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Summary Minutes
Subcommittee on Antimicrobial Susceptibility Testing
Loew's Atlanta Hotel
Atlanta, Georgia
10-12 June 2012

A meeting of the CLSI Subcommittee on Antimicrobial Susceptibility Testing was held on 10-12 June 2012, at the Loew's Atlanta Hotel, Atlanta, Georgia. The following were in attendance:

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

Members Present

Jeff Alder, PhD	Bayer Healthcare
Patricia A. Bradford, PhD*	AstraZeneca
Michael N. Dudley, PharmD, FIDSA	Rempex Pharmaceuticals
George M. Eliopoulos, MD	Beth Israel Deaconess Medical Center
Dwight J. Hardy, PhD	University of Rochester Medical Center
David W. Hecht, MD	Loyola University Medical Center
Janet F. Hindler, MCLS, MT(ASCP)	UCLA Medical Center
Mair Powell, MD, FRCP, FRCPath	MHRA
Richard B. Thomson, Jr., PhD	Evanston Hospital, NorthShore University HealthSystem
John D. Turnidge, II, MD	SA Pathology at Women's and Children's Hospital
Melvin P. Weinstein, MD**	Robert Wood Johnson University Hospital
Barbara L. Zimmer, PhD	Siemens Healthcare Diagnostics, Inc.

* Participated by Conference Call on 11-12 June
** Participated by Conference Call on 11 June

Advisors Present

Paul G. Ambrose, PharmD, FIDSA	ICPD

Karen Bush, PhD	Indiana University
Steven D. Brown, PhD	The Clinical Microbiology Institute
Edward Cox	FDA Center for Drug Evaluation and Research
William A. Craig, MD**	University of Wisconsin School of Medicine
Cynthia L. Fowler, MD	MFHSC
Stephen G. Jenkins, PhD, D(ABMM),F(AAM)	New York Presbyterian Hospital
Ronald N. Jones, MD	JMI Laboratories
Gunnar Kahlmeter, MD, PhD	ESCMID
James S. Lewis, II, PharmD	University of Texas Health Science Center
Brandi Limbago, PhD	Centers for Disease Control and Prevention
Frederic J. Marsik, PhD, ABMM	FDA Center for Drug Evaluation and Research
Linda A. Miller, PhD	GlaxoSmithKline
Harriette L. Nadler, PhD	EUSA USA Pharmaceuticals, Inc.
Robin M. Patel, MD	Mayo Clinic
Sandra S. Richter, MD, D(ABMM)	Cleveland Clinic
Flavia Rossi, MD	University of Sao Paulo
Dale A. Schwab, PhD, D(ABMM)	Quest Disagnostics, Nichols Institute
Jana M. Swenson, MMSc	Consultant
Joseph G. Toerner, MD, MPH	FDA Center for Drug Evaluation and Research

** Participated by Conference Call on 11 June

Reviewers Present

Jane E. Ambler	Astra Zeneca Pharmaceuticals
Johannetsy Avillan	Centers for Disease Control and Prevention
Robert E. Badal	International Health Management Associates Inc.
Cara Bastulli	Thermo Fisher Scientific
Kimberly Bergman	FDA
Sujata M. Bhavnani, PharmD	Ordway Research Institute
Donald Biek, PhD	Cerexa, PhD
Natalie Boyd	Parkland Health & Hosp. System
Lynn Boyer	Siemens Healthcare Diagnostics Inc.
William B. Brasso	BD Diagnostic Systems
Joyce R. Bray	Siemens Healthcare Diagnostics Inc.
Linda Bruno	ACL Labs
Kathy Burtner	Siemens Healthcare Diagnostics Inc.
Dr. Rafael Canton	Hospital Universitario Ramon Y Cajal
Roberta B. Carey, PhD	Centers for Disease Control and Prevention
Diane M. Citron, M(ASCP)	R.M. Alden Research Laboratory
Rob Crink	Merck and Co., Inc.
Ian A. Critchley, PhD	Cerexa, Inc.
Sharon K. Cullen, BS, RAC	Siemens Healthcare Diagnostics Inc.
Todd Davies, PhD	Johnson & Johnson Pharmaceutical Research & Develop., L.L.C.
Michael J. Dowzicky	Pfizer, Inc.
German Esparaza, MSc	Hospital Santa Clara
Rob Eusebio, MSHA, MT(ASCP)	Siemens Healthcare Diagnostics Inc
Gina Ewald, CLS(CA), MT(ASCP)	Siemens Healthcare Diagnostics Inc.

John Farley	FDA
Francis Farnham	The Medicines Company
Sheila Farnham, MT(ASCP)	bioMerieux, Inc.
Lee Ann Feeney	Achaogen
Robert K. Flamm, PhD	JMI Laboratories
David Friedland	Cerexa, Inc.
Lawrence V. Friedrich, Pharm D	Cubist Pharmaceuticals, Inc.
Marcelo Galas	Reference Centres of Latinoamerican Countries
Barb Gancarz	bio Merieux, Inc.
Beth P. Goldstein, PhD	Beth Goldstein Consultant
Paul Grint	Cerexa, Inc.
Meredith Hackel	IHMA, Inc.
Kristina Haeckl	Cerexa, Inc.
Patricia Hogan, MT(ASCP), MBA	Pfizer, Inc.
Denise Holliday, MT(ASCP)	BD Diagnostics
Nicole Holliday	Thermo Fisher Scientific
Rebecca Howie	IMRC/CDC
Romney Humphries	UCLA
Nilda V. Jacobus	Tufts Medical Center
Alena Jandourek	Cerexa, Inc.
Seong Jang, PhD	FDA
Jack L. Johnson	International Health Management Assoc. Inc.
Judith Johnston, MS	Siemens Healthcare Diagnostics Inc.
James H. Jorgensen, PhD	University of Texas Health Science Center
Manette Juvin	Bio-Rad Laboratories
Dr. Maria Karlsson	Centers for Disease Control and Prevention
Scott B. Killian	Thermo Fisher Scientific
Aryun Kim	AstraZeneca R&D
Roberta Knefel	bioMerieux, Inc.
Laura M. Koeth, MT(ASCP)	Laboratory Specialists, Inc.
Thip Kongphet-Tran	Centers for Disease Control and Prevention
Kevin Krause	Cerexa, Inc.
Brigitte Lefebvre	Laboratoire de santé publique du Québec
Heidi Leister-Tebbe	Wyeth Pharmaceuticals
Sarah Blaine Leppanen	Blaine Healthcare Associates, Inc.
Jianguo Li	AstraZeneca
Jim Lindsay	Mast International
David Lonsway	Centers for Disease Control and Prevention
Jennifer Lorbach	Thermo Fisher Scientific
Dyan Luper, BS, MT(ASCP)SM	BD Diagnostic Systems
Linda M. Mann, PhD, D(ABMM)	Siemens Healthcare Diagnostics Inc.
Maureen Mansfield	Thermo Fisher Scientific
Jorge Matheu	PAHO
Erika Matuschek, PhD	ESCMID
Sandra McCurdy	Cubist Pharmaceuticals, Inc.
Hiroshige Mikamo, MD, PhD	Aichi Medical University Graduate School of Medicine
Dr. Greg Moeck	The Medicines Company
Ian Morrissey, MBA, PhD, FRSM	IHMA Europe
Ross Mulder, MT(ASCP)	bioMerieux, Inc.

Susan D. Munro, MT(ASCP)	
Kate Murfitt	Mount Auburn Hospital
Patrick R. Murray, PhD	BD Diagnostics
Sumathi Nambiar	FDA
Jennifer O'Connor	Siemens Healthcare Diagnostics Inc.
Kiyofumi Ohkusu, PhD	Gifu University Graduate School of Medicine
Margaret Ordóñez Smith de Danies	Microbiology Institute of Columbia
Elizabeth Palavecino, MD	Wake Forest University Baptist Medical Center
Samir Patel, PhD, FCCM	Public Health Ontario
Chris Pillar	Micromyx
James A. Poupard, PhD	Pharma Institute of Philadelphia
L. Barth Reller, MD	Duke University Medical Center
Robert P. Rennie, PhD	University of Alberta Hospital
Todd Riccobene	Forest Research Institute
Darcue E. Roe-Carpenter, PhD, CIC, CEM	Siemens Healthcare Diagnostics Inc.
James Ross	JMI Laboratories
Helio S. Sader, MD, PhD	JMI Laboratories
Paul C. Schreckenberger, PhD, D(ABMM), F(AAM)	Loyola University Medical Center
Audrey Schuetz, MD, MPH	Weill Cornell Medical College/ New York Presbyterian Hospital
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I. MEETING/OPENING REMARKS

Dr. Frank Cockerill called the meeting to order at 8:00 a.m. on Monday, 11 June 2012. He then discussed the recent changes to the subcommittee including the addition of Dr. Steve Jenkins from New York Presbyterian Hospital as an advisor. Changes to the leadership of two Working groups include Dr. Jenkins assuming the role as Chairholder for the *Enterobacteriaceae* Working Group to replace Dr. Dudley and Dr. Brandi Limbago assuming the role as Chairholder for the Staphylococcal and Streptococcal Working Group to replace Dr. Patel. He thanked both Dr. Dudley and Dr. Patel for their tremendous work over the years as Working Group Chairholders.

