Beyond Susceptible/Intermediate/Resistant (SIR): Enhancing Laboratory Communication with Reporting Comments

Presenters:

April Abbott, PhD, D(ABMM) – AST Subcommittee

Claire Burbick, DVM, PhD, DACVM– VAST Subcommittee

Tanis Dingle, PhD, FCCM, D(ABMM) – Antifungal Subcommittee

Objectives

- Discuss gaps between breakpoints and clinical practice
- Convey options for real-time reporting of susceptibility based comments
- Discuss mechanisms for communicating susceptibility information beyond S/I/R
- Discuss impact of susceptibility comments to clinical practice

Beyond Susceptible/Intermediate/Resistant (SIR): Enhancing Laboratory Communication with Reporting Comments

AST SC Perspective

April Abbott, Ph.D., D(ABMM)

January 2020 Educational Workshop

Disclosures

- Avails Medical, Accelerate Diagnostics, Beckman Coulter, Cepheid

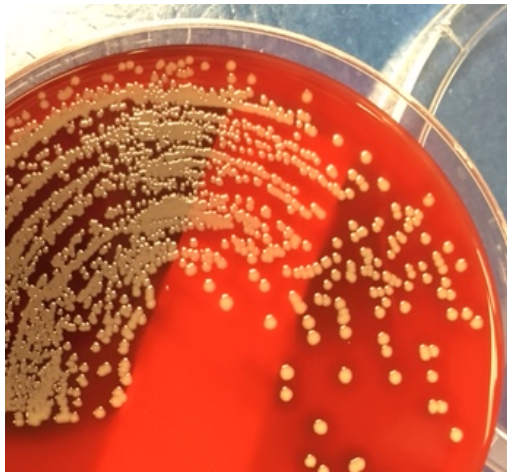
How Susceptibility Comments Are Used

- Convey susceptibility information in the organism name
- Get information into the electronic health record (EHR) that cannot be communicated in the susceptibility table
- Communicate susceptibility information when no antimicrobial susceptibility test (AST) will be performed
- Infection prevention and control (IPC) purposes

Identification of a Mechanism

- Mechanistic testing can occur before, concurrent with, or after routine AST
- Genetic or phenotypic
- Reporting of a mechanism without further interpretation is inappropriate as providers often do not know the correlation between mechanism and antimicrobial resistance

What's in a Name?



Summary

✻	Staphylococcus	1.00 Detected	✻	S. aureus	1.00 Detected
✻	mecA	1.00 Detected			

Detail

✻	Staphylococcus	1.00 Detected	✻	S. aureus	1.00 Detected
	S. epidermidis	Not Detected		S. lugdunensis	Not Detected
✻	mecA	1.00 Detected		Streptococcus	Not Detected
	S. agalactiae	Not Detected		S. pyogenes	Not Detected
	S. pneumoniae	Not Detected		S. anginosus gp.	Not Detected
	E. faecalis	Not Detected		E. faecium	Not Detected
	vanA	N/A		vanB	N/A
	Listeria	Not Detected			

S. aureus, oxacillin resistant

S. aureus, in susceptibility table input oxacillin R

S. aureus, methicillin resistant

MRSA, methicillin-resistant S. *aureus*

S. aureus, mecA positive???

Problem gets worse when you add in molecular resistance; do you need to comment on methodology?

Report Methicillin (Oxacillin) Resistance

Appendix H. (Continued)

Table H1. Strategies for Rep

Indication	Target(s)	L a ir c						
Detecting methicillin resistance in *S. aureus*	**PBP2a**					**agglutination and AST, and consider *mecA* colony NAAT, if available**	**suggested testing, report as methicillin R**	
							result per institutional protocol.	
				***mecA* not detected**	**Cefoxitin S**	**N/A**	**If tested, report phenotypic result as found (methicillin S)**	**3–6**

Table 3E. Test for Detecting Methicillin (Oxacillin) Resistance in *Staphylococcus* spp.

Test	Oxacillin Resistance Using Oxacillin Salt Agar	*mecA*-Mediated Oxacillin Resistance Using Cefoxitin		
Test method	**Agar Dilution**	**Disk Diffusion**		**Broth Microdilution**
Organism group	*S. aureus*	*S. aureus* and *S. lugdunensis*	**Other *Staphylococcus* spp. (excluding *S. pseudintermedius* and *S. schleiferi*)**	*S. aureus* and *S. lugdunensis*
Medium	MHA with 4% NaCl	MHA		CAMHB
Antimicrobial concentration	6 µg/mL oxacillin	30 µg cefoxitin disk		4 µg/mL cefoxitin
Inoculum	Colony suspension to obtain 0.5	Standard disk diffusion		Standard broth microdilution

