015 meeting: Diane Citron, Audrey Schuetz, Karen Anderson, Cindy Knapp, Meredith Hackel, Stephen Jenkins, Hanna Wexler, and Laura Koeth. Absent: Joanne-Dzink-Fox, Nilda Jacobus, and Hanna Wexler

- It was recommended that verbiage associated with *Lactobacillus* spp. be removed from the proposed new Intrinsic Resistance (IR) Table B.5 Anaerobic Gram-Positive Bacilli.
- It was also recommended that *Clostridium ramosum* be removed from the new IR table B.5.

The vote to approve the new/modified IR Table(s) with the above changes passed: Anaerobe Working Group (WG) Vote: 9/0/0. **Approved by Subcommittee 10-0; 1 absent.**

- A discussion ensued regarding the potential need for vancomycin Epidemiological Cut-off Values (ECVs) for gram-positives (in addition to *Clostridium* spp.).
- The point was made that data are needed for agar dilution testing with *Clostridium* spp. and a request was made of persons who might be able to provide such data. The issue will be discussed further during the next ad hoc WG conference call.
- Revisions for the next M11 document will be discussed at the next ad hoc WG conference call and at the June SAST meeting. Gradient diffusion methods will be considered during these discussions. The following related issued were raised:

  - Multiple manufacturers now produce such products (2 additional ex-US).
  - As a WG, a decision needs to be made as to what should be said regarding gradient diffusion methods, particularly as it relates to establishment of ECOFFs.
  - Once decided upon, the WG must decide what will be required to support those decisions.
  - Ribhi Shawar offered to look into what data was used to support approval of Etest strips specifically for antimicrobial susceptibility testing of anaerobes.
  - Concerns were expressed regarding lack of knowledge related to the two additional gradient diffusion products.
  - M23 provides guidance as to how systems can be compared to standard methods to evaluate performance, etc. of such systems.

- Anaerobe Antibiogram changes that need to be published will be further discussed over the next 6 months.

2. **Mueller-Hinton Agar Working Group:**
   Barbara Zimmer gave a brief update on the progress of the ISO document on Mueller-Hinton medium.

- The document received final approval by ISO and will be published in the near future as: ISO16782 Antimicrobial susceptibility testing — Manufacturer's Protocol Criteria for Acceptable Lots of Dehydrated Mueller-Hinton Agar and Broth for Antimicrobial Susceptibility Testing. It will replace CLSI documents M6 and M32 (as one document for both broth and agar).
- The issue will be added to the June 2015 SAST meeting agenda.

3. **Report from the Direct Blood Culture Ad Hoc Working Group:** Romney Humphries, Chairperson; April Abbott, Recording Secretary
   Ad-hoc WG members in attendance at Sunday January 11, 2015 meeting: Lauri Thrupp, Barbara Zimmer, Thomas Kirn, and Melvin Weinstein

- Barbara Zimmer conducted a valuable literature review on the issue (specifically for blood cultures).
- The serum separator or double spin approach to eliminating blood cells was considered the best approach.
- The question was raised as to whether a broth inoculated with the positive blood culture medium and incubated for a few hours prior to adjustment to a 0.5 McFarland could be used. Romney Humphries stated that she shared data with the ad hoc WG demonstrating that this method resulted in lower colony counts than standard methods; this is the rationale for not taking this tack, at least initially.
- The WG agreed to work on standardizing the methods first against both disk diffusion and broth microdilution, and as a subsequent step looking at direct inoculation and/or broth inoculation.
- Bill Brasso indicated that guidance for manufacturers as it relates to these approaches for commercial systems is needed in conjunction with above efforts. Such guidance would be preferred prior to actions on the part of manufacturers as to what equivalency studies would be needed.

4. **Report from the Atypical Staphylococci (also called small variant staphylococci) Ad Hoc Working Group:** Romney Humphries, Chairperson. WG membership: TBD

- Romney Humphries indicated that a collection of such organisms has now been put together.
- The question arose as to whether PBP2a and *mecA* testing might be all that could be used on these organisms.
- Laura Koeth indicated that there were concerns regarding inoculation issues (also with mucoid organisms such as *Pseudomonas aeruginosa*).
- Robin Patel indicated that these organisms are not just important in cystic fibrosis patients, but also in cultures from infected orthopedic implants. Antimicrobial Susceptibility Testing (AST) data are needed in such cases above and beyond *mecA*/PBP 2a testing.

