Summary Minutes
Subcommittee on Antimicrobial Susceptibility Testing
Loews Atlanta Hotel
Atlanta, Georgia
13-15 June 2010

A meeting of the CLSI Subcommittee on Antimicrobial Susceptibility Testing was held on 13-15 June 2010, at the Loews Atlanta Hotel, Atlanta, Georgia. The following were in attendance:

Franklin R. Cockerill, III, MD **Chairholder**	**Mayo Clinic**
Matthew A. Wikler, MD, MBA, FIDSA **Vice-Chairholder**	**IASO Pharma, Inc.**
John H. Rex **Area Committee on Microbiology** **Chairholder**	**AstraZeneca**
Mary Jane Ferraro, PhD, MPH **Area Committee on Microbiology** **Vice-Chairholder**	**Massachusetts General Hospital**

Members Present

Michael N. Dudley, PharmD, FIDSA	Mpex 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
Jean B. Patel, PhD, D(ABMM)	Centers for Disease Control and Prevention
Mair Powell, MD, FRCP, FRCPath	MHRA
Richard B. Thomson, Jr., PhD	Evanston Hospital, University of Chicago Medical School
John D. Turnidge, II, MD	SA Pathology @ Women's and Children's Hospital
Melvin P. Weinstein, MD	Robert Wood Johnson University Hospital
Barbara L. Zimmer, PhD	Siemens Healthcare Diagnostics

Advisors Present

Jeff Alder, PhD	Bayer Healthcare
Paul G. Ambrose, PharmD, FIDSA	ICPD/Ordway Research Institute
Patricia A. Bradford, PhD	Novartis Institutes for Biomedical Research
Steven D. Brown, PhD	The Clinical Microbiology Institute

Karen Carroll, MD	Johns Hopkins Medical Institutions
William A. Craig, MD	Wm. S. Middleton Memorial VA Hospital
Cynthia L. Fowler, MD	bioMérieux, Inc.
Yoichi Hirakata, MD, FJSIM, PhD	Tohoku University Graduate School of Medicine
Ronald N. Jones, MD	JMI Laboratories
Gunnar Kahlmeter, MD, PhD	ESCMID
James S. Lewis, II, PharmD	University of Texas Health Science Center
Frederic J. Marsik, PhD, ABMM	FDA Center for Drug Evaluation and Research
Linda A. Miller, PhD	GlaxoSmithKline
Harriette L. Nadler, PhD	DJA Global Pharmaceuticals Inc.
Freddie Mae Poole, BS, MT(ASCP, ISCLT)	FDA Center for Devices and Radiological Health
Sandra S. Richter, MD, D(ABMM)	University of Iowa Carver College of Medicine
Flavia Rossi, MD	University of Sao Paulo
Lisa Saiman, MD, MPH	Columbia University Medical Center
Paul A. Schwab, PhD, D(ABMM)	Quest Disagnostics, Nichols Institute
Jana M. Swenson, MMSc	Centers for Disease Control and Prevention
Fred C. Tenover, PhD, D(ABMM)	Cephid
Joseph G. Toerner, MD, MPH	FDA CDER

Observers Present

Francis Arhin	The Medicines Company
Eliana S. Armstrong, PhD	Achaogen, Inc
Robert E. Badal	International Health Management Associates, Inc.
Cara Bastulli	Trek Diagnostic
Dr. Susanne Berglund	Siemens Healthcare Diagnostics
Sujata Bhavnani, PharmD	Ordway Research Institute
Charles Bonapace	FDA Div. Anti-Infective Drug Products
William B. Brasso	BD Diagnostic Systems
Joyce R. Bray	Siemens Healthcare Diagnostics
Linda C. Bruno, MA, MT(ASCP)	University of Illinois Medical Center
Laurent Chesnel	Cubist Pharmaceuticals, Inc.
Diane M. Citron, M(ASCP)	R.M. Alden Research Laboratory
Rob Crink	Merck and Co., Inc. Develop., L.L.C.
Michael J. Dowzicky	Pfizer Inc.
Rob Eusebio, MSHA, MT(ASCP)	Siemens Healthcare Diagnostics
Gina Ewald	Siemens Healthcare Diagnostics
Sheila Farnham, MT(ASCP)	bioMérieux, Inc.
Lee Ann Feeney	Achaogen
Robert K. Flamm, PhD	Johnson & Johnson Pharmaceutical Research & Development
Thomas R. Fritsche, PhD, MD	Marshfield Clinic
Barb Gancarz	bioMérieux, Inc.
Evelyn Ellis-Grosse, PhD	E2g Consulting
Beth P. Goldstein, PhD	Beth Goldstein Consultant
Stephen Hawser, PhD	IHMA
Patricia Hogan, MT(ASCP), MBA	Pfizer Inc.
Andre Hsiung, MS	Thermo Fisher Scientific

Michael D. Huband	Pfizer Global R&D
Jack L. Johnson	International Health Management Associates, Inc.
Judith Johnston, MS	Siemens Healthcare Diagnostics
James H. Jorgensen, PhD	University of Texas Health Science Center
Kevin Joyce	Centers for Disease Control and Prevention
Manette Juvin	Bio-Rad Laboratories
Cynthis C. Knapp, MS	Trek Diagnostic Systems
Laura M. Koeth, MT(ASCP)	Laboratory Specialists, Inc.
Dr. Tasi-Lang Lauderdale	National Health Research Institutes
S. Blaine Leppanen	Blaine Healthcare Associates, Inc.
Brandi Limbago, PhD	Centers for Disease Control and Prevention
Jim Lindsey	Mast International
Yan B. Liu	BD Diagnostiac Systems
David Lonsway	Centers for Disease Control and Prevention
Jennifer Lorbach	Trek Diagnostic Systems
Dyan Luper, BS, MT(ASCP)SM	BD Diagnostic Systems
Ann Macone	Paratek Pharmaceuticals, Inc.
Linda M. Mann, PhD, D(ABMM)	Siemens Medical Solutions Diagnostics
Maureen Mansfield	Trek Diagnostic Systems
Dr. Ian Morrissey	Quotient Bioresearch Ltd.
Ross Mulder, MT(ASCP)	bioMérieux, Inc.
Susan D. Munro, MT(ASCP)	Stanford Hospital and Clinics
David O'Kelley, MS, SM(ASCP)	Floyd Medical Center
Susan O'Rourke	BD Diagnostic System
Elizabeth Palavencino, MD	Wake Forest University Baptist Medical Center
Chris Pillar, PhD	Eurofins Medinet
James A. Poupard, PhD	Pharma Institute of Philadelphia
L. Barth Reller, MD	Duke University Medical Center
Dr. Gabe Rensen	Siemens Healthcare Diagnostics Inc.
Dennis Rice	OMJSA
Jim Ross	JMI Laboratories
Helio S. Sader, MD, PhD	JMI Laboratories
Nicole Scangarella-Oman	GlaxoSmithKline
Jeff Schapiro	Kaiser Permanente
Paul C. Schreckenberger, PhD, D(ABMM)	Loyola University Medical Center
Susan Sharp, PhD, D(ABMM)	Kaiser Permanente
Ribbi M. Shawar, PhD, D(ABMM)	FDA Ctr. For Devices/Rad. Health
Sharon Shinn	Siemens Healthcare Diagnostics
Carole Shubert	bioMérieux, Inc.
Kerry Snow	FDA
Janine Spafford	BD Diagnostic Systems
Judith N. Steenbergen, PhD	Cubist Pharmaceuticals
Gregory G. Stone	AstraZeneca Pharmaceuticals
Clyde Thornsberry, PhD	Eurofins Medinet
Lauri D. Thrupp, MD	Univ. of California Irvine Medical Ctr.
Nancy Watz	Stanford Hospital & Clinics
Frank O. Wegerhoff, PhD	Covance Central Laboratory Svcs., Inc.
Jean Whichard	Centers for Disease Control and Prevention
Mary K. York, PhD, ABMM	MKY Microbiology Consulting

CLSI Staff

Tracy A. Dooley, BS, MLT (ASCP)
Glen Fine, MS, MBA, CAE
Marcy Hackenbrack, BA M(ASCP), MCM
Claire Schultz

TABLE OF CONTENTS

PLEASE NOTE: All slide presentations from the plenary session can be found on the CLSI website on the S/C for Antimicrobial Susceptibility Testing webpage under Microbiology by clicking the link provided below:

June 2010 AST Meeting Presentations

I. MEETING/OPENING REMARKS

Dr. Cockerill called the meeting to order at 8:00 a.m. on Monday, 14 June 2010. He thanked everyone for their participation in the Working Groups sessions held on Sunday, especially the Working Group chairholders, recording secretaries, and Working Group members for the significant work they do. He then thanked Dr. Tenover for all the years that he has participated on the subcommittee in various roles, providing his expertise, leadership, and organizational skills to the subcommittee. Mr. Fine presented Dr. Tenover a certificate of appreciation on behalf of CLSI and the AST subcommittee, thanking him for his many contributions over the years.

Dr. Cockerill then introduced and welcomed a new advisor to the subcommittee - Lisa Saiman, MD, MPH, Professor of Clinical Pediatrics Pediatric Infectious Diseases at Columbia University Medical Center and Hospital Epidemiologist at Morgan Stanley Children's Hospital.