Dr. Cockerill then updated the subcommittee on ongoing improvement efforts to the workings of the AST Subcommittee including an Ad Hoc Working Group that was formed to assist the sponsor for the Ceftaroline presentation that will be given this morning. Following some of the process improvement ideas that have been outlined by Dr. Alder and his Process Improvement Working Group, the Ceftaroline ad hoc group worked with the sponsor off-line through scheduled conference calls in an effort to make the presentation go smoothly and prepare for any questions that may arise. Input was obtained upfront from the subcommittee during a review of the data package prior to the scheduled AST meeting, allowing both the ad hoc group and sponsor to bring additional information to address the questions raised. He then noted that the subcommittee will hear additional process improvement suggestions when Dr. Alder gives his Working Group's presentation.

Dr. Patel reviewed the purpose of the subcommittee's mission statement that is provided in electronic tab B of the meeting CD, focusing on the last paragraph as this part is most pertinent to this meeting which is:

"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. The standards and guidelines are meant to be comprehensive and to include all antimicrobial agents for which the data meet established CLSI guidelines. The values that guide this mission are quality, accuracy, fairness, timeliness, teamwork, consensus, and trust."

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 improvements underway to make the workings of the subcommittee more efficient. Some of the process changes outlined by Dr. Alder in January have been piloted and the results of these changes will be seen during these meetings. A great deal of work has been completed off-line outside of these meetings through conference calls by both the User QC Subgroup and a recently formed Ad Hoc Working Group for Ceftaroline. She thanked those involved for their assistance in making these meetings more efficient through the work being done.

CLSI is also in the process of contracting computer program specialists to implement major changes with how CLSI delivers M100. CLSI is creating a web-enabled, interactive electronic M100

document. Ms. Ochs thanked those volunteers who have provided input on what needs to go into this product to ensure it meets our user's needs. This new product is anticipated to be available in 2013.

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
- Claire Evans – Meeting Manager who coordinates all the logistics for these meetings.

III. REVISED MINUTES OF THE 22-24 JANUARY 2012 AST MEETING FOR APPROVAL

The minutes of the 22-24 January 2012 meeting were approved **(12-0)**.

IV. UPDATES TO THE CURRENT AST DISCLOSURE SUMMARY

Dr. Cockerill asked the members and advisors for any updates to the current disclosure summary provided on the CD of meeting materials. Below are the updates provided:

Dr. Bush: Consultant - Theravance
Dr. Eliopoulos: Consultant - Wockhardt Ltd.
Dr. Hardy: Consultant – Cempra Pharmaceuticals
Ms. Hindler: no longer advisor for Forest Laboratories
Dr. Richter: Research funding from Nanosphere
Dr. Turnidge: Visiting speaker for bioMeriuex
Dr. Ambrose: Consultant- Rempex Pharmaceuticals

V. CEFTAROLINE BREAKPOINT PRESENTATION (Tab D)

As part of a new process to streamline the presentation and review of breakpoints as well as prepare for the Sponsor presentation for Ceftaroline breakpoints, an Ad Hoc Working Group was formed to work with the Sponsor to assist in preparing the materials needed to submit for the agenda. The materials provided in Tab D of the meeting materials submitted by the Sponsor along with a report from the CLSI Ad hoc Working Group were circulated to the members and advisors of the subcommittee for a 3-week review and comment period. The goal of this comment/review was to try and address as many issues as possible upfront before the meeting. Responses were provided for all comments received and distributed to all meeting participants prior to the meeting.

Dr. Critchley and Dr. Friedland presented data in support of currently approved FDA interpretive criteria for Ceftaroline. Alternate proposals for some of the organisms were presented by Dr.

Jorgensen representing the CLSI Ad Hoc Working Group. The below were approved by the subcommittee as follows:

Microorganism	FDA MIC Interpretive Criteria Presented by the Sponsor	FDA Disk Diffusion Interpretive Criteria Presented by the Sponsor	WG Suggested MIC Interpretive Criteria	WG Suggested Disk Diffusion Interpretive Criteria	Interpretive Criteria Approved by Subcommittee
S. aureus	1 (S only)	≥24 (S only)	≤1, 2, ≥4	≥24, 21-23, ≤20	**MIC**: ≤1, 2, ≥4 **Disk:** ≥24, 21-23, ≤20 **Test/Report Group**: B in own box **Add note in Tables 1A and 2C**: For *S. aureus* only including MRSA. **Approved – 10-1; 1 abstain.**
Enterobacteriaceae	0.5, 1, 2	23, 20-22, 19	0.5, 1, 2	23, 20-22, 19	**MIC**: ≤0.5, 1, ≥2 **Disk:** ≥23, 20-22, ≤19 **Approved – 10-1; 1 abstain.** **Test/Report Group**: C in own box **Approved 11-0; 1 abstain.**
S. pneumoniae	0.25 (S only)	≥27 (S only)	0.5 (S only)	≥26 (S only)	For nonmeningitis **MIC**: ≤0.5 (S only) – **Approved 11-0; 1 abstain** **Disk:** ≥26 (S only) **Approved 8-3; 1 abstain** **Test/Report Group**: C in own box **Approved 10-1; 1 abstain.**
S. pyogenes	0.015 (S only)	≥24 (S only)	0.5 (S only)	≥26 (S only)	*S. pyogenes* and *S. agalactiae* will be combined and appear in Table 2H-1 for β-Hemolytic Strep **MIC**: ≤0.5 (S only) **Disk:** ≥26 (S only) **Approve 8-2; 1 absent; 1 abstain** **Test/Report Group**: C in own box
S. agalactiae	0.03 (S only)	≥26 (S only)	0.5 (S only)	≥26 (S only)	

					Approved 10-1; 1 abstain
Haemophilus spp.	0.12 (S only)	≥33 (S only)	0.5 (S only)	≥30 (S only)	**MIC**: ≤0.5 (S only) **Disk:** ≥30 (S only) **Approved 10-1; 1 abstain** **Test/Report Group**: C in own box **Add note in Tables 1B and 2E**: For *H. influenzae* only **Approved 10-0; 2 abstain.**

VI. REPORT OF THE STAPHYLOCOCCAL AND STREPTOCOCCAL WORKING GROUP - *Minutes Submitted by Brandi Limbago* (Electronic Tab E in the Meeting Agenda)

Chairholder – Brandi Limbago

Recording Secretary – Sandy Richter

Working Group Members present - Mike Dudley, George Eliopoulos, Susan Sharp
Jana Swenson, Maria Traczewski, Robert Skov, Tom Thomson

Working Group Members absent - Patricia Bradford, William Craig, Dan Sahm, Mel Weinstein,

Presenter: James Jorgensen

Items Proposed for Vote

I. Inducible clindamycin resistance:

A. Jim Jorgensen presented animal data generated in a neutropenic murine thigh model of infection by Bill Craig using strains of *S. pneumoniae*, *S. pyogenes* and *S. agalactiae*. Those strains with inducible clindamycin resistance showed early killing with clindamycin treatment followed by bacteriostatic or later regrowth, providing evidence of clinical relevance of inducible clindamycin resistance in β-hemolytic streptococci (see graphs in Agenda book, tab E, item 2.0).

In addition, four new case reports of patients failing clindamycin therapy, including high-dose therapy, for β-hemolytic streptococcal infections caused by strains with inducible clindamycin resistance [*S. agalactiae* (2), *S. pyogenes*, and Group G streptococcus] were presented (unpublished data). Of note, none of the clinical isolates converted from inducible to constitutive clindamycin resistance following (failed) clindamycin therapy.

Because of this new evidence (animal and human data) showing clinical significance of inducible clindamycin in β-hemolytic streptococci, the working group passed a motion to recommend revising the header for Table 2H-1 Supplemental table 1 (WG vote 8/1/4). After discussion and minor additional changes, the **Subcommittee voted to accept the following revised note (Approved 11-0; 1 absent).**

- **Current Note:** Since the clinical significance of inducible clindamycin resistance among β-hemolytic strep is unclear, it may not be necessary to perform tests for inducible clindamycin resistance on all isolates that are erythromycin resistant and clindamycin susceptible. Isolates from invasive infections may be considered for testing. The 2010 CDC guidelines on prevention of group B streptococcal disease in neonates recommends that colonization isolates from pregnant women with severe penicillin allergy (high risk for anaphylaxis) should be tested for inducible clindamycin resistance[a] (see comment [10] in Table 2H-1).