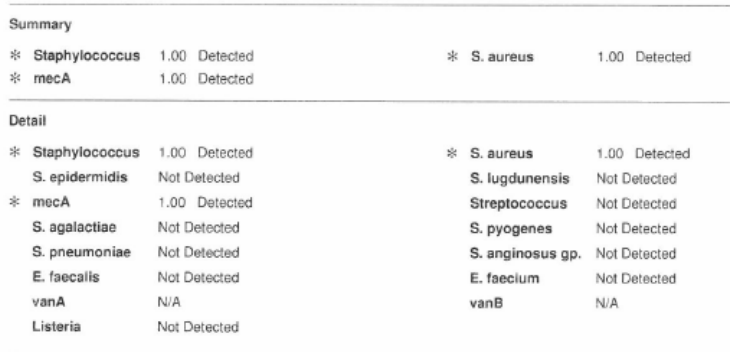
Table 2C. *Staphylococcus* spp. (Continued)

(4) Historically, resistance to the penicillinase-stable penicillins (see Glossary I) has been referred to as "methicillin resistance" or "oxacillin resistance." MRSA are strains of *S. aureus* that express *mecA,* ***mecC,*** or another mechanism of methicillin resistance, such as changes in affinity of penicillin-binding proteins for oxacillin (modified *S. aureus* strains).

(5) Most oxacillin resistance is mediated by *mecA,* encoding PBP2a (also called PBP2'). Isolates that test positive for *mecA* or PBP2a should be reported as oxacillin resistant **(see Appendix H).**

CLSI M100, 29th Ed., 2019: Table 2C, Table 3E, Appendix H

Organism Name MRSA Decision Tree



Summary					
*	Staphylococcus	1.00 Detected	*	S. aureus	1.00 Detected
*	mecA	1.00 Detected			

Detail					
*	Staphylococcus	1.00 Detected	*	S. aureus	1.00 Detected
	S. epidermidis	Not Detected		S. lugdunensis	Not Detected
*	mecA	1.00 Detected		Streptococcus	Not Detected
	S. agalactiae	Not Detected		S. pyogenes	Not Detected
	S. pneumoniae	Not Detected		S. anginosus gp.	Not Detected
	E. faecalis	Not Detected		E. faecium	Not Detected
	vanA	N/A		vanB	N/A
	Listeria	Not Detected			

Provider

Actionable AST data conveyed as the organism name

EHR

Specimen Type	BLOOD, VENOUS
Special Handling	NONE
Gram Stain Result	GRAM POSITIVE COCCI RESEMBLING STAPHYLOCOCCUS AFTER 0.50 DAYS METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS DETECTED BY MOLECULAR METHODS. NEGATIVE FOR ALL OTHER ANALYTES TESTED. SEE TEST DIRECTORY FOR ASSAY INFORMATION.
Organism 1	METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS

IPC

Allergies	HCA: None
No Known Allergies	Language: English
Code: FULL	Infection: MRSA
Adv Dir: None	Isolation: Contact

- Speaking a common language
- Informatics challenge
- Solution that worked for both the providers and IPC

Identification of a Mechanism

Mechanism Detected	What is Reported
mecA	Methicillin-resistant *Staphylococcus aureus* detected by a molecular method.
vanA/vanB	Vancomycin-resistant *Enterococcus* detected by a molecular method.
CTX-M	Extended-spectrum beta-lactam detected by a molecular method.
KPC (or NDM, IMP, VIM, OXA)	Carbapenem-resistant organism detected. Presence of a KPC carbapenemase detected by a molecular method.

- CLSI guidance: report phenotypic results (if available) and consider reporting the presence of molecular target per institutional protocol

MIC.66100 **Final Report** **Phase I**

The final report includes a summary of the test method and information regarding clinical interpretation if appropriate.

NOTE: For example, HIV-1 viral load results may vary significantly depending upon the test method used; including the test method in the report is important information for interpreting the results.

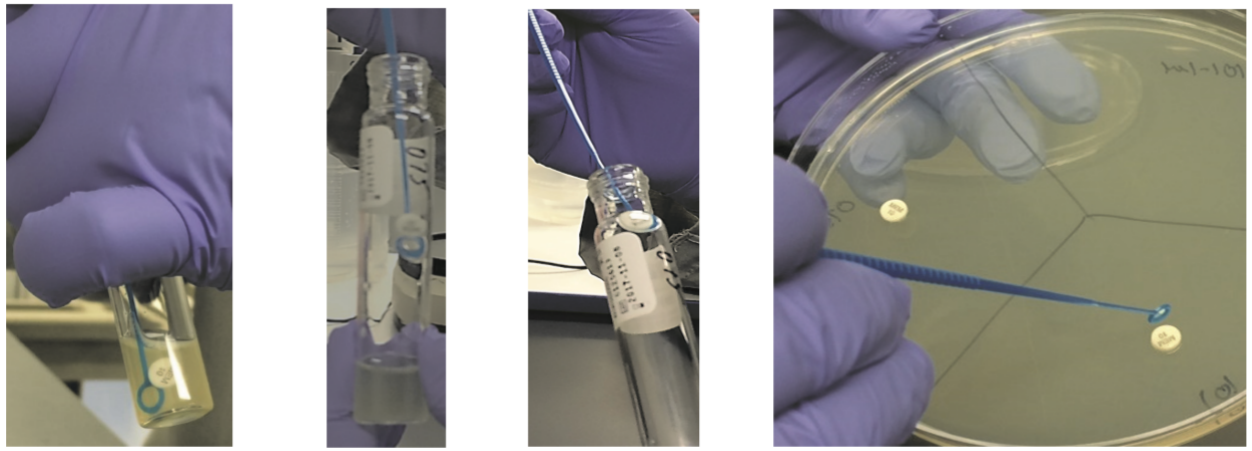
CAP Checklist, 2019: Results Reporting

Carbapenemase Detection

- Carbapenemase production has been associated with poorer clinical outcomes, including increased mortality over non-carbapenemase carbapenem-resistant Enterobacterales