Dr. Wikler reminded everyone the purpose of these meeting as stated in the subcommittee's mission statement that is provided in electronic tab B of the meeting CD. He emphasized the mission statement which is to "to provide useful information to enable laboratories to assist the clinician in the selection of appropriate antimicrobial therapy for patient care". He also emphasized that the values that guide this subcommittee are quality, accuracy, fairness, timeliness, teamwork, consensus, and trust. He asked that everyone keep these principles in mind during the course of these meetings. He then reminded meeting participants that the proceedings were being audiotaped per standard procedure for meetings of this subcommittee; therefore, should there be any questions on topics discussed the tapes could be reviewed.

Mr. Fine, Executive Vice President of CLSI welcomed everyone and thanked them for the tremendous work done by this subcommittee. The expertise of everyone present enables the development and revision of CLSI standards used by the healthcare community to better patient care.

He outlined the CLSI and AST process for management of Disclosure of Interests (DOI). These procedures are in place to ensure that an unbiased process is applied to the development of consensus documents, so individuals who use CLSI's consensus documents have confidence that they were developed without undue, undisclosed influence. Specific to the AST Subcommittee, a Disclosure of Interest Summary is circulated to the members and advisors for review and update prior to the January and June meetings. This summary is included with the agenda materials distributed for the meeting. CLSI also has a formal appeals process for use if a person or organization feels they have been materially or adversely affected by the failure of a CLSI committee to provide "due process" in the application of the CLSI consensus. They may appeal in writing, to the CLSI staff office. These appeals would then be addressed by Mr. Fine and the CLSI Board Executive Committee. CLSI is always looking to improve it's consensus process and will be reviewing recent suggestions.

Mr. Fine then presented information to help clarify CLSI's funding model; where these funds are derived and how they are used. CLSI's revenue is derived from 3 primary sources: document sales, memberships, and restricted grant funding. Restricted grants are targeted towards

implementing CLSI standards and guidelines in Africa, Asia, and South America. CLSI expenses go towards product development including committee meetings, personnel and office expenses, exhibits, catalogs and education. CLSI historically budgets at a 5% operating margin, often less. CLSI membership is made up of various categories with the largest organizational membership being professions with 1700 members that include hospitals, universities, and professional societies. 50 member organizations are from the government sector; 24 companies are from industry-pharmaceutical companies and 121 are from industry-IVD companies. The largest overall organization membership is from hospital laboratories.

II. APPROVAL OF MINUTES OF PRIOR MEETING (Electronic Tab C in the Meeting Agenda)

Summary minutes of the 24-24 January 2010 subcommittee meeting were approved: **(11-0; 1 absent)**

III. 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 meeting materials CD. The below are the updates provided:

Dr. Cockerill provided clarification on the listing of Cockerill Fertilizer on his disclosure summary which is a real estate holding company that also carries various stocks and bonds, some of which are with pharmaceutical companies.

IV. REPORT OF *ENTEROBACTERICEAE* WORKING GROUP (& *PSEUDOMONAS*) *Minutes Submitted by Mike Dudley* (Electronic Tab C in the Meeting Agenda)

Chairholder - Mike Dudley
Recording Secretary – *Enterobacteriaceae* – Jean Patel
Recording Secretary – *Pseudomonas* - Dwight Hardy

Working Group Members present – Paul Ambrose, Bill Craig, Jim Lewis, Ron Jones, Lauri Thrupp, Mel Weinstein, Barbara Zimmer

Working Group Members absent – Karen Bush, Steve Jenkins, Paul Schreckenberger

Agenda/Docket
Items for Vote

- Revised breakpoints for cephalosporins, aztreonam against *Pseudomonas aeruginosa*

Items for Discussion and Input

- Cefazolin breakpoints for *Enterobacteriaceae*
    - Revised breakpoints (John Turnidge)

    - Informational items from Dien Bard/Janet Hindler; Bill Brasso
- Carbapenem, extended spectrum penicillin breakpoints for *Pseudomonas aeruginosa* and other non-fermenting bacteria
- Appointment of task group for developing rationale documents
- Amoxicillin plus clavulanate breakpoints for ESBL-producing *Enterobacteriaceae*

Items for Information Only

- Metallo beta-lactamases in the US (Brandi Limbago)
- Update on MIC distributions for *Enterobacteriaceae* (Ron Jones; material presented at previous meeting and included here for minutes).

Revised Breakpoints in *Pseudomonas aeruginosa* for Cephalosporins and Aztreonam

Breakpoints for the *Enterobacteriaceae* and cephalosporins and aztreonam have recently been revised and published (M100 S20-U June Supplement). During the course of the deliberations for these revisions, the Working Group was also concerned that breakpoints for these drugs and *Pseudomonas aeruginosa*, should be reviewed. Therefore these breakpoints were evaluated at the current meeting. Although PK-PD targets for cephalosporins and monobactams against *P. aeruginosa* are similar, infections due to *Pseudomonas* are generally perceived as more difficult to treat; hence higher breakpoints are inconsistent.

The population distributions of MICs for *P. aeruginosa* for these agents would be bisected if the revised breakpoints for *Enterobacteriaceae* were also used for *P. aeruginosa* . To avoid this, maximal doses/dosage regimens for several agents were proposed. These doses would be consistent with perceptions of more resistance in *P. aeruginosa*. Further, it was noted that several agents are no longer available in the US (e.g., ceftizoxime, cefoperazone, moxalactam), or that the agents (ceftriaxone and cefotaxime) listed in the tables had limited indications (UTI only) for *P. aeruginosa*, and thus are not regarded as important agents for treatment of systemic infections due to this pathogen. Based on the discussion, the Working Group determined (WG vote = 9-0-0) that only aztreonam, cefepime and ceftazidime had clinically relevant activity against *P. aeruginosa*, and thus only breakpoints for these drugs would be published in the table. Additionally, changes in breakpoints only required consideration for ceftazidime and aztreonam; for cefepime the existing *Pseudomonas* breakpoints are identical to the breakpoints for *Enterobacteriaceae* which were not revised.

At the Working Group and full AST subcommittee meeting, there was considerable discussion about the merits of changing breakpoints so as to be the same for Enterobactereaceae or retaining the current breakpoints but indicating that maximal dosing regimens should be applied. The latter decision would not result in a change of breakpoints which would inadvertently bisect the wild type distribution. Consensus was achieved by both groups for the latter decision. The Working Group recommended (WG vote = 7-2-1) and the **AST subcommittee agreed (Approved 11-0; 1 absent**) to retain the current breakpoints in Table 2B-1 for cefepime, ceftazidime, and aztreonam, and to include supportive information on dosage as part of the rationale for the breakpoints. The dosage regimens for ceftazidime were 1 g q 6h or 2 g q 8h and for aztreonam, 1 g q 6h or 2 g q8h. The cefepime dosage regimens are the same as those for

Enterobacteriaceae (1 g q 8h or 2 g q 12 h). These doses are all consistent with FDA-approved maximum doses and indications including systemic infection due to *P. aeruginosa*.

The subcommittee approved the removal of ceftizoxime, cefoperazone, moxalactam, ceftriaxone and cefotaxime from Table 2B-1 since several of these agents are no longer available in the U.S. or have limited indications for *P. aeruginosa* as noted above **Approved 11-0; 1 absent**. ***Sponsors of these 5 drugs will be notified of the subcommittee's intent to remove these drugs from M100. If they have data that should be considered, sponsors are asked to notify the subcommittee and present the data at the upcoming January meeting.***

Revised Breakpoints in *P. aeruginosa* and Other Non-Fermenting Bacteria for Extended Spectrum Penicillins, Beta-lactamase Inhibitor Combinations, and Carbapenems

Dr. Paul Schreckenberger requested the Working Group evaluate breakpoints for carbapenems as a follow up item from the January 2010. Dr. Dudley also reviewed previous deliberations by the Working Group on penicillins and beta-lactamase inhibitor combinations and that action had largely not been taken as the Working Group wanted to examine all the agents at once. Issues concerning breakpoints for these agents to be considered would include dosage regimens that include prolonged infusions. It was noted that many industry sponsors are actively supporting clinical studies on prolonged infusion regimens in the treatment of *P. aeruginosa* infections that would be helpful to the decision making process.

The AST subcommittee agreed and issued a call for interested parties, including sponsors, to submit data and other information that would be useful for evaluation per M23 guidelines.

Rationale Document Generation

The Working Group has been charged with developing rationale documents to support recent decisions on cephalosporin, monobactam, and carbapenem breakpoints. The documents will follow a format similar to that used by EUCAST (with permission), and likely be posted on the CLSI website. Dr Jim Lewis will lead efforts to generate these documents.

Cefazolin and *Enterobacteriaceae*

Cefazolin and Testing Urinary Isolates – Dr. Jennifer Dien Bard and Ms. Janet Hindler submitted questions concerning the potential for using cefazolin susceptibility results to predict oral cephalosporin susceptibility in *Enterobacteriaceae*. Current CLSI recommendations allow for cephalothin susceptibility results (using unchanged, older breakpoints) for predicting susceptibility of oral cephalosporins for use in UTIs only. Since many labs had dropped cephalothin testing years ago (likely due to lack of use of this agent), it would be useful to be able to use cefazolin results for this purpose.

The Working Group discussed the paradigm and concluded that data to support extrapolation of cefazolin results to cephalothin, and thus to oral cephalosporins makes several assumptions for which data do not exist to support. It had been well-established that the more potent cefazolin did

not always predict cephalothin susceptibility in past studies. There are no contemporary data correlating cefazolin activity with that of oral cephalosporins. The Working Group concluded that further work is needed to provide recommendations that would support such a practice.