5. **Report from the Broth Microdilution (BMD) Testing Ad Hoc Working Group:** Bill Brasso, Chairperson
   Ad Hoc WG members: Susan Kircher, Cindy Knapp, Laura Koeth, Katherine Sei, Ribhi Shawar, John Turnidge, Michael Ullery, Halsey Boyd, and Bob Rennie

   The ad hoc WG's approach was to follow two tracks:

   Track 1- Defining the Main Sources of Variability in MIC Testing

   BMD Survey Results & Recommendations

   Track 2 - Dealing with Variability in MIC Testing – What to do with it?

   STATS Team update

Track 1: Results of the survey designed by the BMD Ad Hoc WG to help identify specific areas of variation when using BMD were shared.

- 14 Laboratories completed the survey (3 outside the U.S.).
- Participants were instructed: "Unless specified, the questions will pertain to testing routine, non-fastidious bacterial isolates."
- Issues were broken down in terms of importance into Low, Moderate, or High.
- The frequency of performance of colony counts as a quality assurance measure was quite variable.
  - Additional verbiage on this issue may need to be added to relevant CLSI documents (The SAST recommends quarterly testing.).
- The question on the number of passages performed prior to actual testing indicated differing numbers by laboratory.
- Responses to the question as to how long panels should be allowed to thaw prior to inoculation exhibited wide variation among laboratories. A question was posed by the ad hoc WG as to whether verbiage should be added to the SAST documents addressing this issue. (No current recommendations exist.).
- Variable results were received as to how many trays/plates should be stacked during incubation. SAST documents state that no more than 4 should be incubated in a stack. A suggestion was made that the comment in the documents may need to be emboldened.
- As to the question asking what types of approaches are used to prevent panels from drying out, many different responses were received. The ad hoc WG raised the question as to whether guidance should be provided in SAST documents on this issue as well.
- Approaches to reading panels likewise differed somewhat from laboratory to laboratory. The question was posed: Does the verbiage in our SAST documents require clarification, etc.?
- Additional questions asked by the ad hoc WG included the following:

  - What should people do when there are difficult to read or inconclusive endpoints? Currently there is no direction in the SAST documents to address this.
  - Is the 2-mm button requirement for reading an MIC reasonable? Upon what is it based?
  - How do you deal with trailing endpoints?
  - Following considerable discussion on laboratories' responses to the examples on the slides for reading MICs when skipped wells were seen, the question was asked: "Is a separate appendix need to provide guidance on specific bug/drug combinations that are difficult to read?"
  - What should you do if 3 - 5 isolated colonies are not available?
  - What should you do if colonies are "sticky", and do not produce a homogeneous suspension?
  - What is the best way to prepare a purity plate – from the inoculum or the tray itself?

- Katherine Sei suggested that studies may be needed to assess how these many variables actually impact MICs.

- Sharon Cullen commented on the utility and applicability of these survey results to QC testing and the QC WG. Is there an opportunity for synergy between groups here?
- Implications also exist for fungal and veterinarian WGs.

Track 2: (Dealing with variability in MIC testing): Planned replicate testing with clinical isolates

- AST manufacturers replicate test clinical isolates (from 6-27 replicates) on reference panels as part of their product development.
- This testing is done strictly per CLSI guidelines.
- The ad hoc WG is in the process of reviewing the data, and plan to present it at the June 2015 meeting.
- A "glimpse' at a preliminary review of the findings was presented.

6. **Report from the Joint CLSI/EUCAST ad hoc Polymyxins Breakpoints WG**: John Turnidge, Chairperson
   Ad Hoc WG members: Alasdair MacGowan, Johan Mouton, Stephen Jenkins, L. Martinez, and Roger Nation

   John Turnidge presented an update:

- Sticking is the "sticking point".
  - They bind to plastics and other laboratory materials.
  - The binding is due to an electrostatic interaction.
  - The binding is concentration dependent – there is lower binding at higher concentrations.
- The ad hoc WG hopes to have recommendations for the group on colistin breakpoints for the June meeting.
- No PK/PD data are really available for evaluation of polymyxin B.
- Polymyxins are poly-cationic molecules when in solution, with 5 charges.
- Colistin has 2 components (A and B), whereas polymyxin B has components B1 and B2. The ratios can vary, but available evidence suggests similar potencies.