- Comment used to convey information for treatment and infection prevention and control purposes

Table 3C. (Continued)

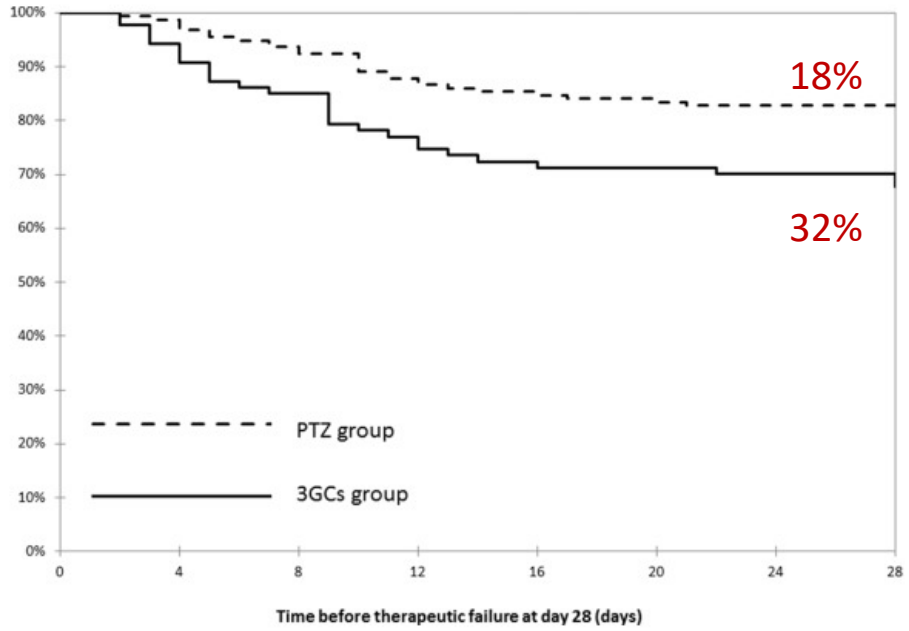


A B C D

CLSI M100, 29th Ed., 2019: Table 3C

“SPICE” Organisms

- Infer potential emergence of resistance based on the identification of the organism alone, without any AST
- Studies have reproducibly demonstrated emergence of resistance and therapeutic failure when third generation cephalosporins (and to some extent piperacillin/tazobactam) are used – but this is very nuanced and hotly debated



- Overall treatment failure rate of 23%
- Emergence of resistance and failure rate was higher in those receiving a third generation cephalosporin

Carrie C et al., J Crit Care. 2019 (56) 6-11

“SPICE” Organisms

(12) ***Enterobacter*, *Klebsiella* (formerly *Enterobacter*) *aerogenes***, *Citrobacter*, and *Serratia* may develop resistance during prolonged therapy with 3rd-generation cephalosporins as a result of derepression of AmpC β-lactamase. Therefore, isolates that are initially susceptible may become resistant within 3 to 4 days after initiation of therapy. Testing repeat isolates may be warranted.

- 60 year old male, status post neurosurgery, presents with infected bone flap

Culture Result

```
MODERATE SERRATIA MARCESCENS
SERRATIA MARCESCENS MAY DEVELOP RESISTANCE UPON EXPOSURE TO THIRD GENERATION CEPHALOSPORINS OR
PIPERACILLIN/TAZOBACTAM. FOR SERIOUS INFECTIONS, CEFEPIME, CARBAPENEM, OR NON-BETA-LACTAM AGENT
 SHOULD BE CONSIDERED.
```

Susceptibility

	Serratia marcescens MIC	
Ampicillin	>16 RESISTANT	Resistant
Ampicillin/sulbactam	>16/8 RESIS...	Resistant
Cefazolin	>16	Resistant[1]
Cefepime	<=2 SUSCEPT...	Sensitive
Ceftazidime	<=1 SUSCEPT...	Sensitive
Ceftriaxone	<=1 SUSCEPT...	Sensitive
Cefuroxime	>16 RESISTANT	Resistant
Ciprofloxacin	<=1 SUSCEPT...	Sensitive
Ertapenem	<=0.5 SUSCE...	Sensitive
Gentamicin	<=1 SUSCEPT...	Sensitive
Levofloxacin	<=0.25 SUSC...	Sensitive
Piperacill/Tazob	<=4 SUSCEPT...	Sensitive
TMP SULFA	<=2/38 SUSC...	Sensitive

- Antimicrobial stewardship function
- Comment automatically appended when organism is reported