Cefazolin Breakpoint Revision - Dr. John Turnidge presented data at the January 2010 meeting concerning the potential to have higher breakpoints for cefazolin to enable continued use in some settings. Current breakpoints bisect the distribution of *Enterobacteriaceae*. Additional data were presented to the Working Group that extended the previous findings, including support for higher dose regimens of 1g q 6h or 2g q 6 or 8h that would support breakpoints of 2/4/8 for susceptible/intermediate/resistant. It was noted that maximum FDA recommended doses are 1.5 g q 6h (6 g per day).

An additional analysis also demonstrated with the higher breakpoints, the disk diffusion test would perform acceptably, with very major, major, and minor errors within acceptable ranges. Disk diffusion breakpoints were not possible with the recently published breakpoints.

Although the Working Group did not reach consensus for a recommendation (WG = 5-4-0 to accept new breakpoints), the AST subcommittee reviewed the presentation and voted to **approve (10-1; 1 absent) the revised breakpoints in Table 2A for cefazolin (2/4/8 for MICs and 23/20-22/19 for disk diffusion zones) with associated dosage information (2g every 8 hr) provided as supportive information.**

Amoxicillin-Clavulanate and ESBL Producing *Enterobacteriaceae*

A request was received concerning evaluation of breakpoints for amoxicillin/clavulanate in light of its use in the treatment of ESBL-producing strains in Hong Kong. A paper describing results with amoxicillin-clavulanate treatment of CTX-M producing strains in Spain was provided, as well as anecdotal experience from Hong Kong on results.

The Working Group noted that breakpoints do exist for Enterobacteriaceae, but that they are likely referenced for UTIs and skin-structure infections and treatment with the oral formulation (the IV formulation in not available in the US). It is not clear if the existing breakpoints would apply to parenteral administration and doses. No further action was recommended at this time due to lack of data.

Metallo Beta-lactamases in the U.S.

Dr. Brandi Limbago (CDC) presented information on detection of metallo beta-lactamases in 3 patients from different geographic locales in the U.S. All patients had a history of encounters to healthcare system in India prior to entry into the U.S. These strains were highly resistant to all beta-lactam antibiotics. Further study of these strains is in progress. The AST was alerted to an upcoming MMWR that will further discuss these cases, and recommendations.

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

Chairholder - Jana Swenson
Recording Secretary - Susan Munro

Working Group Members present - Janet Hindler, Judy Johnston, Dyan Luper, Linda Mann, Dale Schwab, Al Sheldon, Tom Thomson, Mary York

Working Group Members absent - Fred Marsik, Flavia Rossi, and Mel Weinstein

1. Placement of ampicillin and penicillin in Table 1B, Group A for beta-hemolytic streptococci and revision of associated footnote o and comment (3) in Table 2H-1.

- In Jan. 2010, the S/C voted to approve the labeling of penicillin and ampicillin in Table 1B Group A in M100 as follows:

  In the Table the ♦ symbol would be placed next to penicillin and ampicillin with "♦ = routine testing is not necessary (see footnote o" added at the bottom of the table. Final wording of footnote/comment was tabled until June.

- At the current meeting, Footnote o in Table 1B (former Table 1A) and comment (3) in Table 2H-1 was revised as follows:

  "Penicillin and ampicillin are drugs of choice for treatment of beta-hemolytic streptococcal infections. Susceptibility testing of penicillins and other beta-lactams approved by the FDA for treatment of beta-hemolytic streptococcal infections need not be done routinely because nonsusceptible isolates (ie, penicillin MICs > 0.12 and ampicillin MICs > 0.25 µg/mL) are extremely rare in any beta-hemolytic streptococcus and have not been reported for *Streptococcus pyogenes*. If testing is performed, any beta-hemolytic streptococcal isolate found to be nonsusceptible should be re-identified, retested, and, if confirmed, submitted to a public health laboratory. (See Appendix A for further instructions.)"

  Subcommittee approved: 10-0; 2 absent

- Working Group also approved deletion of Table 2H-1, comment (7).

  "(7) Strains of β–hemolytic streptococci with penicillin MICs of greater than 0.12 g/mL or ampicillin MICs of greater than 0.25 g/mL have not been observed; submit such strains to a reference laboratory."

  Subcommittee approved 11-0; 1 absent

2. Revision of Appendix A, Suggestions for Confirmation of Resistant (R), Intermediate (I), or Nonsusceptible (NS) Antimicrobial Test Results and Organism Identification.

Some WG members did not support the proposed Category headings, but the consensus was to keep the proposed headings. The full S/C suggested further revisions, such as removing the footnote h about existence of pen/amp resistance in Group B strep outside the U.S.

The final version approved by the Subcommittee **(Approved 10-0; 1 abstain, 1 absent)** is attached to these minutes as Appendix A.

3. Suggestion to clarify that Table 2E refers to *H. influenzae* and *H. parainfluenzae* only.

- Proposed new comment to be inserted in Table 2E:

"( ) *Haemophilus* spp., as used in this table, includes only *H. influenzae* and *H. parainfluenzae*. See CLSI document M45 for testing and reporting recommendations for other species of *Haemophilus*."

Subcommittee Approved 11-0; 1 absent

4. Correction to Warning Table in M100

"Warning": The following antimicrobial agent/organism combinations may appear active *in vitro* but are not effective clinically and should not be reported as susceptible.		
Location	Organism	Antimicrobial agents that must not be reported as susceptible
Table 2A	ESBL-producing *K. pneumoniae, K. oxytoca, E. coli,* and *P. mirabilis*	Penicillins, cephalosporins, and aztreonam

Following the suggestion of a user that the above entry was in error now that the revised cephalosporin breakpoints are included in M100, the Working Group voted to delete this entry entirely rather than modify it for use with both the new and the old breakpoints.

Subcommittee Approved 11-0; 1 absent

5. Proposal to include comment explaining dosage comments in tables where they occur.

During review of the Table 2A supplement, it was suggested that we include a comment to clarify dosage information. After much discussion in both the Working Group and the Subcommittee, the following comment was approved to be included as a general comment in tables where they exist:

"The dosage regimens shown in the comment column below are those used to derive plasma drug exposures (in adults with normal renal and hepatic functions) on which

breakpoints were derived. When implementing new breakpoints, it is strongly recommended that laboratories share this information with infectious disease practitioners, pharmacists, pharmacy and therapeutics committees and infection control committees. Prescribing information should be reviewed and institutional clinicians consulted for dosage regimens to treat infections in specific patients."

Subcommittee Approved 11-0; 1 absent

6. Suggestion to delete comment i in Table 1A (now Table 1B) (footnote to meropenem) since comment f is adequate:

The following footnote was approved for deletion by both the WG and the S/C:

"i. Clinical indications and relevant pathogens include bacterial meningitis and concurrent bacteremia in association with meningitis caused by *H. influenzae* (β-lactamase and non-β-lactamase-producing strains). "

Subcommittee Approved 11-0; 1 absent

7. Reconsideration of how to handle bolded information in CLSI documents.

During review of M45-A2, the question about the appropriateness of the comment, "Note: Information in boldface type is considered tentative for one year." was asked and given to the WG for discussion. The WG decided that the comment was not being used as is implied in the statement and that its use in documents which are not updated yearly (as M45) is inappropriate. The WG also decided that bolded information was really used mainly to alert the reader to new or updated information since the last edition and therefore recommended that this comment be modified as follows:

"NOTE: Information in **boldface** is new or modified since the previous edition."

Subcommittee Approved 10-0; 2 absent

8. Question about the use of Chloramphenicol vs. Salmonella.

A question was submitted to the ASM division C listserv about whether it is still appropriate to test and report chloramphenicol with *Salmonella* spp. as stated in Table 1A, footnote g:

"g. When fecal isolates of *Salmonella* and *Shigella* spp. are tested, only ampicillin, a fluoroquinolone, and trimethoprim/sulfamethoxazole should be reported routinely. In addition, chloramphenicol and a third-generation cephalosporin should be tested and reported for extraintestinal isolates of *Salmonella* spp."

The question was forwarded to the WG. Although the question was not received through normal channels and therefore did not follow the normal CLSI process, the WG felt that it would be useful to CLSI M100 users for a Q&A to be prepared on this issue and one was prepared and presented to the subcommittee.

However, the full subcommittee did not agree that it should be published, but did agree that footnote g could be modified to soften the wording "should be tested and reported" for chloramphenicol. Consequently the following change was made to the last sentence of footnote g"

"In addition, for extraintestinal isolates of *Salmonella* spp., a third-generation cephalosporin should be tested and reported and chloramphenicol may be tested and reported if requested."

Subcommittee Approved 11-0; 1 absent

9. A question was received about concentrations that need to be included on MIC panels in order to call resistance.

We are using a commercial plate whose format seems to fall one dilution short of being able to call an isolate of *Acinetobacter* resistant. For most antimicrobials, the highest concentration tested is the top of the intermediate range. However when I contacted the manufacturer to address this issue, they assured me that, since CLSI uses two-fold concentrations, if there was growth at the highest concentration (the end dilution to call intermediate) which means no inhibition at that concentration that the MIC could be called resistant. I have an issue with that as the guidelines state that to call resistance it should be greater than or equal to the resistant value (which can't be obtained by using their panel). I have also seen numerous isolates show growth at an intermediate level say 64 but not grow at a resistant level 128, where I would call this intermediate as it did not meet the guideline of being at least equal to 128. Should I use their panel and their suggestions or are my assumptions correct and I should find a panel that goes a dilution above the intermediate value to call resistance?