Methodology WG Vote 1: Can we ignore component polymyxin variation in analyses?
Yes 9; No 0; Abstain 1 (Passed). **Approved by Subcommittee 10-0; 1 absent**

- In humans colistin is approximately 50% protein bound whereas mouse values are approximately 90%.
- The polymyxins act on the inner cell membrane.
- Results of testing for colistin and polymyxin B are not quite comparable.
- PK/PD values indicate that lung infections may not be treatable with colistin; mechanism unknown.
- The PK/PD findings do support efficacy in mouse thigh model.
- A new term in use is: "Exposure Response Cut-off Values".

- Colistin methane sulfonate is not cleared in persons with significant renal failure. Instead, it is slowly broken down to active colistin in the plasma.
- Monte Carlo simulations didn't find correlations between clinical data and mouse data due to the enormous range in exposures among patients with altered renal function.
- A question was posed regarding the decision not to have agar dilution breakpoints. Data that is available from the Mayo Clinic, the University of Washington, and the University of Virginia might be examined as subsequent step.
- The EU has made a label change for the compound in terms of dosing based upon renal function. The question was posed: "Is the FDA considering the same type approach?"
- The polymyxins result in significant reversible renal toxicity at higher AUCs.
- Less variability may be seen with polymyxin B that with colistin.
- Reference method:
  - BMD in Mueller-Hinton with no polysorbate-80
  - P-80 acts synergistically with polymyxins, so "falsely" lowers the MICs
  - Reproducibility established in previously presented QC studies
  - For colistin, the test reagent is colistin sulphate (not methanesulfonate)

Methodology WG Vote 2: Should trays made for the testing of polymyxins be made exclusively of polystyrene? Yes 8; No 0; Abstain 1 (Passed). **Approved by Subcommittee 10-0; 1 absent.**

Related question: Should this also be the policy for other drugs such as oritavancin wherein sticking is also an issue.

Methodology WG Vote 3: Which ECVs/ECOFFs should we go with – calculated vs. eyeball? Discussion ensued regarding the possibility that calculated ECVs could be too close to breakpoint. The calculated epidemiologic cutoff values for *E. coli* and *Enterobacter aerogenes* were one dilution lower than those chosen by the "eyeball" method. This would not, however, impact the values for Enterobacteriaceae as a whole. The 2 approaches gave five identical results.

Comments/question: Both antifungal and veterinarian groups have voted to go with calculated approach with a value of 97.5%. Should this approach be used for all drugs?

Yes: 4; No 1; Abstain 4 (no recommendation approved). Will demonstrate the ECV software at the June meeting.

- Other susceptibility testing approaches:

Disk diffusion – poor correlation
- Gales et al., JCM 2001
- Van der Heijden et al., ACMA 2007

Agar dilution – may be acceptable, needs further work
- Gales et al., JCM 2001 (only 35 isolates)

Gradient diffusion – poor correlation
- Van der Heijden et al., ACMA 2007

Methodology WG Vote 4: Can we confirm that testing will be by BMD only at this point? Yes 8; No 1; Abstain 1 (Passed). Subcommittee discussed this and a motion was passed to review disk diffusion and MIC correlate breakpoints as well as QC ranges for colistin vs *Pseudomonas* and *Acinetobacter.* **Approved 10-0; 1 absent**.

Summary of additional progress and comments:

- Animal model pharmacodynamics
  - Now established for colistin in mouse thigh and lung models
  - Thus far, only for *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
  - Tentative pharmacodynamic cutoffs can be set once approach to MCS has been resolved.
  - Insufficient information on polymyxin B at this point

- Human clinical data
- Many "noisy" single center clinical studies
- Only one true PK/PD-focused study (multi-center NIAID funded) and clinical outcome data are still undergoing analysis, and only for colistin (methanesulfonate)