CLSI M100, 29th Ed., 2019: Table 2A

Dosing Guidance

- Numerous comments in M100 concerning dosing regimen

Table 2A. *Enterobacteriaceae* (Continued)

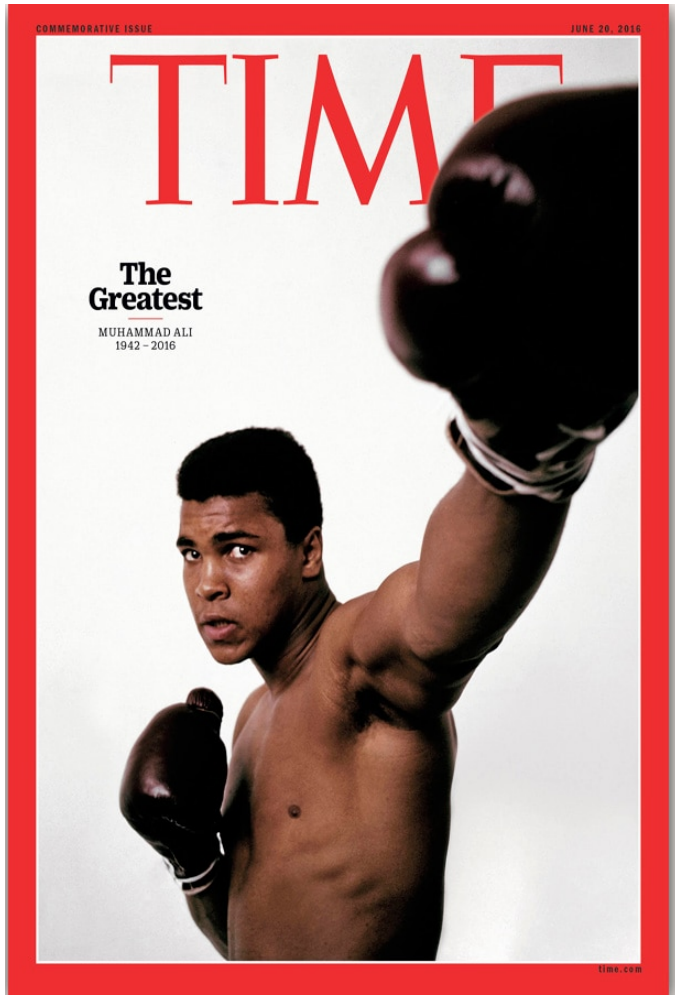
Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL				Comments
			S	SDD	I	R	S	SDD	I	R	
CEPHEMS (PARENTERAL) (Including cephalosporins I, II, III, and IV. Please refer to Glossary I.) (Continued)											
B	Cefepime	30 µg	≥25	19–24	–	≤18	≤2	4–8	–	≥16	**(16)** The breakpoint for susceptible is based on a dosage regimen of 1 g **administered** every 12 h. The breakpoint for SDD is based on dosage regimens that result in higher cefepime exposure, either higher doses or more frequent doses or both, up to approved maximum dosage regimens. See Appendix E for more information about breakpoints and dosage regimens. Also see the definition of SDD in the Instructions for Use of Tables section.
B B	Cefotaxime or ceftriaxone	30 µg 30 µg	≥26 ≥23	–	23–25 20–22	≤22 ≤19	≤1 ≤1	–	2 2	≥4 ≥4	**(17)** Breakpoints are based on a dosage regimen of 1 g **administered** every 24 h for ceftriaxone and 1 g **administered** every 8 h for cefotaxime. See comment (11).

- Determining which dosing comments to include is a challenge

Dispense Dosing Recommendations

- Microbiologists, pharmacists, and ID specialists must partner to determine relevant comments
- Review comments yearly
- Cascade report to limit the number of therapeutic options (and as a result the number of comments)
- Limit the number of orderable regimes in the EHR for a given antimicrobial

Different Doses for Different Organisms/Sites



- Provide guidance when the standard dosing strategy may need to be modified
- Choosing the "best" dose can be a challenge for the provider

Table 2C. *Staphylococcus* spp. (Continued)

Test/Report Group	Antimicrobial Agent	*Staphylococcus* spp. Indications	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL				Comments
				S	SDD	I	R	S	SDD	I	R	
CEPHEMS (PARENTERAL)												
B	Ceftaroline	***S. aureus* only, including MRSA**	30 µg	**≥25**	**20–24**		**≤19**	≤1	**2–4**	–	**≥8**	**(18) The breakpoint for susceptible is** based on a dosage regimen of 600 mg **administered** every 12 h. **(19) The breakpoint for SDD is based on a dosage in adults of 600 mg every 8 h administered over 2 h.**

Table 2H-1. *Streptococcus* spp. beta-hemolytic group

C	Ceftaroline	30 µg	≥26	–	–	–	≤0.5	–	–	**(7)** Breakpoints are based on a dosage regimen of 600 mg **administered** every 12 h.