- **The MIC is defined as the lowest concentration that inhibits growth. Because all our MIC categories are based on a two-fold dilution scheme, if there is growth at 64 µg/ml (i.e., MIC > 64 µg/mL), then there can only be an interpretation of resistant whether or not you test a concentration of 128 µg/ml because the MIC would be ≥ 128 µg/ml. Therefore, it is perfectly acceptable to test only up to the highest concentration in the intermediate range.**

The S/C voted to approve the inclusion of the above Q&A (with some editing of the question shown above).

S/C approved 11-0-1.

10. Question about what are "relevant cephems" as listed in Table 2C, comment (9).

"(9) Penicillin-susceptible staphylococci are also susceptible to other penicillins, β-lactam/-lactamase inhibitor combinations, cephems, and carbapenems approved for use by the FDA for staphylococcal infections. Penicillin-resistant, oxacillin-susceptible strains are resistant to penicillinase-labile penicillins but susceptible to other penicillinase-stable penicillins, β-lactam/-lactamase inhibitor combinations, relevant cephems, and carbapenems. "

After much discussion and several possible revisions (e.g. specifying cephems as "cephems as listed in this table excluding ceftazidime"), the following revision of this comment was approved:

(9) Penicillin-susceptible staphylococci are also susceptible to other penicillins, β-lactam/-lactamase inhibitor combinations, anti-staphylococcal cephems, and carbapenems approved for use by the FDA for staphylococcal infections. Penicillin-resistant, oxacillin-susceptible strains are resistant to penicillinase-labile penicillins but susceptible to other penicillinase-stable penicillins, β-lactam/-lactamase inhibitor combinations, anti-staphylococcal cephems, and carbapenems.

S/C approved 11-0-1.

VI. REPORT OF THE FLUOROQUINOLONE BREAKPOINT WORKING GROUP (Electronic Tab E in the Meeting Agenda)

Chairholder - Karen Bush was unable to be present so the meeting was chaired by Mary Jane Ferraro

Working Group Members present - Sujata Bhavnani, Karen Carroll, George Eliopoulos, Robert Flamm, Cynthia Fowler, Mair Powell, Barth Reller, Helio Sader

- Items Proposed for Vote Today – None
- Items For Discussion and Input - None
- Items For Information Only (FYI):
  - Intend to recommend to full SC in January 2011 revised FQ breakpoints specific for *Salmonella*, regardless of whether fluoroquinolone breakpoints are revised for all *Enterobacteriaceae*; this will likely result in the deletion of the naladixic acid screen test and recommend specific fluoroquinolone testing for *Salmonella*.
  - It was agreed that sufficient data were not included in the June 2010 agenda book to have a formal discussion on whether M23 criteria have been met in order for the Working Group to reevaluate fluoroquinolone breakpoints for all *Enterobacteriaceae*

- It was thought that such data do exist and these should be addressed in January 2011.

Discussion of whether M23 criteria have been met in order for the Working Group to reevaluate fluoroquinolone interpretive criteria for all *Enterobacteriaceae*:

- *Enterobacteriaceae* and fluoroquinolone data will be gathered and included in January 2011 agenda material for the purpose of formal evaluation of data to determine if sufficient criteria exist as outlined in M23 to revise one or more of the existing fluoroquinolone breakpoints.

- **Sponsors are being notified of this plan for formal consideration with a repeated request to submit any relevant information for the January 2011 meeting because it is possible that the Working Group may present a formal recommendation to the full subcommittee in January. If sponsor data cannot be prepared for January, but a sponsor intends to have relevant data for June, the sponsor should send to CLSI a formal letter outlining their intent and defining the data to be submitted for June 2011.**

Data that the Working Group will look at includes:

- Microbiological Data
  - European distribution data (EUCAST/Gunnar)
  - Microbiological distributions over time – show mutations (Helio Sader and Ron Jones)
  - New resistance – plasmid mediated (manuscripts)
  - TRUST data (Bob Flamm)
  - Surveillance data – current and prospective (Jeff Alder)
- Pharmacological Data: Sujata Bhavnani and Bill Craig will provide:
  - Animal PK-PD data
  - Published papers (Forrest; Preston or Drusano & others)
  - Target attainment analyses
- Clinical Data
  - Human clinical data contain in some of the PK-PD manuscripts
  - Database search from sponsors with FQ data (Bob Flamm)
  - Bayer could possibly have clinical data to present in March (Jeff Alder)
  - Other Clinical data
- Other Data
  - Input from device manufacturers on the impact of a breakpoint change with existing panels including what breakpoints could be covered based on appropriate dilutions.
  - Correlative data – MIC vs. disk (EUCAST may have some data as well as Ron Jones)

VII. REPORT OF THE M39 WORKING GROUP *Minutes Submitted by Janet Hindler* (Electronic Tab F in the Meeting Agenda)

Chairholder - Janet Hindler

Working Group Members present - Sharon Erdman, Judy Johnston, Jim Lewis, John Stelling

Working Group Members absent - Michael Barton, Alan Evangelista, Steve Jenkins, Dyan Luper, Ron Master, Graeme Nimmo

1. M39-A3 will be updated with the goal of publishing M39-A4 in 2012.

2. The following areas will be expanded and/or clarified:

    a. Handling cumulative antibiogram with new vs. old breakpoints
    b. Handling cumulative antibiogram when change in testing protocol is made during analysis period (e.g., drug removed or added)
    c. Selective reporting; provide complete examples and focus on variable denominators
    d. Examining trends (e.g., carbapenem resistance); consider number of patients with resistant isolates in addition to % susceptibility trends

3. Addition of the following new sections will be considered:

    a. Examine number and percent of isolates that have specific resistance profiles (e.g., *E. coli* urine isolates susceptible to all drugs, resistant to ampicillin only, resistant to ampicillin plus ciprofloxacin, resistant to ampicillin plus ciprofloxacin plus trimethoprim-sulfa, etc.). Organisms examined will include:
        - *Acinetobacter baumannii*
        - *E. coli* (urine)
        - *Pseudomonas aeruginosa*
        - *Streptococcus pneumoniae*
    b. Compile % susceptible data for all organisms within a group from a specific source irrespective of species identification (e.g., all GNR from blood). Consider segregating by other variables (e.g., age group)

VIII. REPORT OF THE QUALITY CONTROL WORKING GROUP - *Minutes Submitted by Steve Brown* (Electronic Tab G in the Meeting Agenda)

Co-Chairholder - Steven Brown
Co-chairholder - Sharon Cullen
Working Group Members present - Bill Brasso, Stephen Hawser, Janet Hindler, Michael Huband, Ron Jones, Ann Macone, Ross Mulder, Susan Munro, Paul Oefinger, Jean Patel, Bob Rennie

The Quality Control Working Group approved the following acceptable ranges (QCWG vote indicated). These ranges were also approved by the AST subcommittee and are reflected in the tables.

Name	**CXA-101/ Tazobactam**	Previous ID		Abbrev		Working GroupVote (For/Opposed/Abstained/Not present)
Solvent	Water	Diluent	Water	Rev History		WG vote : 25923 8/2/1/1, rest 10/0/1/1
Route of Administration		Class		Subclass		
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	Median	Shoulder %	Variability/Comments
Staphylococcus aureus 25923	~~8-18~~ ~~8-19RF~~ 10-18	~~11~~ ~~12~~ 9	~~99.2~~ ~~99.4~~ 99.0	13.7		Small zone to measure. Smallest zone in tables is currently 11. pg 10
Enterococcus faecalis 29212	NA					
Escherichia coli 25922	24-32 ~~24-31RF~~	9 ~~8~~	99.2 ~~98.8~~	28		Some lab to lab variability
Escherichia coli 35218 on MHA	25-31 ~~24-31RF~~	7 ~~8~~	99.2 ~~98.5~~	28		Note incorrect range on histogram in agenda on pg 26.
K. pneumoniae 700603	17-25 ~~17-21RF~~	9 ~~9~~	99.8 ~~99.4~~	21		Include footnote recommending use as supplemental (not routine) QC
Pseudomonas aeruginosa 27853	25-31 ~~23-32RF~~	7 ~~12~~	99.8 ~~99.6~~	28		Some lab to lab variability
Escherichia coli 35218 on HTM	25-31 ~~22-34~~	7 ~~13~~	99.2 ~~99.2~~	28		
Haemophilus influenzae 49247	23-29	7	99.4	26		
Staphylococcus aureus 29213	7-17 ~~8-18RF~~	11 ~~11~~	92.5 ~~99.5~~	12		Only for CLSI MIC For information only, EUCAST method
Haemophilus influenzae NCTC 8648	23-29 ~~22-29RF~~	7 ~~8~~	99.1 ~~99.8~~	26		Some lab to lab variability For information only, EUCAST method