- **Revised Note:** Antimicrobial susceptibility testing of β-hemolytic streptococci need not be performed routinely (see comment (3) in Table 2H-1). When susceptibility testing is clinically indicated, it should include testing for inducible clindamycin resistance. In accordance with 2010 CDC guidance, colonizing isolates of group B streptococci from penicillin-allergic pregnant women should be tested for inducible clindamycin resistance (see comment (12) in Table 2H-1).[a]

B. At the Subcommittee presentation, a discussion of the optional comment in the supplemental tables regarding reporting of inducible clindamycin resistance for β-hemolytic streptococci and staphylococci, led to a motion to remove the second sentence "Clindamycin may still be effective in some patients." **The motion was approved by the Subcommittee (Approved 10-1; 1 absent).**

C. A motion to add the inducible clindamycin resistance test for *S. pneumoniae* to M100 with a supplemental table including the following comments was recommended by the Working Group (8/1/4 absent) and **approved by the Subcommittee (Approved 11-0; 1 absent):**

- Header NOTE: If testing for clindamycin resistance in *S. pneumoniae* is performed, it should include screening for inducible clindamycin resistance. - Insert comment in Table 2G for clindamycin: Inducible clindamycin resistance can be detected by disk diffusion using the D-zone test or broth microdilution (See table 2G Supplemental Table 1 and section 12 in M02-A11 and section 13 in M07-A9).

II. Group B streptococci (GBS): The Working Group (9/0/4 absent) and Subcommittee **(Approved 9-0; 3 absent**) approved a request from Janet Hindler to remove routine reporting of erythromycin for GBS from β-lactam allergic pregnant women, in order to be in alignment with 2010 CDC guidance.

- Modify Table 2H-1 Comment (12): ***Rx***: Recommendations for intrapartum prophylaxis for Group B streptococci are penicillin or ampicillin. Although cefazolin is recommended for penicillin-allergic women at low risk for anaphylaxis, those at high risk for anaphylaxis may receive clindamycin. Group B streptococci are susceptible to ampicillin, penicillin and cefazolin, but may be resistant to erythromycin and clindamycin. When Group B streptococcus is isolated from a pregnant woman with severe penicillin allergy (high risk for anaphylaxis), erythromycin and clindamycin (including inducible clindamycin resistance) should be tested, and only clindamycin should be reported.

- Same modification to Table 1B, footnote o (*Streptococcus* spp. β-hemolytic group, erythromycin and clindamycin).

III. Table 2C *Staphylococcus* spp. changes:

Action items from the January meeting included a major revision of Table 2C with segregation of the β-lactams and creation of a place for anticipated ceftaroline breakpoints.

A. A sub-group of the Staph/Strep & Text/Tables working groups (Jana Swenson, Barth Reller, Tom Thomson, Mary York and Maria Traczewski) participated in a conference call in April. A summary of their recommendations (agenda Tab E, item 3.0) was discussed by the working group and the following changes were approved by the Working Group (8/0/5 absent) and **Subcommittee (Approved 7-4; 1 absent)**. The subcommittee requested a mock-up of Table 2C including the proposed changes, but there was not time to share this with the subcommittee on the 2nd day of the meeting.

- Removal of the oxacillin disk diffusion test for *S. aureus* to reflect a change passed at the January meeting.
- β-lactam antimicrobial agents reorganized into three categories
    - Penicillinase-labile penicillins: Penicillin
    - Penicillinase-stable penicillins: Oxacillin
    - Cephems (Parenteral): Ceftaroline

- Removal of all β-lactam breakpoints except penicillin, oxacillin, cefoxitin, and ceftaroline.

  Add comment (9) for **Penicillinase-labile penicillins**: Penicillin-susceptible staphylococci are also susceptible to other β-lactam agents with established clinical efficacy against staphylococcal infections. Penicillin-resistant strains are resistant to penicillinase-labile penicillins, such as ampicillin, amoxicillin, azlocillin, carbenicillin, mezlocillin, piperacillin, and ticarcillin.

  Add comment (12) for **Penicillinase-stable penicillins**: Oxacillin (or cefoxitin) is the preferred penicillinase-stable agent for testing and results can be applied to the other

penicillinase-stable penicillins (cloxacillin, dicloxacillin, flucloxacillin, methicillin, and nafcillin). Based on a susceptible oxacillin (or cefoxitin) result, the following are considered susceptible based in the site of infection and appropriate dosing, rather than in vitro testing, for agents with established clinical efficacy against staphylococcal infections:

- β-lactam/ β-lactamase inhibitor combinations (amoxicillin-clavulanic acid, ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanic acid)
- 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), and
- carbapenems (doripenem, ertapenem, imipenem, meropenem).

Oxacillin-resistant staphylococci are resistant to all of the currently available β-lactam antimicrobial agents, with the exception of the newer cephalosporins with anti-MRSA activity. Thus, susceptibility or resistance to a wide array of β-lactam antimicrobial agents may be deduced from testing only penicillin and either cefoxitin or oxacillin. Routine testing of other β-lactam agents except those with anti-MRSA activity is not advised. See comment (4).

- Modification of comment (5) to expand the description of oxacillin resistance to include a novel *mecA* homologue.

Current comment (5):

Detection of oxacillin resistance: Tests for *mecA* or for the protein expressed by *mecA*, the penicillin-binding protein 2a (PBP 2a, also called PBP2'), are the most accurate methods for prediction of resistance to oxacillin and can be used to confirm results for isolates of staphylococci from serious infections. Isolates of staphylococci that carry the *mecA* gene, or that produce PBP 2a (the *mecA* gene product), should be reported as oxacillin resistant. Isolates that do not carry *mecA* or do not produce PBP 2a should be reported as oxacillin susceptible. Because of the rare occurrence of resistance mechanisms other than *mecA*, if MIC tests are performed in addition to disk diffusion, isolates for which oxacillin MICs are ≥ 4 μg/mL and are *mecA* negative or PBP 2a negative should be reported as oxacillin resistant. These isolates may test as susceptible to cefoxitin by disk diffusion.

Revised comment (5):

Detection of oxacillin resistance: In most staphylococcal isolates, oxacillin resistance is mediated by *mecA* encoding the penicillin-binding protein 2a (PBP 2a, also called PBP2'). Other mechanisms of oxacillin resistance are rare and include a novel *mecA* homologue (e.g., *mecC*)[1] which may not be detected by tests for *mecA* or PBP2a. Isolates that test positive for *mecA* or PBP2a should be reported as oxacillin resistant. Isolates for which either the oxacillin MIC,

cefoxitin MIC, or cefoxitin disk diffusion test is in the resistant range should also be reported as oxacillin resistant.

B. Additional changes (#1-4) to Table 2C were recommended by the Working Group (7/0/2 absent) and **approved by the Subcommittee (Approved 9-2; 1 absent):**

1. In Table 1A and Table 2C add footnote "c" (Not routinely reported on organisms isolated from the urinary tract) to minocycline.

2. In Table 1A remove telithromycin because the FDA has a black warning box for use of this drug and its indications for *S. aureus* were removed. In Table 2C the "B" was changed to an "O" for this drug.

3. In Table 1A remove quinupristin-dalfopristin because it is not FDA cleared for MRSA or coagulase-negative staphylococci; for MSSA there are many better drugs with less toxicity. In Table 2C change the Test/Report Group for quinupristin-dalfopristin from "C" to "O".

4. For daptomycin in Table 1A, add the footnote currently in Table 2C (Daptomycin should not be reported for isolates from the respiratory tract).

C. A new footnote for *Staphylococcus* spp. was approved by the Working Group (7/0/2 absent) and **Subcommittee (Approved 10-1; 1absent)**:

Table 1A: For staphylococci that are susceptible, gentamicin is used only in combination with other active agents.
Table 2C: same comment, except replace "gentamicin is" with "aminoglycosides are"

D. A motion to remove aminoglycosides and their breakpoints (amikacin, kanamycin, netilmicin, tobramycin) from Table 2C (because these drugs are not used for treatment of staphylococcal infections in any documented reference) was not approved by the Working Group (4/ 0/ 3 abstain / 2 absent). There was no Subcommittee motion.

Items for Discussion and Input

Decisions to add individual cephalosporin breakpoints back to Table 2C in M100 will be based on M23 criteria.

Reference:

Stegger M, Andersen PS, Kearns A, Pichon B, Holmes MA, Edwards G, Laurent F, Teale C, Skov R, Larsen AR. Rapid detection, differentiation and typing of methicillin-resistant Staphylococcus aureus harbouring either *mecA* or the new *mecA* homologue *mecA*(LGA251). Clin Microbiol Infect.

VII. PLACEMENT OF PHENOTYPIC TESTS IN M100

Previously the AST subcommittee sought input from the Microbiology Consensus Committee on placement of phenotypic tests in M100 that are specifically for epidemiological/infection control purposes (eg, ESBL and KPC detection) vs. those phenotypic tests for AST purposes (eg, Staph/Strep clindamycin D-test, staphylococcal β-lactamase test, enterococcal HLAR, etc.).

Dr. Thomson gave an overview of the discussion at the recent meeting of the Microbiology Consensus Committee and the input/suggestions provided as follows:

- Leave the tables where they are currently placed in M100
- Move only those tables that are specifically for epidemiological/infection control purposes to end of M100
- Move both AST and epidemiological/infection control tables to the end of M100
- Create a new document for all resistance mechanisms and add tests for other mechanisms (eg, ampC, metallo-β-lactamases, etc.)
- Have them part of an electronic document with a link taking the user to the appropriate area on the CLSI web site (eg, rationale document or expert rule)
- Mixture of above

Subcommittee discussion points:

- Since M100 is updated on a yearly basis this allows more of an option should changes need to be made to any of the phenotypic tests vs. creating a new document that may not be updated as frequently.
- With the new electronic version of M100 being developed, possibly there could be an option to have these tests included in this electronic version.
- For those tables that are no longer needed to detect S, I, R, but are for epidemiological/infection control purposes, possibly these can go on the CLSI website.

Conclusion:

The subcommittee agreed that for now having these tables in the M100 document seems to be the best place for these tables at this time. Dr. Thomson will review the tables and make a recommendation to the subcommittee in January as to which tables should possibly be moved to the back of M100.

VIII. REPORT OF THE TEXT AND TABLES WORKING GROUP
Minutes Submitted by Jana Swenson **(Electronic Tab F in the Meeting Agenda)**

Chairholder – Jana Swenson

Recording Secretary – Maria Traczewski

Working Group Members present – Janet Hindler, Judy Johnston, Dyan Luper, Linda Mann, Susan Munro, Flavia Rossi, Dale Schwab, Tom Thomson, and Mary York

Working Group Members absent –Fred Marsik, Jeffrey Schapiro, Al Sheldon, Mel Weinstein

Attended by special request: Barth Reller

Items proposed for vote:

1. Presentation and suggestion for changes to Table 1B for *N. gonorrhoeae*
2. Recommendation for handling drugs with no disk diffusion criteria (ie, MIC criteria only)
3. Recommendation for revision of Table 2G, comment 5

Items for discussion - None
Items for information only - None

1. Presentation and suggestion for changes to Table 1B for *N. gonorrhoeae:*

- **Request that we add Ceftriaxone to Group A, Cefixime to Group B, delete some agents from Group C, and modify footnote h to include therapy recommendations**

Dr. John Papp from CDC presented a request to modify recommendations in Table 1B for *N. gonorrhoeae.* The recommendation included adding ceftriaxone to group A, cefixime to group B, deleting some agents group C and modifying footnote h to include therapy recommendations. The rationale that Dr. Papp gave for his recommendations included:

- The fact that antibiotic resistance is increasing
- The fact that surveillance data is collected but too late to guide clinical therapy
- The hope that clinical labs would consider doing more frequent AST testing for *N. gonorrhoeae* in order to help guide clinical therapy.

The working group discussion centered on the following considerations:

- Should we make changes that would encourage labs to do more testing?
- Should the emphasis be more on those currently treating to use the most effective treatment in the beginning?
- How likely is it that labs would really do GC AST if we were to modify Table 1B?
- What agents should we recommend be tested if testing is done?

Following much discussion the working group recommendations were:

- To put ceftriaxone, cefixime, ciprofloxacin, and tetracycline in Table 1B in Group A [Working Group vote: 7 for, 2 opposed]

- As is done for penicillin and ampicillin with beta strep, indicate with all these agents that routine testing is not necessary despite their placement in group A

- Delete other agents except spectinomycin from Group C. Those agents removed from Group C in Table 1B (eg, cefpodoxime, cefotaxime, cefoxitin, cefuroxime, ofloxacin, and penicillin) will be listed as Group O in Table 2F.

- New footnote to explain when testing should be done:

  "(x) Culture and susceptibility testing of *Neisseria gonorrhoeae* should be considered in cases of treatment failure. Antimicrobial agent recommendations for testing include at a minimum those agents listed in Group A. The most recent CDC guidelines for treatment and testing are available at (*www.cdc.gov).*"

Subcommittee vote: Approved 11-0; 1 absent

2. **Recommendation for handling drugs with no disk diffusion criteria.**

Because of inconsistencies noted in M100 about places where disk diffusion testing criteria did not occur, a subgroup of the working group came up with suggestions to resolve the problem. At the last meeting it was decided that we should remove all these comments from Tables 2 and handle the explanation of this in the Instructions for use and in Tables 1. A subgroup of the working group made the following recommendation to accomplish this:

- Verify placement of asterisks in all Tables 1 where disk diffusion testing cannot be done (*MIC testing only; disk diffusion test unreliable.) A 2nd sentence is added to the '*' as follows: For oxacillin and vancomycin see Table 2C oxacillin, cefoxitin, and vancomycin comments.
- Modified Table 1 Staphylococci column by adding asterisks in front of oxacillin and vancomycin. Place cefoxitin on a second line under oxacillin with footnotes on both oxacillin and cefoxitin.
- Remove all comments in Table 2 where no disk criteria occur
- Revise wording in M100 Instructions for Use to explain about drugs that lack disk criteria.
- Change comment 12 "oxacillin disk intermediate" to Oxacillin disk testing is not reliable. For disk testing see cefoxitin and comments (13) and (14) for reporting oxacillin when using cefoxitin as a surrogate test.

The new wording recommended is:

5. Interpretive Criteria

Interpretive criteria are the MIC or zone diameter values used to indicate susceptible, intermediate, and resistant breakpoints.

For some antimicrobial agents, only MIC criteria may be available. For these agents, the disk diffusion zone diameters do not correlate well with MIC values. Technical issues may also preclude the use of the disk method for some agents.

For example, for antimicrobial X with interpretive criteria in the table below, the susceptible breakpoint is 4 μg/mL or 20 mm and the resistant breakpoint is 32 μg/mL or 14 mm. For agent Y below, no disk diffusion criteria are available; only MIC methods should be used to test and report agent Y.

Antimicrobial Agent	Disk Content	Zone Diameter Interpretive Criteria nearest whole mm			MIC Interpretive Criteria (μg/mL)		
		S	I	R	S	I	R
X	30 ug	≥ 20	15–19	≤ 14	≤ 4	8–16	≥ 32
Y	--	--	--	--	≤ 1	2	≥ 4

Laboratories should only report results for agents listed in the Table 2 specific to the pathogen being tested; it is not appropriate to apply disk diffusion or MIC interpretive criteria taken from an alternate Table 2. However, there may be rare cases where an agent may be appropriate for an isolate but for which there are no CLSI interpretive criteria (e.g. tigecycline). In these cases the FDA prescribing information document for the agent should be consulted.

Subcommittee vote: Approved 10-0; 2 absent

3. Recommendation for revision of Table 2G, comment 5:

Janet Hindler proposed a revision to comment 5 in Table 2G following input from Dr. Jorgensen and CDC (see T&T WG Attachment 1 for background information).

Current comment:

"For nonmeningitis isolates, the penicillin MIC can predict susceptibility to other β-lactams as follows:

Penicillin MICs ≤ 0.06 μg/mL (or oxacillin zones ≥ 20 mm) indicate susceptibility to ampicillin (oral or parenteral), ampicillin-sulbactam, cefaclor, cefdinir, cefditoren, cefpodoxime, cefprozil, ceftizoxime, cefuroxime, imipenem, loracarbef, meropenem, **and penicillin (oral or parenteral)**.

Penicillin MICs ≤ 2 μg/mL indicate susceptibility to amoxicillin, amoxicillin-clavulanic acid, cefepime, cefotaxime, ceftriaxone, and ertapenem."

Proposed revision:

"For nonmeningitis isolates, a penicillin MIC of ≤ 0.06 μg/mL (or oxacillin zone ≥ 20 mm) can predict susceptibility to the following β-lactams: ampicillin (oral or parenteral), ampicillin-sulbactam, amoxicillin, amoxicillin-clavulanic acid, cefaclor, cefdinir, cefditoren, cefepime, cefotaxime, cefpodoxime, cefprozil, ceftaroline, ceftizoxime, ceftriaxone, cefuroxime, **doripenem**, ertapenem, imipenem, loracarbef, meropenem, and penicillin (oral or parenteral)."

Subcommittee vote: Approved 10-0; 2 absent

IX. REPORT OF THE FLUOROQUINOLONE BREAKPOINT WORKING GROUP *Minutes Submitted by Karen Bush* (Electronic Tab G in the Meeting Agenda)

Chairholder – Cynthia Fowler
Recording Secretary – Karen Bush

Working Group Members present - Jeff Alder, Sujata Bhavnani, George Eliopoulos, Robert Flamm, Marcelo Galas, Elizabeth Palavecino, Mair Powell, Barth Reller, Helio Sader, Lauri Thrupp, Barbara Zimmer

Working Group Members absent – Mel Weinstein

Cynthia Fowler presented a summary of the data that were discussed at the Working Group meeting. The focus of the discussion was based on a set of proposals from a letter by Romney Humphries and Janet Hindler affiliated with the Clinical Microbiology Laboratories of UCLA Health Systems (Tab G, 2.0). In addition, a set of MIC and disk diffusion data regarding fluoroquinolone breakpoints was presented by Maria Karlsson (Tab G, 1.0) for a collection of:

- 39 Nalidixic acid Susceptible isolates of non-Typhi *Salmonella*
- 41 isolates of Nalidixic acid Resistant isolates of non-Typhi *Salmonella* with confirmed QRDR mutations.
- 20 isolates of non-Typhi *Salmonella* harboring a plasmid-mediated mechanism and no QRDR mutations.