7. **Report from the Tables 1 and 2 ad hoc Clean-up WG:** Chairperson, Mary York
   Recording secretary: Susan Munro
   Ad Hoc WG members: Dwight Hardy, Tony Mazzulli, Barth Reller, Richard Thomson, Stephen Jenkins,
   Considerations based on the Sanford Guide, IDSA Guidelines, the Medical letter, and other resources

Proposed Changes to Table 1:

- *Acinetobacter* spp. issues:
- Motions were not entertained on the suggestion to move fluoroquinolones, gentamicin, tobramycin, or piperacillin-tazobactam from Group A to Group B
- WG Vote to remove ticarcillin-clavulanate from column entirely – Passed (Yes 8; No 0; Abstain 2)
- WG Vote to remove cefotaxime and ceftriaxone from column entirely - Passed (Yes 5; No 2; Abstain 2)
- WG Vote to change Title of Column to *Acinetobacter baumannii* and to move *Acinetobacter* spp. other than *A. baumannii* into nonfermenters section- Passed (Yes 7; No 0; Abstain 2)

Subcommittee Input: **No changes at this time.** WG needs to continue to work on this to show changes to Table 2's as well and come back and present changes for *Acinetobacter.* **Approved 10-0; 1 absent.**

- *Burkholderia cepacia* issues:

– WG Vote to move levofloxacin from group B into group A- Passed (Yes 8; No 0; Abstain 2). **Approved by Subcommittee 10-0; 1 absent.**

– WG Vote to move ticarcillin-clavulanic acid from Group B to Group C – Failed (Yes 2; No 5; Abstain 2). **No Change.**

- *Stenotrophomonas maltophilia* issues:

– WG Vote to move chloramphenicol from Group B to group C – Passed (Yes 7; No 0; Abstain 3). **Approved by Subcommittee 10-0; 1 absent.**

– WG Vote to move levofloxacin from group B to Group A - Failed (Yes 2; No 3; Abstain 5). **No Change.**

– Motion to remove the following footnote from the bottom of Table 1 - * MIC testing only; disk diffusion test unreliable. Failed (Yes 4; No 3; Abstain 3) **No Change.**

- Motion to remove ofloxacin from the entire Table – WG vote - Passed (Yes 8; No 0; Abstain 0). **Approved by Subcommittee 10-0; 1 absent.**

- Motion to remove telithromycin from entire Table - WG vote Passed (Yes 7; No 0; Abstain 2). **Approved by Subcommittee 9-0; 1 abstain, 1 absent**

- A recommendation from the Ad Hoc WG suggesting the following comment revision <u>was not</u> entertained: 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.**

8. **Molecular Results Reporting Ad Hoc Working Group:** Chairperson, Cathy Petti; Co-chair, Thomas Kirn
   Ad Hoc WG members: Paul Edelstein, Yi Wei Tang, Ferric Fang, Neil Woodford (Note: Karen Carroll will join in June 2015)

   No report at this meeting to the Methods WG per se, but progress is being made.

9. **Alternate Disk Potency Ad Hoc Working Group:** Is in the process of being formed.

10. **Call for Suggestions related to unmet needs:**

- Romney Humphries asked that the WG consider looking at the impact of the addition of polysorbate 80 to MIC test systems including testing of gram-positive organisms with certain antimicrobials.

  – In inoculum preparations

- In drug preparations
- In panels

X. REPORT OF THE QUALITY CONTROL WORKING GROUP (Electronic Folder 9)

Co-Chairholder – Dr. Steven Brown
Co-Chairholder – Ms. Sharon Cullen

Members Present: Bob Flamm, Janet Hindler, Denise Holliday, Ross Mulder, Susan Munro, Patti Conville, Bob Rennie, Mary York

Members Absent: Stephen Hawser, Michael Huband, Frank Wegerhoff

All proposed QC ranges shown below in red for each drug were approved by the Subcommittee (Approved 10-0; 1 absent) as follows:

Name	**AZD0914**	**Previous ID**		**Abbrev**	**TBD**	
Solvent	**DMSO**	**Diluent**	**DMSO**	**Rev**		
Route of Administration		**Class**	**Spiropyrimine trione (a DNA Gyrase inhibitor distinctfrom quinolones)**	**Subclass**	**TBD**	
QC Strain (ATCC®)	**Acceptable limit**	**# mm or dil**	**% In range**	**MODE**	**Shoulder %**	**Variability/Comments**
***S. aureus* ATCC® 29213**		**0.12-05**	**100.0%**	**0.25**		media variability
***E. faecalis* ATCC® 29212**		**0.25-2**	**100.0%**	**0.5**	**93.3% @ 1**	media and lab variability. Rangefinder recommended 3 dil
***E. coli* ATCC® 25922**		**1-4**	**100.0%**	**2**		
***S. pneumoniae* ATCC® 49619**		**0.12-0.5**	**100.0%**	**0.25**		
***H. influenzae* ATCC® 49247**		**0.12-1**	**100.0%**	**0.5**	**82.7% @ 0.25**	Rangefinder recommended 3 dil range
WG vote: 9-0; 1 abstain, 1 absent						

Name	**Delafloxacin**	**Previous ID**		**Abbrev**	**DFX**	
Solvent	**1/2 volume of water, then 0.1 mol/L NaOH dropwise to dissolve**	**Diluent**	**Water**	**Rev History**		
Route	**IV**	**Class**	**Quinolone**	**Subclass**	**FQ**	
QC Strain (ATCC)	**Acceptable limit**	**# mm or dil**	**% In range**	**MODE**	**Shoulder %**	**Variability/Comments**
***E. coli* ATCC® 25922**		**28-35**	**100.0%**	**31**		**Rangefinder range proposed Gavin proposed was 97% in**
***P. aeruginosa* ATCC® 27853**		**23-29**	**99.2%**	**25 & 26**		**Rangefinder & Gavan agree**
***S. aureus* ATCC® 25923**		**32-40**	**98.8%**	**35 & 36**		**Rangefinder & Gavan agree. 60 results from lab 1 were removed as outliers and 6 results from lab 8 were removed (out of QC for control).** **Add statement to troubleshooting guide about zones too large, refer to reading instructions for fuzzy zones.**
***S. pneumoniae* ATCC® 49619**		**29-36**	**99.7%**	**32**		**Rangefinder. 60 results from lab 1 were removed as outliers and 60 results from lab 8 were removed (out of QC for control). Only have 6 labs (M23 requires 6). Both labs read larger. Could age of inoc also contribute? Recommend investigate and new study**
***H. influenzae* ATCC® 49247**		**40-51** ~~**40-52**~~	**97%** ~~**99.2%**~~	**45**		**Note: Largest range for H. influ is 12 mm for clinafloxacin. Combination of range finder and Gavin to get >95% in range using 12 mm zone size**

Delafloxacin (Continued)						
S. aureus ATCC® 29213		0.001-0.008	99.2%	0.002	86.0% @ 0.004	Some lot-to-lot variability with Lot A giving primarily lower MICs and lot C giving higher MICs
E. faecalis ATCC® 29212		0.015-0.12	100.0%	0.06	92.5% @ 0.03	
S. pneumoniae ATCC® 49619		0.004-0.015	98.9%	0.008		
E. coli ATCC® 25922		0.008-0.03	96.3%	0.015	52.70%	Rangefinder suggested 0.004 - 0.03
P. aeruginosa ATCC® 27853		0.12-0.5	99.6%	0.25		
H. influenzae ATCC® 49247		~~≤0.002~~ 0.00025-0.001	100.0%	0.0005		Some off scale but number of results at ≤0.0025 are so few (11) that it wouldn't change the recommendation). In the future, do we need another QC strain that will be on scale with dilutions likely to be tested?
WG vote:12-0						

Name	Solithromycin	Previous ID	CEM101	Abbrev	SOL	
Solvent	0.05% glacial acetic acid	Diluent	water	Rev History		
Route of Administration		Class	fluoroketolide	Subclass		
QC Strain (ATCC®)	Acceptable limit	# mm or dil	% In range	MODE	Shoulder %	Variability/Comments
N. gonorrhoeae ATCC® 49226		~~34-42 mm~~ 33-43 mm	~~95.8%~~ 98.5%	38 mm		Rangefinder 33-43 mm, some disk lot variability, also see result of 43 in media lots
N. gonorrhoeae ATCC® 49226		0.03-0.25	100.0%	0.12	80.5% @ 0.06	By agar dilution, lab variabilty
WG vote:10-0; 2 abstain						

Name	**S-649266**	**Previous ID**		**Abbrev**		
Solvent	**0.85% Saline**	**Diluent**	**0.85% Saline**	**Rev History**		
Route of Administration		**Class**	**ß-lactam**	**Subclass**	**Siderophore cephalosporin**	**To correlate in vitro and in vivo results, need to reduce iron (esp with ITT Acinetobacter spp.). Will pursue modification of reference method for future to address this issue and conduct M23 study to propose QC for modified method (ideally without use of proprietary materials e.g. modification for CAMHB to reduce iron vs use of Iso sensitest and chelex). Proposal for CAMB is an interim proposal. Note: Trailing is observed when reading MIC - suggest further assessment and potential guidance on reading or confirm if instructions for reading sulfonomides could be used. Use of new materials would need to include studies of multiple lots/mfg. Recommendations should go to methods WG first and then do M23 Tier 2 study**
QC Strain (ATCC®)	**Acceptable limit**	**# mm or dil**	**% In range**	**MODE**	**Shoulder %**	**Variability/Comments**
***E. coli* ATCC® 25922**		**0.06-0.5**	**100.0%**	**0.25**		
***P. aeruginosa* ATCC® 27853**		**0.5-4**	**97.5%**	**0.5**	**61.2% @ 1**	
WG vote:11-0; 1 abstain						

Name	**Amikacin/ Fosfomycin (5/2)**	**Previous ID**		**Abbrev**		**Presented by JMI**
Solvent	**Amikacin - Water, Fosfomycin-- Water**	**Diluent**	Amikacin – Water Fosfomycin - Water	**Rev History**		
Route of Administration		**Class**		**Subclass**		**Method: Includes Glucose 6 Phosphate. Concentration listed represents level of amikacin. Do we need to address sections in text with dosage (since it is an infusion). Request QC strains that confirm both adequate amounts of both drugs (e.g., like E. coli 35218). JMI has been running single drugs from same lot concurrently. Note: fosfomycin alone is currently approved only for agar due to skipped wells in broth. This wasn't observed in this combination and agar and broth data meets acceptance criteria.**
QC Strain (ATCC®)	**Acceptable limit**	**# mm or dil**	**% In range**	**MODE**	**Shoulder %**	**Variability/Comments**
***S. aureus* ATCC® 29213**		**0.5-4**	**100.0%**	**2**	**85.8% @ /1**	**Broth range approved also addresses agar dilution data**
***E. faecalis* ATCC® 29212**		**32-128**	**100.0%**	**64**		
***E. coli* ATCC® 25922**		**0.25-2**	**100.0%**	**1**		**Range expanded to 4 dilution to address both broth and agar data**
***P. aeruginosa* ATCC® 27853 by broth**		**1-8**	**99.7%**	**4**	**shoulder 49% at 2**	**Range expanded to 4 dilution to address both broth and agar data**
***H. influenzae* ATCC® 49247**		**0.5-4**	**97.8%**	**1**	**64.3 @ /2**	
***S. pneumoniae* ATCC® 49619**		**8-64**	**100.0%**	**32**	**69.2% @ 16**	
WG vote:11-0; 1 absent						

Name	**Azithromycin**	**Previous ID**		**Abbrev**		
Solvent	**95% ethanol or** glacial acetic acid	**Diluent**	**Broth Media**	**Rev History**		
Route of Administration		**Class**	**Macrolide**	**Subclass**		
QC Strain (ATCC®)	**Acceptable limit**	**# mm or dil**	**% In range**	**MODE**	**Shoulder %**	**Variability/Comments**
***N. gonorrhoeae* ATCC® 49226**		**0.25-1**	**97.6%**	**0.5**		**by agar dilution, some media variability**

Name	**Cefepime/ Tazobactam @ fixed 8 µg/ml**	**Previous ID**	**WCK 4282**	**Abbrev**		**Presemted by JMI, Pharma sponsor Wockhardt**
Solvent	**Cefepime - Phosphate buffer. Tazobactam- water**	**Diluent**	**Cefepime - Phosphate buffer. Tazobactam- water**	**Rev History**		
Route of Administration		**Class**	**β-lactam/β-lactamase inhibitor combination**	**Subclass**		
QC Strain (ATCC®)	**Acceptable limit**	**# mm or dil**	**% In range**	**MODE**	**Shoulder %**	**Variability/Comments**
S. aureus ATCC® 29213		**1-4**	**100.0%**	**2**		
***E. coli* ATCC 25922**		**0.03-0.12**	**100.0%**	**0.06**		
***K. pneumoniae* ATCC® 700603**		**0.12-0.5**	**99.2%**	**0.25**		**Strain is not best to determine TAZ activity. Cefepeme alone = 0.5-1**
E. coli* NCTC 13353		**0.12-0.5 ~~0.06-0.5~~**	**95.8% ~~100%~~**	**~~0.25~~**	**47% @ .5**	**Rangefinder 0.06-0.5. Better indicator of TAZ activity. Cefepeme alone = >4 *This is a supplemental QC strain that should be listed in a footnote for this drug.**
***P. aeruginosa* ATCC® 27853**		**0.5-4**	**100.0%**	**1**	**87.8% @ 2**	**Per Jim Ross: ATCC can get org from NCTC. Request will be made to ATCC to be available prior to market release**
H. influenzae ATCC® 49247		**0.5-2**	**100.0%**	**1**		
S. pneumoniae ATCC 49619		**0.03-0.12**	**100.0%**	**0.06**		
WG vote: 10-0; 1 absent, 1 abstain						

Name	**Meropenem/ RPX7009 @ fixed 8 µg/ml**	**Previous ID**		**Abbrev**		**Presented by JMI, Pharma sponsor Rempex (The Medicines Company)**
Solvent	**9/10 DMSO**	**Diluent**	**Water**	**Rev**		
Route of Administration		**Class**	**β-lactam/β-lactamase inhibitor combination**	**Subclass**		**Follow up question: Which is better QC for combo? Need for tables or potentially for troubleshotoing**
QC Strain (ATCC)	**Acceptable limit**	**# mm or dil**	**% In range**	**MODE**	**Shoulder %**	**Variability/Comments**
S. aureus ATCC 29213		**0.03-0.12**	**100.0%**	**0.06**		
E. coli ATCC 25922		**0.008-0.06**	**100.0%**	**0.03**	**72.0% @ 0.015**	
E. coli ATCC 35218		**0.008-0.06** ~~**0.015-0.06**~~	**100%** ~~**98.3**~~	**0.03**	**60.0% @ 0.015**	**Range Finder 0.015 – 0.06. Some lab and media variability. Request future proposal for Meropenem alone (data is available for one lot but was not included in Agenda)**
P. aeruginosa ATCC 27853		**0.12-1**	**100.0%**	**0.03**	**65.3% @ 0.5**	
K. pneumoniae ATCC 700603		**0.015-0.06**	**99.6%**	**0.03**		
K. pneumoniae ATCC BAA1705		**0.015-0.06**	**97.1%**	**0.25**		
WG vote: 10-0; 1 absent, 1 abstain						

Name	**Meropenem/ RPX7009 @ fixed 4 µg/ml**	**Previous ID**		**Abbrev**		**Request has been withdrawn by sponsor**
Solvent	**9/10 DMSO**	**Diluent**	**Water**	**Rev**		
Route of Administration		**Class**	**β-lactam/β-lactamase inhibitor combination**	**Subclass**		
QC Strain (ATCC)	**Acceptable limit**	**# mm or dil**	**% In range**	**MODE**	**Shoulder %**	**Variability/Comments**
S. aureus ATCC 29213		**0.03-0.12**	**100.0%**	**0.06**		**Request has been withdrawn by sponsor**
E. coli ATCC 25922		**0.015-0.06**	**100.0%**	**0.03**		**Request has been withdrawn by sponsor**
E. coli ATCC 35218		**0.015-0.06**	**100.0%**	**0.03**		**Request has been withdrawn by sponsor**
P. aeruginosa ATCC 27853		**0.12-0.5 0.12-1**	**92.3% 100%**	**0.03**		**Request has been withdrawn by sponsor**
K. pneumoniae ATCC 700603		**0.015-0.06**	**98.6%**	**0.03**		**Request has been withdrawn by sponsor**
K. pneumoniae ATCC BAA1705		**0.015-0.06**	**99.5%**	**0.25**		**Request has been withdrawn by sponsor**

Name	**Eravacycline**	**Previous ID**		**Abbrev**		**Presented by IHMA**
Solvent		**Diluent**		**Rev History**		
		Class	**Tetracycline**	**Subclass**		
QC Strain (ATCC)	**Acceptable limit**	**# mm or dil**	**% In range**	**MODE**	**Shoulder %**	**Variability/Comments**
C. difficile ATCC 700057		**0.06-0.25**	**99.6%**	**0.12**		Agar dilution
B. fragilis ATCC 25285		**0.06-0.25**	**100.0%**	**0.12**		Agar dilution
B. thetaiotaomicron ATCC 29741		**0.12-1**	**100.0%**	**0.25**	**93.6% @ 0.5**	Agar dilution **lab variability**
E. lentum ATCC 43055		**No Range. Results off-scale @ ≤0.03**				
WG Vote – 10-0; 1 absent, 1 abstain						

Name	**Meropenem**					
***S. pneumoniae* ATCC 49619**		**0.03-0.25**	**100.0%**	**0.06**	**79%@ 0.12**	**Original Tier 2- using today's criteria would establish 4 dilution range. Additonal Tier 3 data also supports expansion of range to 4 dilutions.**
WG Vote – 10-1; 1 absent						

XI. AGENDA SUBMISSIONS FOR 14-16 JUNE 2015 MEETING IN ARLINGTON

Materials for the June 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 14-16 June 2015 meeting please:

1) Submit agenda materials electronically as a PDF file **on or before Thursday, 14 May 2015.**

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 6, 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 (franklincockerill@yahoo.com) and also to Tracy Dooley (tdooley@clsi.org) for review.

XII. ADJOURNMENT – The meeting adjourned at 10:50 a.m. on Tuesday, 13 January 2015.

XIII. 2016 MEETING DATES

- 10-12 January 2016 at the Mission Palms, Tempe, Arizona
- 5-7 June 2016 at the Westin San Diego Gaslamp Quarter, San Diego, California

Respectfully submitted,

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

Appendix A.

Table 1A

Cefazolin[c] (~~surrogate test for oral cephalosporins and uncomplicated UTI~~)
Lomefloxacin or ofloxacin Norfloxacin
Nitrofurantoin
Sulfisoxazole
Trimethoprim

c. 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. Cefazolin results also predict susceptibility and resistance to cefazolin when ~~cefazolin is~~ used for uncomplicated UTIs

Table 2A
Parenteral

A	Cefazolin	30 µg	≥ 23		20–22	≤ 19	≤ 2		4	≥ 8	(9) Interpretive criteria for cefazolin when cefazolin is used for therapy of infections other than uncomplicated UTIs due to *E. coli*, *K. pneumoniae*, and *P. mirabilis*. Interpretive criteria are based on a dosage regimen of 2 g every 8 h. See comment (7).
U	Cefazolin	30 µg	≥ 15		–	≤ 14	≤ 16	–	–	≥ 32	Interpretive criteria for cefazolin when cefazolin is used for therapy of uncomplicated UTIs due to *E. coli*, *K. pneumoniae*, and *P. mirabilis*. Interpretive criteria are based on a dosage regimen of 1 g every 12 h. See additional information below under CEPHEMS (ORAL).

U	Cephalothin ~~(surrogate test for oral cephalosporins and uncomplicated UTI)~~	30 µg	≥ 18		15–17	≤ 14	≤ 8		16	≥ 32	(11) Cephalothin interpretive criteria can be used only to predict susceptibility to the oral agents, cefadroxil, cefpodoxime, cephalexin, and loracarbef. Older data that suggest that cephalothin results could predict susceptibility to some other cephalosporins may still be correct, but there are no recent data to confirm this. (12) To predict results for oral cephalosporins when used for therapy of uncomplicated UTIs, testing cefazolin is preferred to testing cephalothin.

Oral

U	Cefazolin ~~(surrogate test for oral cephalosporins and uncomplicated UTI)~~	30 µg	≥ 15		–	≤ 14	≤ 16	–	–	≥ 32	(20) Interpretive criteria when cefazolin results are used to 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. See comment (12).