Ranges approved by the Subcommittee as reflected above 11-0; 1 absent

Name	**PTK-0796**	Previous ID		Abbrev		Working GroupVotes (For/Opposed/Abstained /Not present)
Solvent		Diluent		Rev History		WG: 7/0/2/3
Route of Administration		Class		Subclass		Tetracycline derivative Add footnote from Tigeclycine requiring use of fresh media. (more affected than tetra, but not as much as tigecycline)
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	Mode	Shoulder %	Variability/Comments
B. fragilis 25285 (Broth)	0.12-1 ~~or 0.12-0.25RF~~	4 ~~3~~	100 ~~100~~	0.25	62	3 labs with mode at 0.5, 100% in range with 0.12-0.5, pg9
B. fragilis 25285 (Agar)	~~0.5-2~~ or 0.25-2RF	~~3~~ 4	~~93.8 or~~ 100	1	47	
B. thetaiotaomicron 29741 (Broth)	0.25-1	3	100	0.5		
B. thetaiotaomicron 29741 (Agar)	0.5-4 ~~or 0.5-2RF~~	4 ~~3~~	100 ~~100~~	1	94	
E.lentum 43055 (Broth)	0.06-0.5	4	100	0.25	75	Does Anaerobe group want to make a comment that this isn't the preferred strain?
E.lentum 43055 (Agar)	0.25-2	4	99.5	1	64	Excludes Lab #4 as statistical outlier, RF recmd 6 dil range. Pg 19
C. difficile 700057 (Broth)	0.06-0.25	3	97.1	0.12		Excludes Lab #4 as statistical outlier. Pg 21
C. difficile 700057 (Agar)	0.25-2	4	100	1	86	

Ranges approved by the Subcommittee as reflected above 10-0; 2 absent

Name	BC-3781	Previous ID		Abbrev		Working Group Votes (For/Opposed/Abstained/Not present)
Solvent	Water	Diluent	Water	Rev History		WG: MIC 9/1/1/1, Disk 8/2/1/1
Route of Administration		Class	Pleuromutilin	Subclass		Will need to confirm drug class recmd.
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	Mode or Median	Shoulder %	Variability/Comments
Staphylococcus aureus ATCC® 25923	26-32 or ~~26-33RF~~	7 ~~8~~	97.4 ~~99.3~~	30/29		Slight media difference
Staphylococcus aureus ATCC® 29213	0.06-0.25	3	100	0.12		Slight media difference. Occasionally saw 1 well trailing that should be ignored - no comment recmd at this time.
Streptococcus pneumoniae ATCC® 49619	19-27 or ~~19-28RF~~	9 ~~10~~	99.3 ~~100~~	23		Slight media difference
Streptococcus pneumoniae ATCC® 49619	0.06-0.5	4	98.6	0.12	87	Excluded Lab H with mode of 0.03
Haemophilus influenzae ATCC® 49247	22-28 or ~~21-28RF~~	7 ~~8~~	96.0 ~~98.9~~	25		Significant # out low with 1 media lot, 2 labs. Pg 7,18
Haemophilus influenzae ATCC® 49247	0.5-2	3	94.3	1		pg 7, 1 lab mode at 0.25, 1 lab mode at 2. All out of range were from Lab F, had low/in range with controls. Request review of QC data from clinical trials

Ranges approved by the Subcommittee as reflected above 10-0; 2 absent

Name	GSK 1322322	Previous ID		Abbreviation		Working Group Votes (For/Opposed/Abstained/Not present)
Solvent	DMSO	Diluent	Water	Rev History		WG: 10/0/1/1
Route of Administration		Class	New	Subclass		
QC Strain (ATCC)	Acceptable limit	# mm or dil	% In range	Mode or Median	Shoulder %	Variability/Comments
Staphylococcus aureus 29213	1-4	3	95.6	2		
Streptococcus pneumoniae 49619	0.12-0.5	3	99.4	0.25		
Haemophilus influenzae 49247	0.5-4 ~~or 0.5-2RF~~	4 ~~3~~	100 ~~100~~	1	71	4 labs mode @2, pg 18

Ranges approved by the Subcommittee as reflected above 10-0; 2 absent

Tier 3 Monitoring: Data requested to be sent to Sharon Cullen to compile and review for Jan 2011 meeting.			
QC Strain	**Antimicrobial Agent**	**Method**	**Observation**
Ps. aeruginosa ATCC® 27853	Gentamicin	Disk	At top of range or some out high
Ps. aeruginosa ATCC® 27853	Tobramycin	Disk	At top of range or some out high
Ps. aeruginosa ATCC® 27853	Meropenem	Disk	At top of range or some out high
Ps. aeruginosa ATCC® 27853	Colistin	MIC	At top of range or some out high
E. coli ATCC® 25922	Colistin	MIC	At top of range or some out high

Class Proposal for OPT 80, Fidaxomicin is Macrocycle

A significant number of antibacterial agents are composed of macrocyclic ring (12 to at least 40 member ring) substituted or not with various sugars. Macrocyclic antibacterials are divided into two main subgroups: peptide macrocyclic and non-peptide macrocyclic antibiotics. The first

subgroup, peptide macrocyclic, contains many drugs introduced in clinical practice and under development. It is composed of glycopeptides (such as vancomycin, ristocetin, oritavancin), and lipoglycopeptides (such as teicoplanin, dalbavancin), lipopeptides (such as daptomycin, colistin), depsipeptides (such as ramoplanin), and cyclic peptides. The second group, non-peptide macrocyclic, is composed of two subgroups, an unsaturated lactone ring represented by macrolide/ketolides and an unsaturated lactone ring in which OPT 80 (a tucamicin B derivative) is inserted. OPT 80 belongs to a subgroup of the tucamicin B complex also known as lipiarmycin complex. These molecules are RNA polymerase inhibitors. The classifications are complex due to the structure of these molecular complexes. There are at least two possibilities for classification based on: 1) the mechanism of action or 2) as a group of non-peptide macrocyclic antibacterials (Personal Communication from Andre Bryskier: May 17th 2010 provided to the QC working group).

The Subcommittee approved the class proposal of OPT 80 (Fidaxomicin) to be listed in the Glossaries with the class designation macrocyclic (no vote taken), once the designation was confirmed by Dr. Mike Dudley in consultation with his company's head chemist. Post Meeting: Dr. Dudley received agreement from the Head of Chemistry at Mpex that the macrocyclic designation is appropriate.

Recommendations for QC ranges to Mycoplasma Subcommittee

The QC Working Group provided consultation to the Mycoplasma Subcommittee to assist with setting QC ranges for *M. hominis* ATCC 23114, *M. pneumoniae* ATCC 29342, and *U. urealyticum* ATCC 33175 with 8 antimicrobial agents with broth microdilution and agar dilution methods. Data were collected over 10 years and compiled from multiple studies. CLSI M23 guidelines for establishing QC expected ranges were followed where possible while making allowances for the higher variability with these test methods and in some cases limited data. A total of 46 antimicrobial agent/QC organism/method combinations were reviewed. Ranges were approved for 25 combinations providing coverage for those that are clinically significant. These recommendations are being forwarded to the Mycoplasma Subcommittee for their final consideration and approval.

User QC Question and Proposed Response

There is now a QC range listed for ampicillin with *E. coli* ATCC® 35218. However the Appendix that describes the use of each QC strain indicates that this strain is intended for QC of β-lactam/ β-lactamase inhibitors. Does *E. coli* ATCC® 35218 need to be tested if a β-lactam/β-lactamase inhibitor is not tested?

Response: ***E. coli* ATCC® 35218 provides no additional value over *E. coli* ATCC® 25922 when testing β-lactams alone. This strain is recommended QC when testing β-lactam/β-lactamase inhibitors.**

Proposed footnote to *E. coli* ATCC® 35218 in QC Table: Recommended QC when testing β-lactam/ β-lactamase inhibitors. **Approved by the Subcommittee 9-0; 3 absent.**

IX. REPORT OF ANAEROBE WORKING GROUP (Electronic Tab H in the Meeting Agenda)

Chairholder – David Hecht

Working Group Members present - Diane Citron, David Hecht, Nilda Jacobus, Audrey Schuetz, Hanna Wexler.

Working Group Agenda:

1) Items for vote:

- **Approval of M11A-8 Document**

Dr. Hecht provided an overview of the changes to the M11 document that was in with the agenda materials including:

- Placement of tables (all moving to M100)
- Foreword – consolidated the information on resistance and provided additional references. The information is then further reflected in the antibiogram tables. The subcommittee approved the changes to the Foreword including the wording included for tigecycline (**Approved 11-0; 1 absent**).

Changes to Table 1

- Consolidated columns for:

- *Bacteroides fragilis* group & other BLA-positive or BLA-unknown anaerobes and BLA negative, gram-negative anaerobes combined to read *Bacteroides fragilis* group & other gram-negative anaerobes and included a new note.

- Species of *Clostridium* other than *C. perfringens and Clostridium perfringens,*gram-positive cocci, and nonspore-forming, gram-positive bacilli combined to read Gram-positive anaerobes with a new note included.

- Also changes to the table to make it more consistent with the other Table 1's in M100 were made (eg, Primary choices changed to Primary Test and Report).

The subcommittee approved the changes to Table 1 with the removal of tigecycline and doripenem since there are no interpretive criteria for these drugs in the document. **(Approved 10-0; 2 absent).**

Antibiogram Tables

- Updated the Bacteroides antibiogram table (publish without tigecycline- **Approved 8-3; 1 absent**).

- New Non-Bacteroides antibiogram table – (publish without tigecycline and add a footnote regarding only having 28 isolates for Veillonella- **Approved 10-0; 2 absent)**

X. REPORT OF THE STAPHYLOCOCCAL AND STREPTOCOCCAL WORKING GROUP - *Minutes Submitted by Fred C. Tenover, Chairholder* (Electronic Tab I in the Meeting Agenda)

Chair: Fred C. Tenover
Recording Secretary: Maria Traczewski

Members Group Members present**:** Patricia Bradford, Bill Craig, George Eliopoulos, Sandra Richter, Jana Swenson, Mel Weinstein

Working Group Members absent: Karen Carroll, Mike Dudley, Dan Sahm

Guests: Brandi Limbago, Jim Jorgensen

Working Group – Agenda

- *Items Proposed for Vote:*
  - Broth MIC test for inducible clindamycin resistance (ER/CC in same well) for β-hemolytic streptococci
  - Minocycline placement in Table 1
  - Table 2C, Clarification of comment 11 on penicillin testing
  - FDA versus CLSI breakpoint question (for Q&A section)

- *Items For Discussion and Input:*
  - Disk diffusion testing of *S. aureus* with vancomycin and teicoplanin
  - Inducible clindamycin resistance detection in pneumococci
  - Comment on testing daptomycin on isolates from the respiratory tract

- *Items For Information Only (FYI): None*

Testing Staphylococci with Vancomycin (for discussion only)

- Brandi Limbago from CDC updated the Working Group on the study to identify alternatives to disk diffusion testing of *S. aureus* with a 30 µg vancomycin disk since CLSI deleted the disk diffusion breakpoints in 2008 from M2.
- Data on disk diffusion testing with a variety of disk potencies for vancomycin and teicoplanin were presented
- **Outcome**: No differentiation of VISA and VSSA isolates was observed after testing disks containing:
  - Vancomycin at 5, 10, 15, and 30 µg
  - Teicoplanin at 30 µg

- Pre-diffusion of vancomycin 30 µg disks (for 2, 6, 18 hr at room temperature and 4C)
- Pre-diffusion of teicoplanin 30 µg disks (for 2, 6, 18 hr at room temperature and 4C)

Path Forward for Vancomycin Testing

- The Study Group will determine the sensitivity and specificity of Brain Heart Infusion Agar (BHI agar screen plates) containing 4 or 5 µg/ml of vancomycin (BHI-V4, BHI-V5), or containing 5 µg/ml of teicoplanin (BHI-T5), plus or minus supplements, for three collections of strains (n=75 isolates)
  - CDC VISA collection
  - NARSA VISA collection
  - *S. aureus* for which vancomycin MICs are 2-8 µg/ml as determined by the broth microdilution reference method
- CDC will continue to lead this study

Detecting Inducible Clindamycin Resistance in Streptococci

- Jim Jorgensen of the University of Texas Health Sciences Center at San Antonio presented data from a 5-laboratory collaborative study recommending a single well containing both erythromycin and clindamycin (ER/CC 1 µg/ml + 0.5 µg/ml) to detect inducible clindamycin resistance in beta-hemolytic streptococci.
- This would complement the existing disk diffusion D-zone test assay for β-hemolytic strep (i.e., the testing strategy is not new)
- Dr. Jorgensen also reviewed similar data for testing *Streptococcus pneumoniae* (where there is no existing D-zone disk test).
- A total of 155 beta-hemolytic streptococci were tested including 50 GAS, 48 GBS, 28 GCS, and 29 GGS. Testing was done on media from three different manufacturers
- 95 *S. pneumoniae* isolates were also tested.

Overall Summary of D-test vs. D-Broth

	BBL	**BBL**	**Difco**	**Difco**	**Oxoid**	**Oxoid**
ß-Strep	Em/Cc 1/0.25	Em/Cc 1/0.5	Em/Cc 1/0.25	Em/Cc 1/0.5	Em/Cc 1/0.25	Em/Cc 1/0.5
% Sensitivity	100	100	91	95	99	97
% Specificity	96	96	96	96	96	96
S.pneumo						
% Sensitivity	100	98	100	98	100	98
% Specificity	100	100	100	100	100	100

- The Working Group approved the test with ER/CC concentrations of 1 µg/mL + 0.5 µg/mL (Working Group Vote 5-1-0) for ß-hemolytic Streptococci
- Method to be placed in Table 2H as a supplemental table (**Approved by the Subcommittee 9-0; 3 absent**). Appended to the end of these minutes as Appendix B.
- There was concern expressed that too few isolates of each streptococcal species were tested (155 total but as few as 29 for Group G strep) and discrepancies were retested, but not further characterized.
- M23 doesn't address this directly, but requires 100 organisms for "unique categories" (e.g., enterococci, pneumococci, gonococci) for disk diffusion
- A mock up of a revised Table 2H Supplement was prepared by Jana Swenson from CDC and reviewed by the Working Group
- Key changes suggested and approved by Working Group for the Table:
    - Indicate that only "Beta-hemolytic *Streptococcus* spp. from invasive infections" need to be tested
- The following change was not directly voted on by the Working Group (data were presented but not specifically discussed), but was approved by the Full Subcommittee
    - Medium could be MHA or TSA supplemented with sheep blood (5% v/v)
- The ER/CC D-zone broth test for *S. pneumoniae* was Tabled until to January 2011 by the Working Group (vote 6-0) for the following reasons:
    - Currently, no D-zone disk test for pneumococci is available (although one is in use in several laboratories and appears to work well). The Working Group requested a total package in January 2011 including:
        - Reference PCR test results
        - Disk diffusion results
        - Broth MIC single well results
        - Clinical context for testing (not clinical data, but rationale for testing)
        - Total of 100 organisms (currently 95 tested)

Minocycline in Table 1 (now changed to be Table 1A)

Issue: Should minocycline be added to Table 1 (now changed to be Table 1A) under staphylococci in Group B with tetracycline and doxycycline?

- **Rationale:** Footnote b to Table 1 mentions all three drugs as though it should be there (i.e., looks like a simple omission).
- The latest (2010) "Sanford Guide" lists "TMP-SMX-DS or doxycycline or minocycline" plus drainage for CA-MRSA abscesses, so clinical indication is there.
- Working group voted 5-0 to put minocycline in Table 1 in Group B with no "or" between drugs.
- Full subcommittee agreed **(Approved 9-0; 3 absent)**

Questions from CLSI Office for Discussion

- A question was raised about how to report moxifloxacin results for staphylococci since there are differences between CLSI and FDA breakpoints, and the breakpoints used by the AST instrument manufacturer were those of FDA.
    - FDA/AST instrument, <= 2 S, 4 = I, >= 8 R.

- CLSI standards, <=0.5 S, 1 = I, >=2 R.

The Working Group suggested adding a "Q and A" to M100, such as "The AST device manufacturer is using FDA-approved breakpoints not CLSI breakpoints. See M100-21 page 18, for explanation of differences."

This was similar to a previous question for which the following response was provided by CLSI in M100-S19 as follows:

Although there are several reasons why the CLSI and FDA moxifloxacin breakpoints for staphylococci differ, the most important point for the laboratorian to understand is that CLSI breakpoints can be used for all staphylococci including MRSA, whereas the FDA breakpoints apply only to methicillin-susceptible staphylococci (per the FDA label for clinical use of the drug), so the laboratory should not report the drug on MRSA if using the FDA breakpoints. If a susceptibility testing device includes antimicrobial test concentrations sufficient to allow interpretation of susceptibility to an agent using the CLSI MIC breakpoints, a laboratory could, after appropriate validation, choose to interpret and report results using CLSI breakpoints."

- Full subcommittee approved using the previous longer response as an answer to the question for Q &A. **(Approved 9-0; 3 absent).**

Clarification of Comment 11 in Table 2C regarding beta-lactamase testing of *S. aureus*

The Working Group approved minor modifications of the comment provided by Dyan Luper regarding comment 11.

"Perform an induced β-lactamase test on all *S. aureus* isolates for which the penicillin MICs are $\leq$0.12 or zones $\geq$ 29 mm before reporting as penicillin susceptible. Rare isolates of staphylococci that contain genes for β-lactamase production may not produce a positive induced β-lactamase test. Consequently, for serious infections requiring penicillin therapy, laboratories should perform MIC tests and induced β-lactamase testing on all subsequent isolates from the same patient. PCR testing of the isolate for the *bla*Z β-lactamase gene may be considered.

Full subcommittee approved the comment shown above as modified during discussion. (Approved 9-0; 3 absent)

- Additional data will be presented in January 2011 to further refine this comment.

Question on susceptibility testing with Daptomycin

- Question: "The M100 contains guidance when reporting drugs on CSF and urine specimens. I am wondering if CLSI is considering adding a comment to the M100 to not report daptomycin on lower respiratory specimens? This was pointed out in the final critique of CAP Bacteriology Survey D-C 2009, specimen D-19".

Working Group discussion suggested that a comment such as "**Daptomycin should not be reported for isolates from the lower respiratory tract"** could be added to M100 but this should be discussed in full subcommittee.

- This is consistent with package insert but concurrence from manufacturer is important.
- The Working Group Chair, Dr. Tenover discussed the issue with Dr. Judith Steenbergen (Cubist), who agreed with inclusion of such a comment since it is consistent with the product label.
-

Comment shown above in bold approved by Full Subcommittee to add to Tables 2C, 2D, and 2H-1 (Approved 9-0; 1 abstain, 2 absent).

XI. REPORT OF THE TOPICAL AGENTS WORKING GROUP *Minutes Submitted by Mair Powell* (Electronic Tab J in the Meeting Agenda)

Chairholder: Mair Powell
Recording secretary: Fred Marsik

Working Group Members present: Farah Babakhani, Harriette Nadler, Lisa Saiman, Jeffrey Shapiro, Lauri Thrupp

Working Group Members absent: Karen Carroll (conflict with another Working Group that ran over)

The meeting was opened with a reintroduction to the reason for the working group and a summary of the first meeting of the working group held at the January 2010 CLSI meeting. At this second meeting it was planned that there would be three presentations – one a general overview on experience with topical products from the US FDA and two that focused on some of the five areas of topical use that the WG had identified at the first meeting. In brief, these presentations highlighted the following issues:

- Fred Marsik presented information on the topical products typically reviewed in the Division of Anti-infectives and Ophthalmology Products of the US FDA. Standardized microbiological protocols for the development of these types of products currently do not exist. For products intended to treat acute bacterial infections of the eye there is an expectation that time-kill data will be obtained during development. However, product approval has been based on clinical outcome data. In some indications (e.g. treatment of acne) microbiological data are not collected. When baseline organisms and susceptibility data are provided no correlation has been demonstrated between in-vitro susceptibility and clinical outcome. Currently, product labeling for topical products includes QC ranges only i.e. there are no interpretative criteria for susceptibility testing.

- Harriet Nadler summarized some features of the product information for ophthalmological topical products approved by the US FDA and listed others currently in the review process at the FDA. Tim Morris summarized the information that Bausch and Lomb provided to the FDA to obtain approval of besifloxacin (OPTURA^{TM}) for the treatment of bacterial conjunctivitis. It was noted that this fluoroquinolone has not been developed for systemic use. Time-kill studies were done. MICs of besifloxacin were determined for baseline organisms and organisms obtained from clinical failures. The data did not allow for determination of any correlation between MICs and outcomes and there was no discernible relationship between specific types of organisms and failures.

- Jeff Alder summarized some of the data available on the potential use of inhaled antibacterial agents for treatment of respiratory tract infections in patients who do not have cystic fibrosis (e.g. with hospital-acquired and/or ventilator-associated pneumonia). While data support high local concentrations achieved after inhalation these are thought to wane rapidly, mainly due to mechanical clearance. Newer formulations (e.g. liposomal preparations) aim to enhance the maintenance of high local concentrations. The assessment of outcomes in relation to in-vitro susceptibility of pathogens is complicated by the fact that inhalational antibacterials have generally been used in addition to systemic treatment. Currently it has not been possible to determine a relationship between in-vitro susceptibility and outcomes. In general, clinical results for aerosol antibacterial therapies in pulmonary conditions excluding cystic fibrosis have been modest at best.

Working Group Discussion:

The Working Group and attendees acknowledged the potential difficulties raised in the presentations for setting interpretative criteria. In addition, there are issues regarding biofilm formation should be taken into account. It was proposed that within each of the five areas originally selected for focus the Working Group might eventually select out a one or a few specific indications for detailed consideration of the data that would be needed, and conceivably could be generated, to facilitate the setting of relevant interpretative criteria.

Action Items:

The Working Group discussed that the next meeting should be devoted to follow-up with leads and available information of possible relevance on the three other types of topical antibacterial usage previously identified for focus: 1) agents that can be deposited into periodontal pockets; 2) agents that can be inserted directly into bone (excluding prophylactic uses e.g. during joint replacement); and 3) agents administered into the gut that are intended to exert an intra-luminal antibacterial effect (e.g. for treatment of travelers' diarrhea or for *C. difficile.* As seemed indicated, representatives from companies actively engaged in such research might be invited to present their experience.

Following consideration of the other three areas it was discussed that the Working Group might then be able to identify specific indications in which it seemed most promising that data could be gathered to support setting interpretative criteria. Therefore before the January 2011 meeting the leads in the three other areas (F. Babakhani, L. Saiman and L. Thrupp) would prepare a summary

of their investigations/considerations and/or invite company representatives to attend and present relevant experience.

To take into account the potential complications of using topical treatments for indications where biofilm formation could be an important issue it was discussed *post hoc* that R. Rennie would join the group as a member. Also, that J. Alder would join as a member.

Following the January 2011 meeting it was intended that in each specific indication deemed to be most promising to lend themselves to setting interpretative criteria for topical products the WG would summarize what is and is not known and which types of data could feasibly be generated to assist the process. Eventually it is intended that a document could be produced to consider the data that could be generated that would strongly support interpretative criteria.

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

Chairholder – Barbara Zimmer
Recording Secretary – Dyan Luper

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

Working Group Members absent - Jeff Alder, Kate Murfitt,

Topics for Discussion:

1. The Enterobacteriaceae Table (see table appended at the end of these minutes as Appendix C. NOTE: The highlighted "R's" will be checked/verified by the working group prior to the final version of the table going into M100-S21) was approved by the subcommittee for inclusion in M100 as a new Appendix (**Approved 8-1; 3 absent**). Introductory text for the new appendix was also approved (**Approved 7-2; 3 absent**).

   Some specifics in the table that were discussed:

   - List *E. coli, P. mirabilis* – note in table there is no intrinsic resistance to beta-lactams for these organisms.
   - List *Salmonella* and *Shigella* – refer the user to Table 2A comment 6 for reporting
     - References – each listing will have a reference that can be made available. Those currently highlighted still need to be checked by the working group including piperacillin for *C. koseri, E. hermanni, K. pneumoniae, Y. enterocolitica;*ampicillin-sulbactam for *H. alvei* Delete tigecycline so there is just a column for tetracyclines.
     - Delete colums for piperacillin-tazobactam and ticarcillin-clavulante. List these 2 drugs at the bottom of the table in the footnote.

2. Table – Gram Positive – the Working Group will continue to work on this table and present it to the subcommittee in January for consideration. Items for discussion as the table is being finalized:

- Remove Novobiocin – not for treatment
- Combine *S. capitis* and *S. saprophyticus*
- Combine Other Coagulase- negative staphylococci and *S. aureus*
- Questions about *Staphylococcus* and Ceftazidime (as documented in EUCAST) – needs a reference (Steve Brown or George Eliopoulos to possibly provide)
- *Enterococcus* – leave as "R" but add a footnote – see Table 1 for *Enterococcus* and Table 11 for *Listeria* in M45. _Check with the for Subcommittee – do they want cephlosporins listed at all? If they come out, so do *Listeria*?
- Teicoplanin – is "S" for Vancomycin; include this as footnote with R* in vancomycin column
- Low Level Resistance – should this be listed? YES
- Clindamycin – is there a reason it is here?
- *Streptococcus* spp – Low Level Resistance for aminoglycosides – is that correct?

XIII. VOTE ON M100-S21

Dr. Cockerill requested comments from meeting participants regarding the voting draft M100-S21, *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement.*

The subcommittee members voted to accept the M100-S21 supplemental tables with the changes approved at the January and June meetings and recommend the M100-S21 Tables to the Area Committee on Microbiology for approval to be published as supplemental tables.

A tally of the votes follows:

Total Subcommittee Members	= 12
Votes to Accept	= 10 (M. Dudley, G. Eliopoulos, D. Hardy, D. Hecht, J. Hindler, J. Patel, R. Thomson, J. Turnidge, M. Weinstein, B. Zimmer)
Votes to Accept with Comment	= 0
Votes to Reject	= 0
Votes not Received	= 2 (K. Bush, M. Powell)

XIV. AGENDA BOOK SUBMISSIONS FOR 9-11 January 2011 MEETING

Materials for the January meeting will be distributed to the subcommittee on a CD 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.

To meet the schedule for completing and shipping the CDs, submission due dates and requirements must be met. In order to present at the 9-11 January 2011 meeting please:

1) Submit agenda materials electronically as a PDF file **on or before Wednesday 1, December 2010.**

2) E-mail proposed agenda topics to 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.

XV. ADJOURNMENT - The meeting adjourned at 11:30 a.m. on Tuesday, 15 June.

Respectfully submitted,

Tracy A. Dooley, BS, MLT (ASCP), Standards Administrator

Appendix A:

Revised Appendix A. Suggestions for Confirmation of Resistant (R), Intermediate (I), or Nonsusceptible (NS) Antimicrobial Susceptibility Test Results and Organism Identification

Organism or Organism Group	Resistance Phenotype Detected [a]	Occurrence and Significance of Resistance and Actions to Take Following Confirmation of Results [a]		
		Category I	**Category II**	**Category III**
		Not reported or only rarely reported to date	**Uncommon in most institutions**	**May be common but is generally considered of epidemiologic concern**
		Action Steps:		
		• Confirm ID and susceptibility (see footnote a) • Report to infection control • Send to public health laboratory • Save isolate *Note: may be appropriate to notify infection control of preliminary findings prior to confirmation of results*	• Confirm ID and susceptibility if uncommon in your institution (see footnote a) • Check with infection control in your facility to determine if special reporting procedures or further action are needed. • Check with your local public health department to determine which isolates should be reported to them and when isolates should be sent to the public health laboratory.	• Confirm ID and susceptibility if uncommon in your institution (see footnote a) • Check with infection control in your facility to determine if special reporting procedures or further action are needed.
Any *Enterobacteriaceae*	carbapenem - I or R[b]		x	
	amikacin, gentamicin and tobramycin - R			x
Escherichia coli *Klebsiella* spp. *Proteus mirabilis*	extended-spectrum cephalosporin[c] – I or R			x
Salmonella spp.[d]	cephalosporin III and/or fluoroquinolone - R		x	
Acinetobacter baumannii	colistin/polymyxin - R		x	
	carbapenem - I or R			x
Pseudomonas aeruginosa	colistin/polymyxin - I or R		x	
	amikacin, gentamicin and tobramycin – R carbapenem - I or R			x
Stenotrophomonas maltophilia	trimethoprim-sulfamethoxazole - I or R		x	

Haemophilus influenzae	carbapenem – NS extended-spectrum cephalosporin[c] – NS fluoroquinolone – NS	x		
	amoxicillin-clavulanic acid - R ampicillin - R and β-lactamase-negative		x	
Neisseria gonorrhoeae	extended-spectrum cephalosporin[c] -NS		x	
	fluoroquinolone-I or R			x
Neisseria meningitidis	ampicillin or penicillin – R extended-spectrum cephalosporin[c] - NS meropenem - NS minocycline – NS	x		
	ampicillin or penicillin - I aziththromycin – NS rifampin - I or R		x	
	chloramphenicol - I or R fluoroquinolone - I or R			x
Enterococcus spp.	daptomycin - NS linezolid – R		x	
	vancomycin - R high-level aminoglycoside – R			x
Staphylococcus aureus	vancomycin MIC ≥ 8 µg/ml [e]		x[e]	
	daptomycin - NS linezolid – R quinupristin-dalfopristin - I or R vancomycin MIC = 4 µg/ml		x	
	oxacillin – R			x
Staphylococcus, coagulase-negative	daptomycin - NS linezolid – R quinupristin-dalfopristin - I or R vancomycin – I or R[f]		x[f]	
Streptococcus pneumoniae	linezolid - NS vancomycin – NS	x		
	fluoroquinolone - I or R imipenem or meropenem - I or R quinupristin-dalfopristin - I or R rifampin – I or R		x	
	using nonmeningitis breakpoints: amoxicillin or penicillin - R extended-spectrum cephalosporin[c] - R			x

Streptococcus, beta-hemolytic group[g]	ampicillin or penicillin – NS extended-spectrum cephalosporin[c] - NS daptomycin - NS ertapenem or meropenem - NS linezolid - NS vancomycin – NS	x		
	quinupristin-dalfopristin - I or R		x	
Streptococcus, viridans group	daptomycin – NS ertapenem or meropenem – NS linezolid – NS quinupristin-dalfopristin - I or R vancomycin - NS	x		

Nonsusceptible (NS): A category used for isolates for which only a susceptible interpretive criterion has been designated because of the absence or rare occurrence of resistant strains. Isolates that have MICs above or zone diameters below the value indicated for the susceptible breakpoint should be reported as nonsusceptible.

NOTE 1: An isolate that is interpreted as nonsusceptible does not necessarily mean that the isolate has a resistance mechanism. It is possible that isolates with MICs above the susceptible breakpoint that lack resistance mechanisms may be encountered within the wild-type distribution subsequent to the time the susceptible-only breakpoint is set.
NOTE 2: For strains yielding results in the "nonsusceptible" category, organism identification and antimicrobial susceptibility test results should be confirmed. (see footnote a).

[a] Ensure antimicrobial susceptibility test results and organism identification are accurate and reproducible. Consider the following steps:

1. Check for transcription errors, contamination, or defective panel, plate, or card.
2. Check previous reports on the patient to determine if the isolate was encountered and confirmed earlier.
3. Repeat organism identification and antimicrobial susceptibility tests with initial method to ensure they reproduce (For category I and II, may elect to skip step 3 and go to steps 4 and 5. For category III repeat and/or confirmatory testing may not be needed if resistance is common in your institution).
4. Confirm organism identification with second method performed in-house or at a referral lab.
5. Confirm antimicrobial susceptibility results with second method (e.g., in-house or referral lab). The second method might be a CLSI reference method (e.g., broth microdilution, agar dilution, or disk diffusion) or an FDA-cleared commercial test.

[b] Imipenem MICs for *Proteus* spp., *Providencia* spp., and *Morganella morganii* tend to be higher (e.g., MICs in the new intermediate or resistant range) than those with meropenem or doripenem MICs. These isolates may have elevated MICs by mechanisms other than production of carbapenemases**.**
[c] Extended-spectrum cephalosporin = cephalosporin III or IV (see Glossary I).
[d] When submitting report to a public health department, include antimicrobial susceptibility results for *Salmonella* spp. that are intermediate or resistant to 3rd-generation cephalosporins (cephalosporin III) and/or intermediate or resistant to fluoroquinolone or resistant to nalidixic acid.

[e] Rarely encountered. Because of significant infection control and public health implications, follow Category I recommendations for notifying infection control and public health authorities.
[f] There are some species of CoNS for which vancomycin MICs may test within the intermediate range. In contrast, vancomycin-resistant CoNS are rare.
[g] Confirm that groups C and G are large colony and not small colony variants. Group C and G small colony variants are included with the viridans group.

Appendix B:

Supplemental Table 2H-1-S1. Screening Test for Inducible Clindamycin Resistance for *Streptococcus* spp., Beta-hemolytic Group for Use With Table 2H-1

Screen Test	Inducible Clindamycin Resistance	
Organism group	**Beta-hemolytic *Streptococcus* spp. from invasive infections**	
Test method	Disk diffusion	Broth microdilution
Medium	MHA or TSA supplemented with sheep blood (5% v/v)	CAMHB lysed horse blood (2.5-5 % v/v)
Antimicrobial concentration	15-µg erythromycin disk and 2-µg clindamycin disk spaced 12 mm apart	1 µg/mL erythromycin and 0.5 µg/mL clindamycin in same well
Inoculum	Standard disk diffusion Recommendations	Standard broth microdilution recommendations
Incubation conditions	35 ± 2 °C; 5% CO_2	35 ± 2 °C; ambient air
Incubation length	20 - 24 hours	20 – 24 hours
Results	Flattening of the zone of inhibition adjacent to the erythromycin disk (referred to as a D-zone) = inducible clindamycin resistance. Hazy growth within the zone of inhibition around clindamycin = clindamycin resistance even if no D-zone apparent.	Any growth = inducible clindamycin resistance; No growth = no inducible clindamycin resistance
Further testing and reporting	Report isolates with inducible clindamycin resistance as "clindamycin resistant." A comment that "This isolate is presumed to be resistant based on detection of inducible clindamycin resistance. Clindamycin may still be effective in some patients" may be included.	
QC recommendations	*S. pneumoniae* ATCC® 49619 for routine QC of disks; See Appendix B for use of supplemental QC strains	*S. pneumoniae* ATCC® 49619 *S. aureus* ATCC® BAA-976 or *S. aureus* ATCC® 29213 – no growth *S. aureus* ATCC® BAA-977 – growth

Appendix C:

Appendix B. Intrinsic Resistance - *Enterobacteriaceae*

Intrinsic resistance is defined as inherent or innate (not acquired) antimicrobial resistance which is reflected in wild-type antimicrobial patterns of all or almost all representatives of a species. Intrinsic resistance is so common that susceptibility testing is unnecessary. For example, *Citrobacter* species are intrinsically resistant to ampicillin and ticarcillin.

The table can be helpful in at least 3 ways: 1) it provides a way to evaluate the accuracy of testing methods, 2) it aids in the recognition of common phenotypes and 3) it can assist with verification of cumulative antimicrobial susceptibility test data. In the table, an "R" occurring with an organism-antimicrobial combination means that strains should test resistant. A small percentage (1-3%) may appear susceptible due to method variation, mutation or low levels of resistance expression.

A "susceptible" result should be viewed with caution. Ensure antimicrobial susceptibility test results and identification are accurate and reproducible. See Appendix A, footnote a.

Organism \ Antimicrobial Agent	Ampicillin	Amoxicillin-clavulanate	Ampicillin-sulbactam	Piperacillin	Ticarcillin	Cephalosporin I: Cefazolin, Cephalothin	Cephamycins: Cefoxitin, Cefotetan	Cephalosporin II: Cefuroxime		Tetracyclines	Nitrofurantoin	Polymyxin B Colistin
Citrobacter freundii	R	R	R			R	R	R				
Citrobacter koseri	R	R	R	R	R							
Enterobacter aerogenes	R	R	R			R	R	R				
Enterobacter cloacae	R	R	R			R	R	R				
Escherichia coli	There is no intrinsic resistance to beta-lactams in this organism.											
Escherichia hermannii	R			R	R							
Hafnia alvei	R	R	R			R	R					
Klebsiella pneumoniae	R			R	R							
Morganella morganii	R	R				R		R		R	R	R
Proteus mirabilis	There is no intrinsic resistance to beta-lactams in this organism.									R	R	R
Proteus penneri	R					R		R		R	R	R
Proteus vulgaris	R					R	R	R		R	R	R
Providencia rettgeri	R	R	R			R				R	R	R
Providencia stuartii	R	R				R				R	R	R
Salmonella & Shigella spp.	There is no intrinsic resistance to beta-lactams in these organisms; see table 2A comment 6 for reporting.											
Serratia marcescens	R	R	R			R	R	R			R	R
Yersinia enterocolitica	R	R		R	R	R						

Cephalosporins III, cefepime, aztreonam, ticarcillin-clavulanate, piperacillin-tazobactam, and the carbapenems are not listed as there is no intrinsic resistance in Enterobacteriaceae.