Halsman, Phillipe. *Time*, June 20, 2016, Vol. 187. No 23
CLSI M100, 29th Ed. Table 2C and Table 2H-1

Source-specific Dosing Guidance

- Important for privileged sites where drug levels may be lower than systemic levels (e.g. CSF for meningitis) and in compartments where concentrations of the agent may be higher than systemic levels (e.g. urine for uncomplicated urinary tract infection)

Culture Result	>=100,000 COL/ML ESCHERICHIA COLI
Status	01/14/2020 FINAL
EDI Organism	ESCHERICHIA COLI

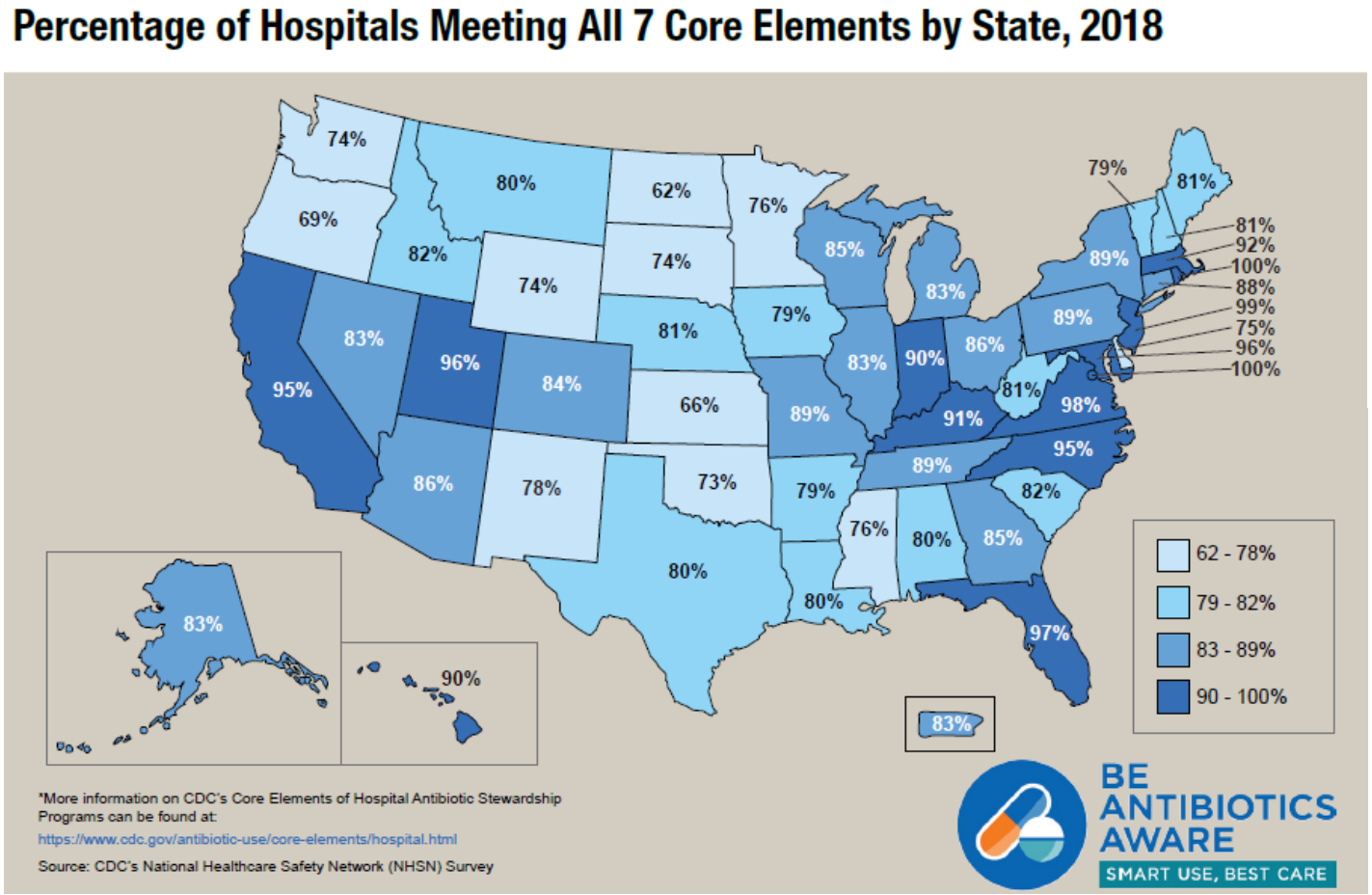
Susceptibility

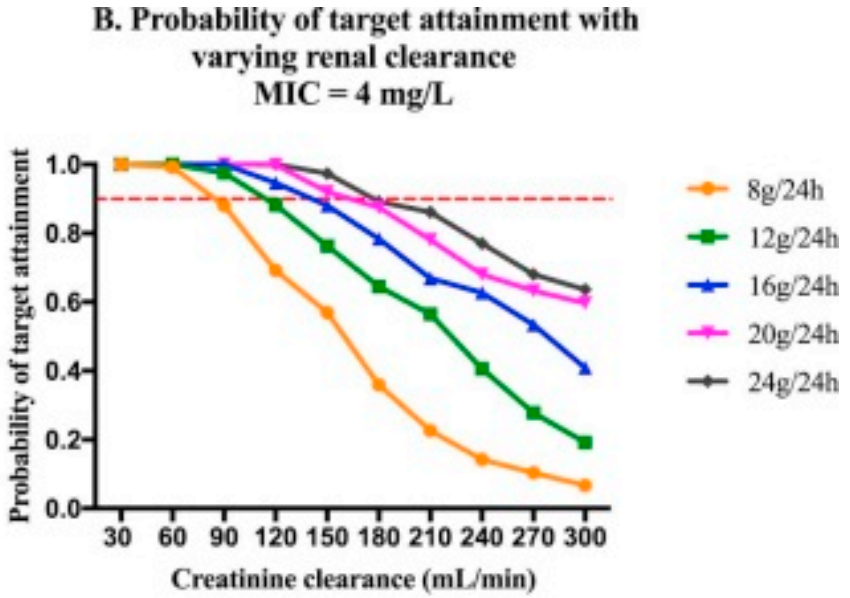
	Escherichia coli MIC	
Ampicillin	<=8 SUSCEPT...	Sensitive
Ampicillin/sulbactam	2/1 SUSCEPT...	Sensitive
Cefazolin	<=2 [1]	
Cefepime	<=2 SUSCEPT...	Sensitive
Ceftazidime	<=1 SUSCEPT...	Sensitive
Ceftriaxone	<=1 SUSCEPT...	Sensitive
Cefuroxime	<=4 SUSCEPT...	Sensitive
Ciprofloxacin	<=1 SUSCEPT...	Sensitive
Ertapenem	<=0.5 SUSCE...	Sensitive
Gentamicin	<=1 SUSCEPT...	Sensitive
Levofloxacin	<=0.25 SUSC...	Sensitive
Nitrofurantoin	<=32 SUSCEP...	Sensitive
Piperacill/Tazob	<=4 SUSCEPT...	Sensitive
TMP SULFA	<=2/38 SUSC...	Sensitive

[1] SEE NOTE:
FOR UNCOMPLICATED URINARY TRACT INFECTIONS, A MIC <=16 FOR CEFAZOLIN INDICATES SUSCEPTIBILITY TO CEFACLOR, CEFDINIR, CEFPODOXIME, CEFPROZIL, CEFUROXIME, CEPHALEXIN, AND LORACARBEF. FOR COMPLICATED URINARY TRACT INFECTIONS, A MIC OF <=2 INDICATES SUSCEPTIBILITY TO CEFAZOLIN, BUT MAY NOT BE PREDICTIVE OF ORAL CEPHALOSPORIN SUSCEPTIBILITY.

* Alternative reporting strategy is to create two antimicrobials, cefazolin and oral cephs, as an example

Expertise and Resources





- In 2018, 85% of acute care hospitals met all seven of the Core Elements
- Evaluating literature and implementing new practice requires resources

Dhaese SAM, Int J Antimicrob Agents. 2018 (4) 594-600

Communicate Predictable Susceptibility or Resistance Based on Identification

CLSI: “Susceptibility testing of penicillins... does not need to be performed routinely, because non-susceptible isolates are extremely rare in any beta-hemolytic streptococcus…”

- Most laboratories utilize a version of this comment
- Weekly requests for full AST
  - Technologists first evaluate EHR for penicillin allergy status
  - Work with the provider to determine reason for request

CLSI M100, 29th Ed., 2019: Table 2H-1

Communicate Intrinsic Resistance

- Agent may not be routinely released as part of routine AST
- Ability to provide clinically important information prior to AST
- Driven by a provider question

- Scenario: provider contacts the laboratory to request vancomycin susceptibility on *Pediococcus*
  - *"Pediococcus* species are intrinsically resistant to vancomycin. Isolates are generally susceptible to ampicillin and penicillin. Contact Microbiology if susceptibility testing is warranted."

CLSI M45, 3rd Ed. 2015: Table 18

Provide Surrogate Data

- Agent not routinely released on AST panel

- Scenario: provider contacts the laboratory to request piperacillin/tazobactam on *Enterococcus faecalis*
  - "Susceptibility of *Enterococcus faecalis* to piperacillin/tazobactam can be inferred from susceptibility to ampicillin."

Comments
(6) 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*.
(7) Enterococci susceptible to penicillin are predictably susceptible to ampicillin, amoxicillin, ampicillin-sulbactam, amoxicillin-clavulanate, and piperacillin-tazobactam for non–β-lactamase-producing enterococci. However, enterococci susceptible to ampicillin cannot be assumed to be susceptible to penicillin. If penicillin results are needed, testing of penicillin is required.

CLSI M100, 29th Ed., 2019: Table 2D

Reference Alternative AST Source

- Due to inability to perform AST in-house
- May be used when clinical significance is questionable
- Sources: CLSI standard, antibiogram, literature

“Anaerobe isolate held in lab for 7 days. Anaerobic antibiograms available on Dweb in the Antimicrobial Stewardship page. Contact Microbiology if susceptibility testing required.”

Influence of Comments on Prescribing

- Clinical survey of vignettes to assess prescribing choices based on comments added to culture results

Microbiology report in question 3A	Microbiology report in question 3B
Gram stain: no polymorphs; 2+ epithelial cells; 1+ Gram-positive cocci; 1+ Gram-negative bacilli. Culture: mixed skin flora including *Pseudomonas* spp. Comment: *Pseudomonas* are frequent colonizers of skin ulcers, therefore antimicrobial therapy is not always indicated. Susceptibilities may be provided on request.	Gram stain: no polymorphs; 2+ epithelial cells; 1+ Gram-positive cocci; 1+ Gram-negative bacilli. Culture: skin flora including heavy growth (3+) of *Pseudomonas aeruginosa*. Reported susceptibilities: Ciprofloxacin S Gentamicin S Piperacillin + Tazobactam S Ceftazidime S S=Susceptible

Papanicolas L, et al. JAC. 2017; (72) 1202-1205

Influence of Comments on Prescribing

- Scenario 1: Uncomplicated sore throat
- Scenario 2: Asymptomatic bacteriuria
- Scenario 3: Chronic wound
- Scenario 4(1): Colonization with MDR organism
- Scenario 4(2): intravenous drug user with bacteremia

Table 1. Survey results with *P* values indicating significance of difference between answers in versions A and B of each scenario.

Scenario no.	No. of completed answers returned	Percentage of doctors selecting to use antibiotic in answer	*P* value
1A	32	3%	<0.001
1B	38	42%	
2A	38	47%	0.0035
2B	32	81%	
3A	32	12%	<0.001
3B	38	71%	
4A(1)	13	53%	0.695
4B(1)	13	46%	
4A(2)	24	67%	0.618
4B(2)	19	74%	

Reporting of AST Results – One Size Doesn't Fit All

- Variation in testing methods/practices
- Differences in laboratory information (LIS) and electronic health record (EHR) systems – often, these are electronic hurdles
- Differences in expertise
  - Antimicrobial stewardship programs, pharmacists, specialists – can't touch every patient
- Variation in prescribing (e.g. dose/duration)
- Differences in infection prevention and control practices
- The Microbiology Laboratory is the first line of defense in getting clinically relevant AST information in the medical record

What Guidance is Available?

- Few publications endorsing exact language/recommendations

TABLE 5 Examples of acceptable therapy-related comments added to patient clinical microbiology reports to improve prescribing of antimicrobials

Category	Examples
CLSI-recommended comments (M100-S25)[a]	Cefazolin results predict results for oral agents cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef when used for therapy of uncomplicated urinary tract infections due to *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* Rifampin should not be used alone for antimicrobial therapy in infections with *Staphylococcus* or *Streptococcus* spp. Use of penicillins or third-generation cephalosporins for pneumococcal meningitis requires therapy with maximum doses Dose of intravenous penicillin of at least 2 million units every 4 h in adult with normal renal function (12 million U/day) can be used to treat nonmeningeal pneumococcal infections due to strains with penicillin MICs of ≤2 μg/ml; strains with an intermediate MIC of 4 μg/ml may require penicillin doses of 18 to 24 million U/day in adults with normal renal function Penicillin- or ampicillin-intermediate isolates may require combined therapy with an aminoglycoside for bactericidal action in streptococcal infections Combination therapy with ampicillin, penicillin, or vancomycin (for susceptible strains) plus an aminoglycoside is usually indicated for serious enterococcal infections such as endocarditis unless high-level resistance to both gentamicin and streptomycin is documented; such combinations are predicted to result in synergistic killing of the *Enterococcus*

Morency-Potvin P, et al. Clin Microbiol Rev.2016; (30)381-407

Published Guidance on Interpretive Comments

Table 9.3: Examples of comments that interpret antimicrobial susceptibility results

Specimen type and indication	Reporting comment	
Pus or skin swab with methicillin-susceptible *Staphylococcus aureus*	*S. aureus* susceptible to flucloxacillin/dicloxacillin is also susceptible to cefazolin, cefalexin and amoxicillin–clavulanate. (Flucloxacillin/dicloxacillin result reported as susceptible based on cefoxitin test.)	Surrogate
Any site where *Pasteurella* species is isolated	*Pasteurella* species are always resistant to dicloxacillin/flucloxacillin.	Intrinsic Resistance
Respiratory tract or blood isolate (meningitis absent) where *Streptococcus pneumoniae* is isolated	In pneumonia, benzylpenicillin 1.2 g IV every 6 hours is enough treatment for isolates with MIC ≤0.5 mg/L. Use 1.2 g every 4 hours for isolates with MIC ≤1 mg/L. Use 2.4 g every 4 hours for isolates with MIC ≤2 mg/L. Alternative therapy should be selected for isolates with MIC ≥4 mg/L – please discuss with the on-call clinical microbiologist. (Comment derived from EUCAST.)	Dosing

AUSTRALIAN COMMISSION ON SAFETY AND QUALITY IN HEALTH CARE

Antimicrobial Stewardship in Australian Health Care, 2018.
Chapter 9: Role of the clinical microbiology service

Summary

- Comments are necessary to communicate AST information to providers
- No one-size fits all approach
- Few resources directed at exact recommended language
- Lacking peer-reviewed literature of outcome data
- Challenges:
  - Differences between AST systems, electronic systems (LIS, EHR), expertise and oversight, resources, and clinical practice

Reporting From the Rabbit Hole

Claire Burbick, DVM, PhD, DACVM

Washington State University

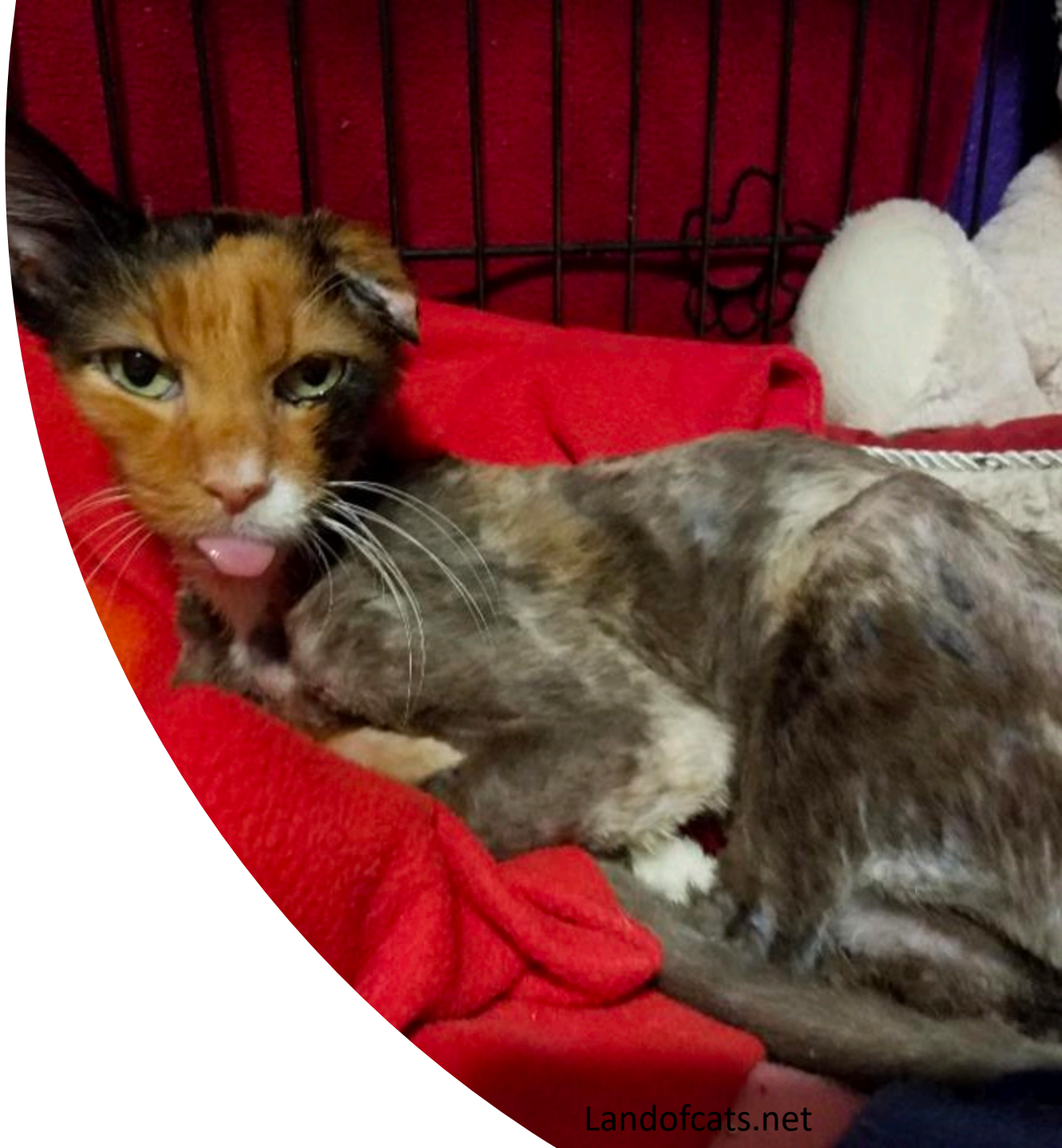
Systemic Challenges to Effective Communication

Lack of knowledge	Veterinarians Diagnostic Labs
Lack of Specialists or Specialties	ID Veterinarians ID Pharmacists Clinical Microbiologists
Lack of money	Little infrastructure to support this area of veterinary medicine • Modern equipment • Information technology • Training or continuing education • Research and outcomes assessment
Many Stakeholders	Production medicine (multiple species and systems) Small animal medicine (multiple species) Exotic/zoo/wildlife Aquatic species
Regulations	AMDUCA

Specific Challenges

Case 1: Merlot

- Signalment: 18 year old Fe spayed, DSH
- History:
  - Chronic kidney disease
  - Treatment-refractory anemia (darbepoetin)
- Recent findings:
  - Thickened gall bladder wall and bile sludge (US)
  - Pulmonary mass (rads)
- Submitted
  - Bile
  - Urine



Case 1: *E.coli* isolated from bile and urine

- