

Methods Application and Interpretation Working Group

CLSI AST Subcommittee Meeting

June 4, 2018

MAI WG Membership

- Brandi Limbago (co-chair)
- Tom Kirn (co-chair)
- Trish Simner (recording secretary)
- Darcie Roe-Carpenter (Text & Tables liaison)
- Sandra Richter (Text & Tables liaison)
- J. Kristie Johnson*
- Joseph Kuti
- Susan Sharp
- Samir Patel
- Virginia Pierce
- Stephen Jenkins

Agenda

- Info and Vote
 - I AHWG
 - Anaerobe AHWG
 - Intrinsic Resistance AHWG
 - Fosfomycin AHWG Report
- Additional informational content

“I” AHWG

- Susan Sharp
- Tom Kirn
- Kristie Johnson
- Avery Goodwin
- Romney Humphries
- Joe Kuti
- Lauri Thrupp
- Stephanie Mitchell
- Alice Grey

EUCAST AND CLSI Presentation Jan 2018

Two presentations identified the same areas of concern:

- I/ Intermediate category has become a junk drawer of intents
- Labs have no way to distinguish which meaning is being used
 - Test variability
 - Important concern for getting approval of AST devices
 - Accommodate bug/ drug combinations where dosing impacts interpretation
 - Alternate dosing
 - Alternate administration
 - Physiologic concentration of drug

Trend towards establishing no “I” or “S-DD” categories

- Recent examples:
- Cefepime and Ceftazidime for *Pseudomonas aeruginosa*
 - FDA breakpoints are 8/-/16
 - CLSI breakpoints are 8/16/32
- Colistin
 - CLSI breakpoints are 2/-/4
- Ceftazidime-avibactam
 - FDA and CLSI breakpoints are 8/-/16
- Daptomycin
 - CLSI and FDA breakpoints are:
 - Enterococcus 4/-/- (NS)
 - Staphylococcus 1/-/- (NS)

And yet,

- MIC variability exists when testing these agents
- Drug exposure may predict improved outcome if MIC on high end of S / low end of R (e.g., daptomycin)

Different philosophies for addressing concern

EUCAST

Dosing

- S = Susceptible, standard dose
- I = Susceptible, increased exposure
- R = Resistant

Technical uncertainty

- Repeat test
- Repeat with MIC method
- Do not report
- Report as R
- Push a consultation

CLSI

Susceptible Dose Dependent

- Increased dose (state explicitly)
- Alternate dosing
- Physiologic concentration
- Does name reflect concept adequately?

Intermediate

- Accounts for technical variation

S-I-SDD-R

Concerns & Discussion

- 2 different AST organizations using “I” for separate definitions will add further confusion to defining the terms
- What about drugs that are physiologically concentrated –would they be placed in the “I” or “SDD” category?
- How to designate drugs that have both *dosing* and *technical variability*?
- How would SDD be used in practice? Can it be reported in LIS?
 - If CLSI continues SDD, LIS will likely adapt.
 - Outreach programs will be required for education.
- Without intermediate categories it will be difficult for device mfrs to validate the tests
 - Consider rebranding “I” category to **indeterminate** consistent with molecular based assays
 - Much of the *technical variation* is a function of the antimicrobial resistance mechanism

“I” AHWG Charge

- To make a recommendation to the Methods Application and Interpretation WG (and from there to the AST Subcommittee) regarding the continued use, discontinuation, modification, or replacement of “Intermediate” category for antimicrobial susceptibility test reporting.
- Bring two or more options, complete with pros and cons, to the MAI WG and the AST SC for consideration along with a recommendation.

“I” AHWG

- The “I” Ad Hoc WG achieved consensus that all drugs should have 3 categories which take into account testing variability, as we are not aware of any antibiotic/organism combination for which inherent testing variability does not exist, and that the small proportion of results that are in the borderline (“I”) range should be communicated to the clinician

Options for consideration

S-I-R

- No changes to current S and R definitions, but eliminates SDD.
- Intermediate definition: Basically unchanged, but proposes two new footnotes be added to Tables 2 to denote (a) alternate dosing possible, or (b) anatomic site concentration.
- Isolates with an “I” result approach susceptible if exposures are maximized by alternative dosing regimens. An “*” in M100 Tables 2 indicates antibiotics where “I” implies the potential for an increased/alternative dosing regimen.
- Isolates with “I” result approach susceptible if infection is at an anatomical location where the drug concentrates (e.g., urine) but alternate dosing regimens not feasible. An “^” in M100 Tables 2 indicates antibiotics where “I” has the potential for concentration at an anatomical site.
- “I” results also provide a buffer zone for inherent variability in AST. Isolates with an “I” result could be “S” or “R”; proceed with caution.

S-I-R OR S-SDD-R

- No changes to current S and R definitions.
- Intermediate definition: Will no longer include drugs for which higher dosage or exposure can be used (now SDD).
- I definition:
 - Isolates with “I” result approach susceptible if infection is at an anatomical location where the drug concentrates (e.g., urine). An “^” in M100 Tables 2 indicates antibiotics where “I” has the potential for concentration at an anatomical site (as above).
 - Provides a buffer zone for inherent variability in AST. Isolates with “I” result could be “S” or “R” – proceed with caution.
- SDD definition:
 - Can be considered susceptible if higher exposure or doses can be used as approved by the FDA or supported by literature and reviewed by CLSI.
 - Provides a buffer zone for inherent variability in AST (as does “Intermediate”).

S-I-R Pros/Cons

Pros

- Maintains the current definition of “I” and a historical comfort level.
- Consistent with proposed EUCAST nomenclature (but not necessarily the definition).
- As most clinicians do not understand what SDD means or the difference between the inherent variability in testing from drugs that can be dosed higher or those that concentrate at certain body sites, the “*” and “^” in Tables 2 may help to clarify these differences.
- No need to make accommodations in LIS, HIS and instruments to report SDD.
- Retains “I” category which enables instrument manufacturers to achieve FDA clearance under current requirements.
- Incorporates the buffer zone for inherent test variability and allows for both the possibility of increased exposures or of anatomic concentration while indicating the differences in Tables 2.

Cons

- Routine “I” results reported by individual laboratories may not differentiate drugs that can be dosed higher or those that concentrate at certain body sites.
- “I” will have a different definition compared to EUCAST.
- A path for redefining breakpoints for drugs with only S/R or S/NS may need to be determined.
- Clinicians may still be reluctant to use drugs reported as “I” (lack of confidence with I), leading to increased use of broader spectrum antibiotics (e.g., increased carbapenem use for ESBLs that fall in cefepime 4-8 mg/L range). The primary purpose of the SDD concept would be lost.
- The new “*” or “^” footnotes in Tables 2 may not be communicated to the clinician unless individual laboratories (or LIS) choose to do so.
- CLSI may cause some confusion if SDD is dropped, since it remains in the Fungal Guidance and was adopted in recent years after extensive discussion.

S-I-R OR S-SDD-R Pros/Cons

Pros

- SDD is already in use for cefepime for AST and azoles for AFST.
- Clearly identifies drugs that can be dosed using alternate regimens with reasonable expectation of safety and efficacy.
- Inherent variability is covered by both SDD and I definitions.
- Encourages increased utilization of SDD drugs (with continued education) rather than broader antibiotics (e.g., carbapenems).
- Daptomycin/*E. faecium* BP WG proposal is an example of ideal application of SDD where an increased dosage is needed (as supported by peer reviewed literature and society guidelines) to treat many VRE infections. Without SDD, ~ of 80% of VRE (*E. faecium*) could be categorized as intermediate based on proposed BPs, which could discourage use of this first line VRE agent.
- Leaves an option for new antibiotic developers considering indications for two different doses (e.g., ceftolozane/tazobactam).
- Additional SDD designations (e.g., cefepime/*Pseudomonas*) would foster enhanced awareness of the clinical/ stewardship value of SDD.

Cons

- Would not agree with proposed EUCAST nomenclature.
- SDD with cefepime has not been widely accepted nor understood.
- Continued use of SDD may result in the need to evaluate all drugs for which SDD is a possibility to define alternative dosing strategies.
- CLSI has some responsibilities to conform with the FDA in conjunction with the 21st Century Cures Act. Some drugs may have an SDD option (e.g., carbapenems, daptomycin for *Enterococcus* spp.) but no corresponding FDA dose that define SDD.
- Optimal reporting of SDD may require significant changes to LIS, HIS and instruments.
- FDA does not currently recognize the SDD category except for anti-fungal. If FDA does decide to recognize SDD, depending on how it is classified, this could lead to errors being categorized as Major or Very Major. This would likely decrease the ability of device manufactures to develop a test that will get approval. To address this, M23 would require revision to address calculation of minor errors (inclusive of SDD).

AHWG Vote - Discussion

S-I-R

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 - Provides a buffer zone for inherent variability in AST (as does “Intermediate”).

Anaerobe Working Group

Anaerobe Working Group

Darcie Roe-Carpenter

Audrey Schuetz

Joanne-Dzink-Fox

Hanna Wexler

Diane Citron

Steve Jenkins

Laura Koeth

Karen (Kitty) Anderson

Cindy Knapp

Meredith Hackel

Working Group Minutes:

- *B. fragilis* group – discussion continued – Group
 - “group” nomenclature outdated
 - M11 change from *B. fragilis* group to *Bacteroides* spp. and *Parabacteroides* spp. (consisting primarily of members of the formerly defined *B. fragilis* group)
- Rifampin *Cutibacterium (Propionibacterium)*– AST testing – Update – Steve/Audrey – Anaerobe Meeting Poster July
 - 83 isolates – agar and gradient strip
 - Rifampin - ≤ 0.03 $\mu\text{g/ml}$ by agar dilution
 - Add footnote to the antibiogram - **VOTE**
- Piperacillin/Tazobactam Susceptibility Anaerobe MIC paper
 - Clinical failure with old breakpoints
- Additional agents – discuss for breakpoint changes – Group
 - Metronidazole – no update - present at January 2019 meeting
 - Beta-lactamase inhibitors – ECV for anaerobes – no funding for needed data collection
- Antibiogram Manuscript Update – Darcie – No progress
- M11 Status Update – Darcie – finalizing edits
- Gradient Strip – Antibiogram anaerobe data going forward
 - Allow inclusion of gradient strip generated MICs with associated documentation that not all data was generated with the reference method and in accordance with the device indications.

Appendix D. (Continued)

NOTE: Isolates collected from selected US hospitals from 1 January 2013 to 31 December 2016.^a

D2. Anaerobic Organisms Other Than *Bacteroides fragilis* Group

Anaerobic Organisms	Number of Strains		Ampicillin-sulbactam		Number of Strains		Piperacillin-tazobactam		Number of Strains		Imipenem		Number of Strains		Meropenem		Number of Strains		Penicillin	
	%S	%R	%S	%R	%S	%R	%S	%R	%S	%R	%S	%R	%S	%R	%S	%R	%S	%R		
Percent susceptible (%S) and percent resistant (%R)^d																				
Breakpoints, µg/mL			≤ 8/4	≥ 32/16			≤ 32/4	≥ 128/4			≤ 4	≥ 16			≤ 4	≥ 16			≤ 0.5	≥ 2
<i>Prevotella</i> spp.	29 ^b	97 ^b	3 ^b		63	100	0		29 ^b	100	0		92	98	0		63	100	0	
<i>Fusobacterium</i> spp. ^b	20 ^b	100 ^b	0 ^b		55	96	2		75	95	4		20 ^b	10 ^b	0 ^b		— ^f	— ^f	— ^f	
Anaerobic gram-positive cocci ^e	— ^f	— ^f	— ^f		185	99	1		134	99	0		1647	10	0		164	100	0	
<i>Cutibacterium</i> (formerly <i>Propionibacterium</i>) <i>acnes</i> ^g	— ^f	— ^f	— ^f		18 ^b	100 ^b	0 ^b		17 ^b	94 ^b	0 ^b		— ^f	— ^f	— ^f		— ^f	— ^f	— ^f	
<i>Clostridium</i> <i>perfringens</i>	15 ^b	100	0		410	100	0		23 ^b	100 ^b	0 ^b		417	10	0		402	90	4	

g. 83 isolates of *Cutibacterium (Propionibacterium) acnes* from two of the sites generated MIC values for rifampin ≤0.03µg/ml using agar dilution method. There are no interpretive breakpoint for this organism/antimicrobial agent combination.

M100 –S28 page 234

MAIWG Vote
Vote: 9 approved; 0 opposed; 0 abstained

Intrinsic Resistance Working Group

Membership and Agenda June 2018

- *Barbara Zimmer, Dyan Luper (Recording Secretary), Jeff Alder, Rafael Canton, German Esparza, Sandy Richter, Susan Sharp, Carole Shubert, Tom Thomson, Susan Butler-Wu, Mark Fisher, Rosemary She*

Conference call May 18, 2018 and meeting June 4, 2018

- *Reviewed SC decisions from January 2018*
- *Reviewed that there was (still) not enough proof to add IR to ampicillin/sulbactam for *P. stuartii**
- *Voted to delete *Acinetobacter* vs. ampicillin/sulbactam footnote*
- *Discussed intrinsic resistance and *Burkholderia*, came to some conclusions with compromise vote*
- **Acinetobacter baumannii* complex speciation and next steps assigned*

Intrinsic Resistance Working Group

Acinetobacter and ampicillin/sulbactam

- **Sent:** Tuesday, May 23, 2017 8:21 AM
To: DivC <divc@mail.asmus.org>
Subject: [divc] Acinetobacter and Ampicillin-Sulbactam
- “Per CLSI (Intrinsic Resistance Appendix B2. Non-Enterobacteriaceae): Amp/Sulbactam has an * for Acinetobacter baumannii/calcoaceticus complex stating **may appear to be susceptible to ampicillin-sulbactam due to the activity of sulbactam with this species.** The “may appear” is making me wonder if we should report Amp/sulb as Resistant for Acinetobacter baumannii complex (we rarely isolate calcoaceticus). How do you interpret the comment?”
- WG Discussion: do we need this comment at all? Comment is referring to ampicillin, not sulbactam. Does this belong in IR tables or in Table 2B-2?
- **WG Decision: Remove from IR table**
- **MAIWG Vote 9 approved; 0 opposed; 0 abstained**

Intrinsic Resistance Working Group

Burkholderia cepacia

- Reviewed Rosemary She's presentation from June 2017, made after consultation with John Lipuma
- Reviewed EUCAST IR table for Burkholderia & "no BP" rationale
- **What is intrinsic resistance?**
- Two new recent publications – also indicating that not all drugs are testing as resistant
- Re-iterated WG previous decision to remove cefepime and imipenem from IR table.
- Other drugs up for review (from Rosemary's paper) - Current data suggest reconsideration of pip/tazo, aztreonam, ceftriaxone, trimethoprim, ertapenem, and perhaps all beta-lactams from the table due to lack of conclusive data for intrinsic resistance.
- Also possible listing of *B. vietnamensis* as an exception to aminoglycoside
- **WG discussion: can we use IE or ** and explain the difference?**
- **What is intrinsic resistance?**

CLSI vs. EUCAST (v3.1): *B. cepacia* complex

	Ampicillin	Amoxicillin-clavulanic acid	Ampicillin-Sulbactam	Ticarcillin	Ticarcillin-clavulanic acid	Piperacillin	Piperacillin-tazobactam	Cefazolin, cefalothin, cephalexin, cefadroxil Cefotaxime	Ceftriaxone	Ceftazidime	Cefepime	Aztreonam	Ertapenem	Imipenem	Meropenem	Ciprofloxacin	Chloramphenicol	Aminoglycosides	Trimethoprim	Fosfomycin	Tigecycline	Polymyxin B/Colistin
CLSI	R	R	R	R	--*	R	R	--*	R	R	R	R	R	R		--*		R	R	R		R
EUCAST	R	R	R	R	R	R	R	R	R			R	R			R	R	R	R	R		R

* drug not listed in table

Blank = listed in table with no indication of intrinsic resistance

Definition of “Intrinsic Resistance”

Appendix B. Intrinsic Resistance

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* spp. are intrinsically resistant to ampicillin.

These tables can be helpful in at least three ways: 1) they provide a way to evaluate the accuracy of testing methods; 2) they aid in the recognition of common phenotypes; and 3) they can assist with verification of cumulative antimicrobial susceptibility test data. In the tables, an “R” occurring with an antimicrobial agent/organism combination means that strains should test resistant. A small percentage (1% to 3%) may appear susceptible due to method variation, mutation, or low levels of resistance expression.

Each laboratory should decide which agents to test and report in consultation with institutional leaders representing infectious diseases practitioners, the pharmacy and therapeutics and infection control committees of the medical staff, and the antimicrobial stewardship team. If tested, the result for an antimicrobial agent/organism combination listed as having intrinsic resistance should be reported as resistant. Consideration may be given to adding comments regarding intrinsic resistance of agents not tested. See Appendix A, footnote “a.”

B1. Enterobacteriaceae

Intrinsic Resistance Working Group

Burkholderia cepacia

Drug	
Cefepime	Previously recommended to remove IR
Imipenem	Previously recommended to remove IR
Pip-Tazo	Remove IR?
Ceftriaxone	Remove IR?
Aztreonam	Remove IR?
Ertapenem	Remove IR?
Trimethoprim	Remove IR?

Do we need a footnote or “IE”?

A 17-Year Nationwide Study of *Burkholderia cepacia* Complex Bloodstream Infections Among Patients in the United States Veterans Health Administration

Nadim G. El Chakhtoura,^{1,2,3,4} Elie Saade,^{1,2,3} Brigid M. Wilson,³ Federico Perez,^{1,2,3} Krisztina M. Papp-Wallace,^{1,3,5} and Robert A. Bonomo^{1,2,3,4,5,6,7}

¹Department of Medicine, University Hospitals Cleveland Medical Center, ²Medicine and ³Research Services and ⁴Geriatrics Research, Education and Clinical Center, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, and Departments of ⁵Pharmacology and ⁶Biochemistry and ⁷Molecular Biology and Microbiology, Case Western Reserve University School of Medicine, Cleveland, Ohio

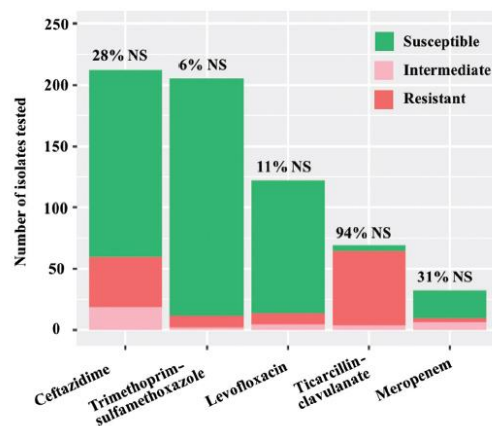


Figure 3. Results of antimicrobial susceptibility testing of isolates of *Burkholderia*

In Vitro Activity of Ceftolozane-Tazobactam and Other Antimicrobial Agents against *Burkholderia cepacia* Complex and *Burkholderia gladioli*

Dale M. Mazer,^a Carol Young,^b Linda M. Kalikin,^c Theodore Spilker,^c John J. LiPuma^c

Departments of Internal Medicine,^a Pathology,^b and Pediatrics and Communicable Diseases,^c University of Michigan Medical School, Ann Arbor, Michigan, USA

ABSTRACT We tested the activities of ceftolozane-tazobactam and 13 other antimicrobial agents against 221 strains of *Burkholderia cepacia* complex and *Burkholderia gladioli*. Most strains (82%) were cultured from persons with cystic fibrosis, and most (85%) were recovered since 2011. The ceftolozane-tazobactam MIC was ≤ 8 $\mu\text{g/ml}$ for 77% of the strains. However, the MIC range was broad (≤ 0.5 to >64 $\mu\text{g/ml}$; MIC_{50/90}, 2/32 $\mu\text{g/ml}$). Significant differences in susceptibility to some antimicrobial agents were observed between species.

KEYWORDS *Burkholderia*, ceftolozane, cystic fibrosis

TABLE 1 Activities of ceftolozane-tazobactam and comparator agents against *Burkholderia* strains

Species or group (<i>n</i> ^a)	Antibiotic(s)	MICs ($\mu\text{g/ml}$)		
		Range	MIC ₅₀	MIC ₉₀
<i>Burkholderia</i> , all isolates (221)	Ceftolozane-tazobactam	≤ 0.25 to >64	2	32
	Amikacin	≤ 16 to >64	64	>64
	Aztreonam	≤ 4 to >32	16	>32
	Ceftazidime	≤ 0.5 to >64	4	16
	Chloramphenicol	≤ 8 to >32	16	32
	Ciprofloxacin	≤ 2 to >8	≤ 2	>8
	Doripenem	≤ 1 to >8	4	8
	Levofloxacin	≤ 1 to >8	≤ 1	>8
	Meropenem	≤ 1 to >16	2	8
	Minocycline	≤ 1 to >16	2	8
	Piperacillin-tazobactam	≤ 4 to >128	≤ 4	128
	Tigecycline	≤ 2 to 16	≤ 2	8
	Tobramycin	≤ 2 to >16	>16	>16
Trimethoprim-sulfamethoxazole	≤ 1 to >8	≤ 1	2	



International Journal of Antimicrobial Agents 25 (2005) 95–109

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Review

Antimicrobial susceptibility of uncommonly isolated non-enteric Gram-negative bacilli

Helio S. Sader^{a,b,*}, Ronald N. Jones^{a,c}

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<i>B. cepacia</i> (269)	same bkpts for all? True for 2006 vs. 2018 non-enteric.					
Ceftriaxone		32	>32	≤0.25→32	35.3	37.2
Ceftazidime		4	>16	≤2→16	81.0	10.8

H.S. Sader, R.N. Jones / International Journal of Antimicrobial Agents 25 (2005) 95–109

99

Table 2 (Continued)

Antimicrobial agent (no. tested)	MIC (mg/l)			% susceptible ^a	% resistant ^a
	50%	90%	Range		
Cefepime	8	>16	≤0.12→16	57.2	29.4
Piperacillin	8	128	≤1→128	60.2	9.7
Piperacillin/Tazobactam	8	>64	≤0.5→64	68.8	13.8
Ticarcillin/Clavulanate	>128	>128	≤1→128	15.6	74.7
Aztreonam	16	>16	≤0.12→16	31.2	49.8
Imipenem	4	>8	≤0.5→8	50.6	20.1
Meropenem	2	>8	≤0.06→8	82.1	20.1
Ciprofloxacin	1	>2	≤0.25→2	53.9	29.4
Gatifloxacin	2	>4	≤0.03→4	65.1	21.6
Levofloxacin	2	>4	≤0.5→4	69.1	18.2
Amikacin	>32	>32	≤0.25→32	16.0	69.5
Gentamicin	>8	>8	≤2→8	10.8	85.5
Tobramycin	>16	>16	≤0.12→16	12.3	82.5
Tetracycline	>8	>8	≤4→8	9.3	85.1
Trimethoprim/Sulphamethoxazole	≤0.5	2	≤0.5→2	90.7	9.3
Polymyxin B ^b	>8	>8	≤1→8	12.1	87.9

Chryseobacterium spp. (83)

There bcep bkpts for t/c but n

surprising

Discussion

- Felt that we needed to keep *B. cepacia* complex in Appendix for colistin
- Did not have data for ertapenem in papers reviewed.
- If we remove “R” we probably need note explaining why.
- Burkholderia is probably the worst case, but want to go back through others in appendix
- Consensus vote

30																						
31	B2. Non-Enterobacteriaceae																					
32	Antimicrobial																					
33	Agent	Ampicillin, Amoxicillin	Piperacillin	Ticarcillin	Ampicillin-sulbactam	Amoxicillin-clavulanate	Piperacillin-tazobactam	Cefotaxime	Ceftriaxone	Ceftazidime	Cefepime	Aztreonam	Imipenem	Meropenem	Ertapenem	Polymyxin B Colistin	Aminoglycosides	Tetracyclines Tigecycline	Trimethoprim	Trimethoprim-sulfamethoxazole	Chloramphenicol	Fosfomycin
34																						
35																						
36																						
41	<i>Acinetobacter baumannii</i> / <i>Acinetobacter calcoaceticus</i> complex	R			remove a	R						R			R				R		R	R
42																						
43																						
44	<i>Burkholderia cepacia</i> complex	R	R	R	R	R	*	*	*		*	*	*		???	R	*		*			R
45																						
46	<i>Pseudomonas aeruginosa</i>	R			R	R		R	R						R			R	R	R	R	
47																						
48	<i>Stenotrophomonas maltophilia</i>	R	R	R	R	R	R	R	R			R	R	R	R		R	^b	R			R
49																						
50																						
51																						

MAIWG Vote: 8 approved; 1 opposed; 0 abstained

Intrinsic Resistance Working Group

Burkholderia cepacia

- CLSI Burkholderia cepacia complex intrinsically resistant table comment: (from Tom Thomson)
- * =
- Burkholderia cepacia complex isolates have chromosomal genes that encode resistance mechanisms that may not be expressed, resulting in susceptible or low MIC testing results. Recall, intrinsic resistance implies the presence of resistance mechanisms in natural or wild-type strains that result in phenotypic resistance for all or nearly all strains. Environmental B. cepacia complex strains have low MICs to many antimicrobials whereas clinical strains, such as those from cystic fibrosis patients, have very high MIC values to most antimicrobials. There is insufficient clinical evidence to confirm whether or not strains that test susceptible, in spite of the presence of chromosomal resistance genes, will be eradicated in vivo. Therefore, the Intrinsic Resistance Working Group was unable to confirm strains as intrinsically resistant. **Consult ID/Micro! Look at Table 2!**

Fosfomycin Susceptibility Testing Ad Hoc Working Group

Amy Mathers, MD, D(ABMM) (Co-chair)

Robert K. Flamm, Ph.D. (Co-chair)

Mandy Wootton, PhD (EUCAST)

Karen (Kitty) Anderson, PhD

Lauri D. Thrupp, M.D.

Kiofumi Ohkusu Ph.D.

Laura M. Koeth, PhD

Betsy Hirsch, PharmD, RPh

Virginia Pierce, MD

Agenda for June Meeting

1. Review and finalize a recommendation on interpretation of colonies within the zone for interpreting disk diffusion for *E. coli*.
2. Clarify wording in M100 to guide laboratorians about not testing Enterobacteriales other than *E. coli* **VOTE**
3. Other outstanding issues, including new data re. breakpoints

Current M100

- For testing and reporting of *E. coli* and *E. faecalis* urinary tract isolates only
- The 200- μg fosfomycin disk contains 50 μg of glucose-6-phosphate
- Only approved MIC method for testing is agar dilution using agar supplemented with glucose-6-phosphate
- Broth dilution MIC testing should not be performed

Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, $\mu\text{g}/\text{mL}$			Comments
			S	I	R	S	I	R	
U	Fosfomycin	200 μg	≥ 16	13–15	≤ 12	≤ 64	128	≥ 256	(16) For testing and reporting of <i>E. coli</i> urinary tract isolates only. (17) The approved MIC testing method is agar dilution. Agar media should be supplemented with 25 $\mu\text{g}/\text{mL}$ of glucose-6-phosphate. Broth dilution testing should not be performed. (18) The 200- μg fosfomycin disk contains 50 μg of glucose-6-phosphate.

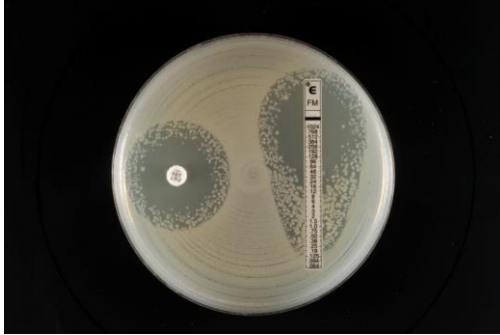
Can we ignore the inner colonies?

From January 2018

- Should we change to ignore the inner colonies on *E. coli* when tested by disk diffusion?
 - This is what EUCAST does
- Not enough data to decide in January
- Review of recent data on inner colonies
- Literature review of fitness related to resistance
- Review data and decision from EUCAST
- Would need guidance images for the document

Examples of zones (and Etest ellipses) in relation to WGS results

SE133: Fosfomycin resistance genes NOT likely, but results are uncertain (uhpB: M75T)



ES 151: Fosfomycin resistance genes likely, but results are uncertain



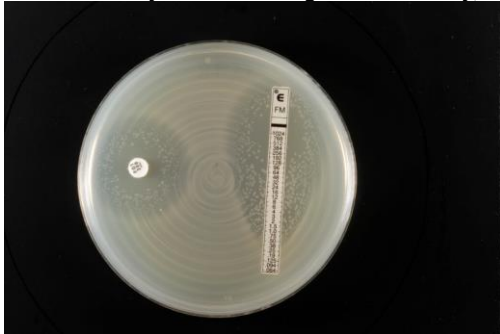
FR 158: Fosfomycin resistance genes NOT likely, but results are uncertain (bad assembly in cyaA gene)



ES 111: Fosfomycin resistance genes likely, but results are uncertain (uhpC: I109M)



ES 78: Fosfomycin resistance genes NOT likely, but results are uncertain (uhpB: Q141H)



Summary of discussion

- Inner colonies in *E. coli* are relatively infrequent
 - 3% of isolates tested; 1/3 repeat
- It appears most of this is accounted for with mutations which confer fitness cost to the bacteria
- There was concern guidance around ignoring inner colonies in *E. coli* other species would be extrapolated where the data is less clear

AHWG Motion

Motion to continue to leave document as is without additional comment to ignore colonies within the zone

7- for leaving as is; 0-opposed

Methods A&I:

No change, no vote

Fosfomicin susceptibility testing frequently requested on non-*E. coli*

- Clinical impact is not known
- Needs PK/PD
- However, many non-*E. coli* Enterobacteriales and *Pseudomonas aeruginosa*
 - have higher MIC₉₀ than *E. coli*
 - have frequent colonies within the zone of inhibition
 - have additional mechanisms of resistance to fosfomicin (FosA)
- Suggested we provide additional clarification in comment 16 for not performing fosfomicin testing non-*E. coli*?

Potential comment change

Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
			S	I	R	S	I	R	
U	Fosfomycin	200 µg	≥ 16	13–15	≤ 12	≤ 64	128	≥ 256	(16) For testing and reporting of <i>E. coli</i> urinary tract isolates only. (17) The approved MIC testing method is agar dilution. Agar media should be supplemented with 25 µg/mL of glucose-6-phosphate. Broth dilution testing should not be performed. (18) The 200-µg fosfomycin disk contains 50 µg of glucose-6-phosphate.

(16) These testing methods and interpretive criteria apply only to *E. coli* urinary tract isolates and should not be extrapolated to other species of Enterobacteriales.”

Methods A&I voted to modify (16) as above:

10 in favor, 0 opposed

Presentation about PK/PD, urine concentration and impact of absence of G-6-P in urine and influence on current breakpoint

In Vitro Susceptibility Testing of Fosfomycin Does Not Predict Ex Vivo Urinary Antibacterial Activity

Eric Wenzler, PharmD, BCPS, AAHIVP
Assistant Professor
University of Illinois at Chicago
Chicago, IL, USA

ClinicalTrials.gov Identifier NCT02570074
Funding Sponsor: National Institute of Allergy and Infectious Diseases
Funding Mechanism: DMID 1UM1AI104681-01

CLSI Committee Week Meeting
Methods Development and Standardization Working Group
San Diego, CA
June 2018



No conflicts of interest relative to the content of this presentation



Next steps for AHWG?

- Additional education/ outreach to clinical laboratories to NOT test non-E. coli Enterobacteriales
- Should the current urine breakpoint be revisited?
- Review closely all data about G-6-P
- Need PK/PD/animal data to understand other species and BP
- Upcoming clinical trial data timing
- Fosfomicin IV may be coming to US

Informational items

Should ESBL testing be recommended for *Raoultella* (former *Klebsiella*)?

- EUCAST recommendation:

3.4.1 ESBL-screening in Enterobacteriaceae

A. Screening in group 1 Enterobacteriaceae (*E. coli*, *Klebsiella* spp., *Raoultella* spp., *P. mirabilis*, *Salmonella* spp., *Shigella* spp.)

The recommended methods for ESBL screening in group 1 Enterobacteriaceae are broth dilution, agar dilution, disk diffusion or an automated system (13, 20, 21). It is required that both cefotaxime (or ceftriaxone) and ceftazidime are used as indicator cephalosporins, as there may be large differences in MICs of cefotaxime (or ceftriaxone) and ceftazidime for different ESBL-producing isolates (14, 22, 23).

The algorithm for screening and phenotypic ESBL confirmation methods for group 1 Enterobacteriaceae that are positive in screening tests are described in Figure 1 and Table 2.

- Question: Did they have data, or was this inferred?
- Per E. Matuschek & C. Giske
 - No new data; placement in group 1 was extrapolated from *Klebsiella* (and many still report *Raoultella* as *Klebsiella*)

ESBL testing in Raoultella (2)

- Raoultella infrequently isolated; only fraction would need ESBL test
 - Raoultella n ~50/ year; approx. 10% ctx-R
- Need data re. presence of ESBL in this species AND performance of ESBL tests before we could consider including
 - Request for any existing data from CDC
- Don't encourage those who are STILL using only cephalosporin breakpoints

How should labs report Intrinsic Resistance when drugs aren't tested

Susan Butler Wu

Janet Hindler

Romney Humphries

Audrey Schuetz

Issue #1

- Laboratories often ask whether they should report “R” results for an antimicrobial agent to which an isolate has intrinsic “R” (IR) but is not tested
 - Current guidance not clear
- **Why report?**
 - Patient may be receiving the drug
 - Lack of clinician awareness of the drug’s activity – patient safety issue - enhance antibiotic stewardship
- **How often might a laboratory be asked to do this?**
 - On request (infrequent; MD may not be aware of IR)
 - Always (ASP asks them to add process to SOP)

How should results for “IR” be reported?

- Drug listed in panel with “R”
- Comment added to AST report?

Intrinsic Resistance

Appendix B. Intrinsic Resistance

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.

These tables can be helpful in at least three ways:

- 1) they provide a way to evaluate the accuracy of testing methods;
- 2) they aid in the recognition of common phenotypes; and
- 3) they can assist with verification of cumulative antimicrobial susceptibility test data. In the tables, an “R” occurring with an organism-antimicrobial agent combination means that strains should test resistant. A small percentage (1% to 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.”

Specimen: BAL
Diagnosis: VAP

Example – potential for erroneous extrapolation

Stenotrophomonas maltophilia

	<u>MIC ($\mu\text{g/ml}$)</u>
ceftazidime	≤ 1 S
levofloxacin	≤ 1 S
minocycline	≤ 1 S
trimeth-sulfa	$\leq 0.5/9.5$ S

Risk of extrapolating **meropenem-S** because
ceftazidime-S

Solution #1

Specimen: Pleural fluid
Diagnosis: Empyema

Pseudomonas aeruginosa

	<u>MIC (µg/ml)</u>
amikacin	>32 R
cefepime	>32 R
ceftolozane-tazobactam	>16/4 R
ciprofloxacin	>4 R
ertapenem	R
gentamicin	>16 R
imipenem	>8 R
meropenem	1 S
piper-tazobactam	>128/4 R
tobramycin	>16 R

Report ertapenem as R (without MIC), even if not tested for AST.

Pro:

- Patient Safety: *If report as R there is not misunderstanding. No one reads the comments*

Con:

- If report "R" inconsistently, clinicians may think the drug may be ineffective for current isolate but perhaps could be a consideration for other isolates.

Solution #2

Specimen: Pleural fluid
Diagnosis: Empyema

Pseudomonas aeruginosa

	<u>MIC (µg/ml)</u>
amikacin	>32 R
cefepime	>32 R
ceftolozane-tazobactam	>16/4 R
ciprofloxacin	>4 R
gentamicin	>16 R
imipenem	>8 R
meropenem	1 S
piper-tazobactam	>128/4 R
tobramycin	>16 R

Report Comment:
“All *Pseudomonas aeruginosa* are intrinsically resistant to ertapenem.”

Pro:

- Aligns w/ report comments currently used
- Expert rules can facilitate IR reporting with use of automated systems
- Circumvents any issues associated with reporting a drug not tested

Con:

- Often difficult to accomplish adding comments with current LIS/HIS systems
- Comments often not read

What do the regulators say?

- Our group reached out to Dr. Elizabeth Palavecino – kindly offered to reach out to CLIA folks on our behalf:
 - Karen Dyer, director of the division of laboratory services at CLIA
 - Regina Van Brakle, microbiology, CLIA
- Response: *“We have an issue with reporting an antibiotic as resistant that was never tested, even if it is intrinsically resistant, unless it is reported as either IR or reported with a comment.”*

- Final recommendation to leave the language about reporting as is
- No vote necessary

M100-S28E

The results of ampicillin susceptibility tests should be used to predict the activity of amoxicillin. Ampicillin results may be used to predict susceptibility to amoxicillin-clavulanate, ampicillin-sulbactam, and piperacillin-tazobactam among non- β -lactamase-producing enterococci. Ampicillin susceptibility can be used to predict imipenem susceptibility, providing the species is confirmed to be *E. faecalis*.

- From Table 1A footnote "n" & Table 2D, comment "5"

Update on ampicillin as a predictor of imipenem and piperacillin for *E. faecalis*

- Presented in January two reports (Greece and Brazil) where penicillin was a better predictor of piperacillin and imipenem than ampicillin
- May be because of an emerging resistance mechanism
- Suggestion to gather isolates and data to understand the degree of the issue
- Verbally heard that there may be more penicillin-R ampicillin-S isolates on the West Coast

Looks like there are very few PCN-R AMP-S Isolates on the East Coast

Division of Infectious Diseases and International Health

Rutgers, NJ

Navaneeth Narayanan, PharmD, BCPS

E. faecalis:

2014 (MicroScan):

633 isolates with 6 demonstrating penicillin resistance

+Ampicillin resistant = 3 isolates (630/633 = >99% S)

+Ampicillin susceptible=3 isolates (627/630 = >99% S among amp-S)

2017 (BD Phoenix):

643 isolates with 11 demonstrating penicillin resistance

+Ampicillin-resistant = 6 isolates (637/643 = 99% S)

+Ampicillin susceptible = 5 isolates (632/637 = 99% S)

NY-Presbyterian Hospital/Weill Cornell Medical Center

Steve Jenkins PhD F(AAM), D(ABMM) *E. faecalis*:
(5,125 isolates of tested)

99% were susceptible to both ampicillin and penicillin (no breakdown available of ampicillin susceptible penicillin resistant isolates).

University of Virginia Medical Center

Lindsay Donohue, PharmD

E. faecalis

20 consecutive isolates with 1 isolate with penicillin resistance

100% (20/20) ampicillin susceptible

95% (19/20) ampicillin susceptible penicillin resistant (by E-test)

Call for Data/ Isolates – Amp/Pen Enterococcus

- Please contact Dr. Mathers

Issues sent to Text & Tables

- Strengthen recommendation for Inducible Clindamycin Resistance testing
- How to interpret differences in reported significant digits