The UCLA group was concerned about the recent approval of two ciprofloxacin (CIP) breakpoints of *Salmonella enteric* serovar Typhi and for *Salmonella* extraintestinal isolates of any serovar. They also requested that CLSI remove the comment in M100 regarding the use of maximal oral or parenteral ciprofloxacin dosing for isolates testing in the intermediate range.

At the AST Subcommittee meeting, several motions were made based on the UCLA proposals.

Proposal #1.

A motion was made to modify comments 32 and 33 in M100-S22, Table 2A as follows:

(32) For testing and reporting against *Enterobacteriaceae* except for *Salmonella* spp. (including *S. typhi*)

(33) For testing and reporting against *Salmonella* spp. (including *S. typhi*). Routine testing and reporting is indicated for *Salmonella* spp. (including *S. typhi*) from extraintestinal sources. Routine testing of *Salmonella* spp. from intestinal sources is not recommended.

Subcommittee Vote: 8-1; 1 abstain; 1 absent Approved

Proposal #2

A motion was made to remove comment 34 in Table 2A in M100-S22 regarding the use of high dose ciprofloxacin for isolates testing in intermediate range

Subcommittee Vote: 9-1; 1 abstain; 1 absent Approved

Proposal #3

It was proposed that a comment in the ciprofloxacin section of the MIC table in M100-S22 should indicate that labs should read the nalidixic acid comment #36 about testing of both nalidixic acid and ciprofloxacin. Wording should not mandate testing, but would allow labs to test nalidixic acid and a fluoroquinolone of choice. The intention was that Laboratories MAY test both nalidixic acid and ciprofloxacin by disk diffusion if labs are unable to implement the new ciprofloxacin MIC breakpoints and report using the *Salmonella* spp. interpretive criteria

The following motion was made:
Add the following to the ciprofloxacin MIC box in M100-S22, Table 2A, "If MIC testing is not performed, see comment (36).

Comment (36) In addition to testing urine isolates, nalidixic acid may be used to test for reduced fluoroquinolone susceptibility in isolates from patients with ~~extraintestinal~~ *Salmonella* infections. Strains of *Salmonella* that test resistant to nalidixic acid may be associated with clinical failure or delayed response in fluoroquinolone-treated patients with ~~extraintestinal~~ salmonellosis.

However, nalidixic acid may not detect all mechanisms of fluoroquinolone resistance. Therefore, *Salmonella* strains may also be tested with ciprofloxacin and reported using the *Salmonella* spp. interpretive criteria above. ~~See comments (32) and (33).~~

In the discussion, it was noted that nalidixic acid may not detect all mechanisms of fluoroquinolone resistance. Therefore, *Salmonella* strains may also be tested with a ciprofloxacin disk and reported using the *Salmonella* spp. interpretive criteria above. If either drug tests as I or R, the isolate should be reported as ciprofloxacin-resistant.

Subcommittee Vote: 3-6; 2 abstain; 1 absent
The motion failed.
The major objections were based on the decision to call these strains resistant.

A second motion was made to accept the proposal as recommended with no explanation as to how to interpret results.
Subcommittee Vote: 7-2; 2 abstain; 1 absent Approved

Proposal #4:

The ofloxacin breakpoint should be one dilution higher than for levofloxacin against *Salmonella* spp. Several possibilities for breakpoints were possible.

Levofloxacin: S/I/R	$\leq$0.12 / 0.25-1 / $\geq$2
Ofloxacin proposed S/I/R	$\leq$0.25 / 0.5-2 / $\geq$4

This proposal was based primarily on PK/PD data (Bhavnani – January 2011 Agenda Book Tab C 9.3) and MIC distributions (Karlsson, Tab G, 1.0).

A second set of ofloxacin breakpoints were based on clinical data (Parry, CM et al. PLoS Neglected Tropical Diseases. 5(6):e1163, 2011 Jun; preprint in June 2011 agenda book: Ofloxacin S/I/R $\leq$0.12 / 0.25-1 / $\geq$2.

A motion was made to set the ofloxacin breakpoints for *Salmonella* spp: at S/I/R

$\leq$0.12 / 0.25-1 / $\geq$2 based on clinical data (Parry et al.)

Subcommittee Vote: 11-0; 1 absent Approved

In discussing levofloxacin and ofloxacin breakpoints, the Working Group decided to wait to set disk diffusion breakpoints. Currently a multi-lab international study is underway to evaluate MIC/disk diffusion correlations for multiple fluoroquinolones for the *Enterobacteriaceae*. The Working Group anticipates having the data by January or at the latest, by June 2013.

X. REPORT OF THE QUALITY CONTROL WORKING GROUP

***Minutes Submitted by Sharon Cullen* (Electronic Tab H in the Meeting Agenda)**

Co-Chairholder - Steven Brown

Co-chairholder - Sharon Cullen

Working Group Members present- Bill Brasso, Janet Hindler, Ron Jones, Ross Mulder, Susan Munro, Bob Rennie, Frank Wegerhoff

Working Group Members absent – Stephen Hawser, Michael Huband, Ann Macone

1) Items Proposed for Vote

- New M23 QC Study for POL7080
  - *P. aeruginosa* ATCC 27583,
  - Range 0.06-0.25
  - Same range for formulation with or without P80
  - Sponsor to specify reference method prior to publication (same range)
  - **Subcommittee approved – 10-0; 2 absent**

Solvent	Water	Diluent	Water	Rev History	NA	Study by JMI, Sponsored by Polyphor Ltd.
Route of Administration	?	Class	Cyclic peptide	Subclass	NA	
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	Mode	Shoulder %	Variability/Comments
P. aeruginosa 27853 (without P-80)	0.06 – 0.25	3	98.3	0.12	NA	Slight shift ▲with Media A
P. aeruginosa 27853 (with P-80)	0.06 – 0.25	3	100	0.12	NA	Slight shift ▲ with Media A
P. aeruginosa A3140 (without P-80)	0.25 - 1	3	100	0.5	56%	Informational Purposes Only Slight shift ▲with Media A 56% shoulder @ 0.25
P. aeruginosa A3140 (with P-80)	0.12 – 1	4	99.6	0.5	98%	Informational Purposes Only Slight shift ▲with Media A 98% shoulder @ 0.25. Strain shows larger shift with P-80.
Comments/Other Actions: Both ranges of 0.06-0.25 ug/ml for POL vs *P. aeruginosa* 27853 were approved. Sponsor will select reference formulation (with or without P-80) prior to publication.						
Note: Gentamicin control - all in range but 87.5% at bottom of range						

Votes (For/Opposed/Abstained/Not present): QC Working Group: 7/0/1/4 for 27853 for both formulations (with & without surfactant). No motion was made by the Subcommittee to approve *P. aeruginosa* ATCC A3140, data was provided for informational purposes only.

- Tier 3 QC Proposals
  - *P. aeruginosa* ATCC 27853 QC
    - Tobramycin: change range from 19-25 to 20-26mm
    - Gentamicin: change range from 16-21 to 17-23 mm
    - Note: QC range changes match those proposed by EUCAST
    - **Subcommittee Approved 10-0; 2 absent**

Tier 3 Proposed Ranges: Tobramycin						
QC Strain (ATCC)	**Acceptable limit**	**# mm or dil**	**% In range**	**Median**	**Shoulder %**	**Variability/Comments**
P. aeruginosa 27853 (current)	**19-25**	**7**	**95.8%**	**23-24**	**NA**	**Small # at bottom (0 @ 19, 2% @ 20), Large # at top (4% @ 26, 15% @ 25)**
P. aeruginosa 27853 (proposed)	**20-26**	**7**	**99.5%**	**23-24**	**NA**	
Comments/Other Actions						
Results include 837 results from 6 labs, >3 media/disk mfg from 2004-2011. Complaints from multiple labs with results at top of range and/or frequent out of range high. QC range change also proposed by EUCAST						
Votes (For/Opposed/Abstained/Not present): QCWG 7/0/0/5 for 20-26 mm for tobramycin vs. *P. aeruginosa*						

Tier 3 Proposed Ranges: Gentamicin						
QC Strain (ATCC)	**Acceptable limit**	**# mm or dil**	**% In range**	**Median**	**Shoulder %**	**Variability/Comments**
P. aeruginosa 27853 (current)	**16-21**	**6**	**88.5%**	**21**	**NA**	**Small # at bottom (0 @ 16, 1% @ 17), Large # at top (11% @ 22, 2% @ 23)**
P. aeruginosa 27853 (proposed)	**17-23**	**7**	**99.0%**	**21**	**NA**	
Comments/Other Actions:						
Results include 1621 results from 6 labs, >3 media/disk mfg from 2004-2011. Complaints from multiple labs with results at top of range and/or frequent out of range high. QC range change also proposed by EUCAST						
Votes (For/Opposed/Abstained/Not present): 5/1/0/6 for 17-23 mm for gentamicin vs. *P. aeruginosa* 27853.						

Tier 3 Proposed Ranges: Teicoplanin						
QC Strain (ATCC)	**Acceptable limit**	**# mm or dil**	**% In range**	**Mode**	**Shoulder %**	**Variability/Comments**
E. faecalis 29212 (current)	**0.25-1**	**3**	**91.0%**	**0.50**	**33%**	**8% out of range low @ 0.12, 5% at top of range @ 1**
E. faecalis 29212 (proposed)	**0.12-1**	**3**	**99.6%**	**0.50**	**33%**	
Comments/Other Actions						
Includes 1117 results from 6 labs, >3 media/disk mfg from 2005-2011. Complaints from multiple labs with results at top of range and/or frequent out of range low. Shift 1 dilution lower with some media lots. Mode with tween was 0.25. Mode without tween and with agar was 0.5.						
Votes (For/Opposed/Abstained/Not present): QCWG: No vote was taken. Concerns expressed about taking action based on mixed QC data (with and without surfactant). Discussed whether or not surfactant should be used in reference method for this antimicrobial agent. Subcommittee recommended studies to evaluate drug availability in vitro (similar to studies done for colistin) and/or full M23 QC study.						

- Reduce QC required to convert from daily to weekly testing (new AST system or to add new antimicrobial to existing system) See Attachment 2 for Statistician's Summary for Alternative QC Frequency Testing Proposal

  – Current protocol: 1 replicate x 20-30 days
  – New plan advantages

    • Uses concepts of "Equivalent QC plan" from CLSI EP23-A
    • Provides similar statistical confidence
    • Reduce testing by 25%,
    • Detect problems & complete faster
    • Future opportunities based on risk/failure modes

  – New plan: 15 replicate (3 x 5 day) plan
    • Phase 1: 3 replicates for 5 days using individual inoculum preparations

  – Accept if 0 or 1 out of range
  – Fail if ≥4 out of range
  – Proceed with Phase 2 if 2-3 out of range
    • Phase 2 (if needed): repeat phase 1 (3 replicates for 5 days)

  – Accept if 2-3 out of range for all 30 replicates, Fail if ≥4 out of range
    • Revise Tables 3C and 4F, Q&A as proposed
    • Develop future M2 and M7 text revisions (to align text and tables)

    Subcommittee approved 10-0; 2 absent

- Minimum vs Routine QC

  – See Letter for Minimal QC report_Atlanta
  – Replace "minimal" with "routine" in text boxes in Tables 2A thru 2J
    • Interim improvement to reduce confusion
    • Plan to improve further in 2013

    Subcommittee approved 10-0; 2 absent

2) Items For Discussion and Input

- Various QC procedure improvements planned for future

  – See Susan Munro's Letter for Minimal QC report_Atlanta
  – Clarify situations where a QC strain may be preferred

    • Indicate where a QC strain better detects potency deterioration (e.g., *P. aeruginosa* 27853 & Imipenem, *E. coli* 35218 & β-lactamase inhibitors).
    • Should QC strain tested resemble genus or growth requirements for clinical strains being tested?

- Add references to troubleshooting guide for specific situations.
- What strain(s) to test for single drug (one or more QC strains)?
- What strain(s) to test when multiple QC strain(s) are available eg, *H. influenzae*?
- Value of QC strain when ranges are "off scale"?

- QC Working Group proposals initially planned for Jan 2013 publication but additional follow up will be required due to concerns voiced after Working Group meeting:

  – Ampicillin with ATCC 25922

    - Proposed additions to troubleshooting guide to address out of range low disk QC and double zones (e.g., incubation time, inner or outer zone, transmitted or reflected light).
    - Question: Is issue with QC strain only or with clinical isolates?
    - Action Plan: Reconsider comments & option to shift QC range slightly.

  – *P. aeruginosa* ATCC 27853

    - Proposed to add *P. aeruginosa* ATCC 27853 to Table 2A for *Enterobacteriaceae* "Routine QC" box and include comment from Troubleshooting guide regarding *P. aeruginosa* 27853 ability to detect carbapenem deterioration.
    - Action Plan: Complexity requires further consideration since table refers to disk & MIC methods (e.g., value is greater for MIC than disk, may not be needed for other antimicrobial agents).

- Request to include *E. coli* ATCC 25922 vs Colistin, MIC with surfactant in future Tier 2 QC study

  – Previous meetings discussed low drug availability and variability (especially with MICs ≤1) without surfactant.
  – CMI is considering leading this study.

- *E. faecalis* ATCC 29212 with Teicoplanin

  – Concerns expressed about taking action based on mixed QC data (with and without surfactant).
  – Discussed whether or not surfactant should be used in reference method for this antimicrobial agent.
  – Recommend additional studies with & without surfactant (e.g., drug recovery/availability, M23 QC study).
  – Lack of sponsor is problematic & volunteers requested.

Remaining Tier 3 QC Concerns

M23 Tier 3 requirements: 3 labs, 2 media lots, 10 reps/lab and 50 reps per media, 2 disk lots for a total of 250 results with MIC and 500 with disk diffusio

QC Strain (ATCC)	Antimicrobic	Method	Current Range	Action Request	Concern
E.coli 25922	Ampicillin	Disk	16-22	Add info/data*	Out low, double zones
P. aerug27853	Cefepime	DD	24-30,	Monitor	Out high
H. influ 49247	Cefepime	DD	25-31	Monitor	Out high
S. pneumo 49619	Cefepime	DD	28-35	Monitor	Out high
E. coli 25922	Meropenem	Disk	28-34	Request data*	Out high
K. pneumo 700603	Amox/clav	MM	N/A	Monitor	Addn QC strain needed?
B. fragilis 25285	Pip/tazo	Agar MIC	0.12-1	Monitor	Out low
E. coli 25922	Cefixime	Disk	23-27	Monitor	Out low
P. aerug 27853	Etrapenem	MIC	2-8	Monitor	Out low
S. aureus 29213	Quinupristin/ dalfopristin	MIC	0.25-1	Monitor	Out low
H. influ 49247	Tigecycline	MIC	0.06-0.5	Monitor	Out high
E. faecalis 29212	Teicoplanin	MIC	0.25-1	Add info/data*	Variable
E. coli 25922	Colistin	MIC	0.25-2	Need Tier 2	Variable

*Submit reference MIC or disk data to Sharon Cullen prior to Dec 2012

XI. REPORT OF THE INTRINSIC RESISTANCE WORKING GROUP
***Minutes Submitted by Barb Zimmer and Dyan Luper* (Electronic Tab I in the Meeting Agenda)**

Chairholder – Barb Zimmer

Recording Secretary – Dyan Luper

Working Group Members present – Kate Murfitt, Paul Schreckenberger, Tom Thomson, Sandy Richter, Susan Sharp, Carole Shubert

Working Group Members absent – Jeff Alder, Eliana Armstrong

Note: Rafael Canton and German Esparza were present and were requested to join the Working Group

1) Discussion and decision on philosophy of intrinsic resistance for antibiotics not listed in Table 2.

a) Choice A: If it's not in the table, there are no interpretations, and it should not be in the Intrinsic Resistance table.
b) Choice B: If it is a drug that could be tested, and the organism is naturally resistant, it should be in the IR table.
c) All Working Group members agreed on CHOICE B

2) Discussion and decision on philosophy of including antibiotics which do not appear in the CLSI tables, e.g. fusidic acid. Previously, we have removed a tetracycline because it was not included in the CLSI tables.

a) All Working Group members agreed to include a drug if it was in glossary (e.g. fusidic acid, fosfomycin)

i) Tigecycline - as part of tetracycline group (in QC table and glossary), **future activity** to add since we did not have all references available.

3) Discussion of specific tables. Members of the Working Group felt like the tables worked best if separated for gram-positive organisms.

4) Nonfermenters table (**Approved 8-0; 4 absent**) - The Working Group agreed to a new table, and to add a comment - IR to the gram- positive drugs (and others listed).

a) Other general agreements:

i) Ciprofloxacin only fluoroquinolone listed at present (Jeff Alder to follow up on other fluoroquinolones)
ii) Doripenem not listed (yet)
iii) 4 organisms only to be listed*: A. baumannii/calcoaceticus, P. aeruginosa, B. cepacia, S. maltophilia*
iv) Interest in adding *Achromobacter xylosoxidans,* and may look at *P. fluorescens/putida* as a **future activity**

b) Acinetobacter spp. table was discussed and agreed to, with some specific notes:

i) A/S: should be "R" with note similar to EUCAST note.
ii) Cefotaxime, ceftriaxone, and ceftazidime – is there a difference? There doesn't appear to be documentation that you shouldn't use cefotaxime or ceftriaxone to treat Acinetobacter spp. Paul to do some research. Tabled for this meeting and **future activity. Should refer this to Acinetobacter WG?**

c) *B. cepacia* table was discussed and agreed to, with some specific notes:

i) Ticarcillin-Clavulanate, Chloramphenicol – Breakpoints listed, but discussion whether these should be reported. IR table will not list as "R", but recommend **future discussion** with *Burkholderia cepacia* experts (Barb to follow up)

d) *P. aeruginosa* was discussed
e) *S. maltophilia* table was discussed and agreed to, with some specific notes:

i) Ceftazidime – Breakpoints listed, but much discussion whether these should be reported. References available. IR table will list as "R", and **recommend follow up with Table 1 and 2 WG?**
ii) Need to wordsmith tetracycline column, or footnote

5) *Enterococci* table (**Approved 8-0; 4 absent**)

a) Teicoplanin – WG would like to keep in table to show difference with vancomycin
b) Erythromycin – some references exist to show IR, but in CLSI tables. BZ followed up with George Eliopoulos – said there isn't IR. Will not appear in table at this time and column will be deleted.
c) Fosfomycin – we do not have references at the present time. Would add if we find references.

6) Staphylococci table (**Approved 8-0; 4 absent**) - was discussed and agreed to, with some specific notes:

a) Ceftazidime – depending on current Text and Table revisions. Note: Subcommittee voted to exclude ceftazidime, but keep *S. aureus, S. lugdunensis, S. epidermidis* and *S. haemolyticus* with comment explaining that there is no intrinsic resistance.

7) *Enterobacteriaceae* (**Approved 8-0; 4 absent**) – Imipenem: The current Enterobacteriaceae table, with a proposed additional column for reduced susceptibility of *Proteus, Providencia,* and *Morganell*a was discussed and agreed to. Used asterisks with note from current table for Modified Hodge Test. Note: The Subcommittee voted to add comment (k) – note that says that if they test "S" it is okay to report as "S".

XII. PROCESS IMPROVEMENT WORKING GROUP

Chairholder – Jeff Alder

Working Group Members - Susie Sharp, Ron Jones, Fred Marsik, George Eliopoulos, Barb Zimmer, John Turnidge

Ms. Ochs provided background for the Process Improvement initiative starting with the 2010/ early 2011 survey of the AST subcommittee conducted by the Center for Opinion Research of Franklin and Marshall College. The results highlighted some opportunities for improvement including suggestions to change the current model of deliberations to update M100 including the time period required for decisions to change breakpoints as well as the reorganization of some of the current working groups.

Based on the results of the survey Dr. Alder outlined potential options for process improvement broken down by two parts: 1) tactical – how do you review a drug with there is not a sponsor; and 2) strategic – how to determine which drug or class of drugs should be reviewed.

1) Tactical approach – use of a Rapporteur system has seemed to work well for the Ceftaroline Ad Hoc working group that was formed to work with the drug sponsor for presenting at this meeting. Work was done outside of this meeting to prepare a data package that was then circulated to the full AST subcommittee for a 30-day review and comment prior to the meeting. This review allowed the Ad Hoc group and the sponsor to then address any comments received and bring additional data as necessary making the process more efficient at the meeting.

2) Statistical approach – how to determine which drug or drug class should be reviewed. The current process for determining drugs for breakpoint review is an *ad hoc* decision to review susceptibility criteria during Working Group sessions and/or during the plenary subcommittee meeting. Current Working Groups are organized in a non-systematic manner: mix of bacterial groupings, metabolic process, drug class, and drug use with these two factors leading to a difficult process for determining breakpoint review needs.

Some of the options outlined for addressing how to move forward include:

1. Reorganization of Working Group by drug class
2. Creation of a standing breakpoint Working Group
3. Creation of a standing Breakpoint Working Group and Methods Working Group
4. Status quo (AST subcommittee creates an ad hoc breakpoint group- rapporteurs- as needed)

Dr. Alder will circulate his slide presentation with the suggested process improvement options to obtain feedback from the subcommittee on how best to move forward. In the meantime the subcommittee will continue to have smaller ad hoc working groups meet off line through conference calls to make better use of the time during face-to-face meetings.

XIII. REPORT OF *ENTEROBACTERICEAE/PSEUDOMONAS AERUGINOSA* WORKING GROUP - *Minutes Submitted by Patricia Bradford* (Electronic Tab K in the Meeting Agenda)

Chairholder – Steve Jenkins

Recording Secretary *Enterobacteriaceae* – Patricia Bradford (participated by conference call)

Recording Secretary *Pseudomonas*/Nonfermenters – Dwight Hardy

Working Group Members present – Mike Dudley, Jim Lewis, Paul Schreckenberger, Audrey Schuetz, Lauri Thrupp, John Turnidge, Barb Zimmer

Working Group Members absent - Paul Ambrose, Bill Craig, Ron Jones, Mel Weinstein

I. Meeting objectives

A. Address issues related to perceived increase in resistance among urinary tract isolates of Enterobacteriaceae resulting from revised cefazolin breakpoints
B. Discuss and formulate recommendations regarding use and placement of phenotypic tests for

detection of antibiotic resistance among gram-negatives

C. Establish a plan to develop breakpoints for the polymyxins and to assess whether optimal testing methodologies were employed for generation of data that will be considered. Assess whether appropriate QC ranges exist and, if so, whether they were used during such testing.

D. Establish a plan of action to conduct a full data review for cefepime for purposes of reevaluating its breakpoints

E. Assess interpretive criteria for *Acinetobacter* spp. for the carbapenems (other than doripenem). *Reminder*: Doripenem breakpoints were approved at the June 2011 meeting for *Acinetobacter* spp., but at the request of the sponsor, will not be published until action is taken on other carbapenems. Call for data.

II. Items for Discussion/vote

A. Cefazolin

1. Resistance rates issues
   a) Cefazolin frequently tested by clinical microbiology laboratories
   b) Concentrations of drug low enough for interpretation of results using revised CLSI breakpoints are not available on some commercial systems
   c) E-test strips for cefazolin are not manufactured
   d) For laboratories that have implemented the revised breakpoints, very significant increases in "resistance" rates have been seen among isolates of E. coli and other Enterobacteriaceae

NYP Hospital/WCMC

E. coli % Susceptibility to Cefazolin

	2009*	2010**	2011***
Outpatient	90 (3,218)	36 (549)	47 (3,307)

*Breakpoints employed in 2008 and 2009 were: 8/16/32

** Breakpoints employed were: 1/2/4

***Breakpoints employed were: 2/4/8

Additional data

- % *E. coli* susceptibility for urinary tract isolates at a children's hospital (n = 195)

MICs in µg/mL	
8/16/32	2/4/8
92	52

2. Cefazolin susceptibility testing issues

   a) Cephalothin testing remains an option, but (see comment 10 in Table 2A) the results should only be used to predict the activity of the following oral agents: cefadroxil, cefpodoxime, cephalexin, and loracarbef
   b) IDSA Guidelines list the following as potential therapeutic agents for treatment of simple cystitis: cefdinir, cefaclor, cefpodoxime-proxetil, and possibly cephalexin
   c) Cephalexin frequently used in pediatrics for treatment of UTIs
   d) Unless laboratories choose to test cefdinir and/or cefaclor separately, no approach currently available to predict the activity of these compounds
   e) In addition, false susceptibility occurs with disk testing of *Providencia*, *Citrobacter*, and *Enterobacter* spp. with cefdinir (see comment 18 in Table 2A)
   f) Some laboratories have chosen to use current CLSI breakpoints for isolates outside of the urinary tract and to retain the old interpretive criteria (historical CLSI breakpoints) for UTI isolates

3. What is the utility of β-lactams for the treatment of UTI?

   - Utility of β-lactams for treatment of UTIs again recently questioned[1,2]

     [1]Deresinski S. Beta-Lactam Therapy of Urinary Tract Infection Fails Again. March 2012.

     [2]Hooton TM, Roberts PL, Stapleton AE. Cefpodoxime vs ciprofloxacin for short course treatment of acute uncomplicated cystitis: a randomized trial. JAMA 2012; 307:583-9.

     1) 300 women ages 18-50 received 3 days of ciprofloxacin (500 mg twice daily) or cefpodoxime proxetil (100 mg twice daily)
     2) Clinical cure rate 93% for ciprofloxacin (139/150) vs 82% for cefpodoxime (123/150); 95% CI, 3%-18% (Note: empiric therapy including enterococci)
     3) Bacteriologic eradication rates 96% vs 81%

4. Discussion:

a) The discussion centered on the utility of reporting separate urine breakpoints vs. one set of breakpoints for all isolates. Suggestions were made to separate out lower UTI (cystitis) from systemic infections. Would it be possible for the laboratory to know which infection type was represented by the urine sample? Should the laboratory report susceptibility testing results using both sets of breakpoints (systemic vs. cystitis)?

b) How do we test?

1) Should we work on cephalothin to see if that can be a surrogate for oral cephalosporins
2) Should we use cephalexin as the class agent for testing oral cephalosporins? Cephalexin is the least active, so it wouldn't be 100% predicative of susceptibility.

A motion was made to return to using cefazolin breakpoints for isolates from lower urinary tract infections (Susceptible breakpoint of 8 µg/mL) and use the recently revised CLSI breakpoints for all other isolates. *Working Group vote did not pass (2 for; 8 opposed)*

A motion was made to generate a dataset to compare MICs and disk diffusion results for cefazolin and cephalothin on UTI isolates, and compare those results to those from the testing of all of the oral cephalosporins with clinical indications for treatment of urinary tract infections to determine if the old breakpoints for cefazolin, cephalexin and cephalothin accurately predict susceptibility. *Working Group Vote 9-1*

B. Placement of phenotypic tests for detection of resistance mechanisms among Gram-negatives: Refer to Section VII. Placement of Phenotypic Tests in M100 for this discussion.

C. Polymyxin Breakpoints

1) Charged with establishing a plan to attempt to develop breakpoints for the polymyxins with the *Enterobacteriaceae*

a) Assess whether optimal testing methodologies have been used for generation of data that will be considered
b) Assess whether appropriate QC ranges exist and, if so, whether they were used during such testing

2) Propose to outline a process to accomplish these assessments

3) Issues to be considered include:
a) Increased use in treatment of infections caused by MDR gram-negatives (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia*)
b) Narrow therapeutic index: recent clinical trials describing nephrotoxicity associated with use in 40 – 60% of recipients[1,2]

[1]Kubin CJ eta al. 2012. Incidence and predictors of acute kidney injury associated with intravenous polymyxin B therapy. J Infect. 65: 80-87.

[2]Pogue JM et al. 2011. Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. CID. 53:879-884.

4) Studies demonstrating changes in MICs at institutions as well as among individual patients[1]

5) Increasing understanding of resistance mechanisms (i.e., changes in membrane proteins; PhoP/*pmr*CAB locus)

6) Current breakpoints for colistin/polymyxin B

   a) *P. aeruginosa*: ≤2/4/≥8
   b) *Acinetobacter spp*.: ≤2/-/≥4
   c) Other non-*Enterobacteriaceae* (eg. *Pseudomonas* spp. in Table 2B-5) ≤2/4/≥8
   d) None for *Enterobacteriaceae*

[1]Lee J et al. 2009. Decreased susceptibility to polymyxin B during treatment for carbapenem-resistant *Klebsiella pneumoniae* infection. JCM. 47:1611-1612.

7) QC Working Group Data and Charges Previously Addressed

   a) Tier 2 study needed to assess surfactant (0.002% polysorbate-80 [Tween-80]) in wells of susceptibility testing trays containing polymyxin B or colistin
   b) Influence of plastics: 2 studies demonstrated that the presence of a surfactant will lower MICs of polymyxin B and colistin by 2 – 8 fold
   c) Studies also indicated that different types and/or treatment of plastic can affect MICs (MICs lowest for untreated plastic). Partially a function of the electric charge on the trays.
   d) Also, some loss of recovery likely due to sticking to plastic and glass during preparation of stock solutions and tray filling process
   e) Significant reduction in available drug in wells with ≤1 μg/mL when no surfactant used (8% vs 62%)
   f) Similar effects with untreated plastic
   g) No current specifications for panel plastics in reference method, and manufacturers use various treatment methods
   h) Although MICs generally lower with surfactant, MIC breakpoints may still work (2.5% VM errors in one study [based upon total # of strains])
   i) Not known whether current MIC breakpoints were developed with or without use of a surfactant (some older ranges were)
   j) Any changes in QC ranges will require a new M23 study

8) Questions for the Working Group

   a) Do we have sufficient QC data (e.g., media effects, plastic effects, correct control strains)?

b) For Enterobacteriaceae, do we have sufficient strains for which the MICs fall in the 2 – 8 µg/mL range to assess any proposed breakpoints?
c) Are the current breakpoints correct based on new findings regarding the need for wetting agents for accurate testing?
d) Are there activities currently in progress regarding the polymyxins by EUCAST and/or FDA?
e) Are there new data or ongoing clinical trials that might assist in the analyses?

9) Discussion

a) The appropriate methodology must be determined because "new" polymyxins are under development and they must be somehow compared to the older compounds.
b) Regardless of the methodology, the current breakpoints are probably not correct because there are new recommendations for dosing regimens.
c) A suggestion was made to work with EUCAST to tackle this issue.
d) Does the methodology belong to this Working Group or the QC working group? Will the QC WG focus solely on the reproducibility, rather than what is the correct MIC?
e) Gradient tests are very difficult to read.
f) The WG should also work with FDA if possible in developing these methods and breakpoints.

A motion was made for the WG to reach out to EUCAST to work with them to gather sufficient data to develop a testing method and subsequently to develop breakpoints for the polymyxins. Working Group Vote: *m/s/c vote unanimous.* Subcommittee Vote – Approved 9-0; 3 absent

D. Cefepime breakpoints revisited….again…

1. Charge: Establish a plan of action to conduct a full data review for cefepime for purposes of re-evaluating its breakpoints

a) Organism population distributions (possibly by resistance mechanism; e.g., ESBL and CTX-M)
b) Examine previous as well as any new patient outcomes data (published and or clinical trial)
c) Evaluation of PK/PD at various dosing regimens taking into consideration recent findings on possible increased toxicity at higher doses

There was considerable discussion regarding the reasoning for not changing the breakpoints when such changes were made for the other cephalosporins. At the time that there was a strong rationale for not changing. However, without the ESBL test, there are now strains of Enterobacteriaceae producing ESBLs that will test susceptible to cefepime. Several attendees went through the decision making process that supported the past decisions.

Discussion also ensued regarding new findings regarding the hydrolysis of cefepime by various beta-lactamases and potential false susceptibility when testing *bla*KPC-producing

Enterobacteriaceae for susceptibility to cefepime using some of the commercially available systems.

Pursuant to the vote of the SAST at the January 2012 meeting, this process will move forward and a decision will be made whether it will be conducted by the EWG per se or by a specialized WG following one of the suggested approaches discussed at the Process Improvement session earlier in the day.

E. Assessment of Carbapenem Breakpoints for *Acinetobacter* spp.

1. Doripenem breakpoints approved in June 2011, but will not be published (based upon sponsor request) until other carbapenems have been re-addressed for this genus
2. There has been no response to call for data for imipenem or meropenem
3. Next steps?
4. Discussion

    a) There has been no animal model data presented for Acinetobacter spp. treated with doripenem
    b) Several attendees commented that MICs will be similar for doripenem and the other carbapenems.

A motion was made to publish the doripenem breakpoints (1/2/4 µg/mL) that were approved in 2011. Working Group Vote m*/s/did not carry* 1/8/1

    c) A request was made to take another look at the data that was presented as well as more recent data reflecting current carbapenem resistance issues among Acinetobacter spp. to make certain that the breakpoints are still applicable.
    d) It is unclear whether follow-through occurred on the action item from the January, 2012 meeting (Dr. Cockerill to contact S. Lynch from J &J with a request to come back to the Working Group with additional data regarding the failed HAP study and how it relates to the breakpoints decided upon for *Pseudomonas*). S. Jenkins will follow up on this issue.

III. Other Business:

A. Involve individuals in the Working Group with evolving interest in these issues, keeping in mind various constituencies; e.g., industry, clinical microbiology, infectious diseases, government, pharmacy.

B. Request volunteers to address specific items based on multiple charges (concept of Rapporteur with first and second reviewers).

C. Institution of periodic teleconferences (limited members) to assess progress in the various areas of investigation (establishment of time lines).

XIV. REPORT OF THE DATA ANALYSIS WORKING GROUP
***Minutes Submitted by John Turnidge* (Electronic Tab L in the Meeting Agenda)**

Chairholder – John Turnidge

Working Group Members present: Steve Brown, Bob Rennie, Ian Morrisey, Bob Badal

The Data Analysis Working Group had presentation from John Turnidge (Chair) and Gunnar Kalhmeter on epidemiological cutoff values (ECOFFs or ECVs), including definitions and methods for establishing them. It was proposed, and approved by all 5 members present, that a document be developed describing the establishment of epidemiological cutoff values, including a suggestion that this be developed in conjunction with EUCAST, and co-branded with them.

XV. AGENDA BOOK SUBMISSIONS FOR 13-15 JANUARY 2013 MEETING

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 13-15 January 2013 meeting please:

1) Submit agenda materials electronically as a PDF file **on or before Monday, 3 December 2012.**

   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 13-15 January 2013 meeting will be held in Tampa, Florida at the Grand Hyatt Tampa Bay hotel. Additional meeting details will be provided in September when the announcement is circulated.

XVI. ADJOURNMENT – The meeting adjourned at 1:25 p.m. on Tuesday, 12 June 2012.

Respectfully submitted,

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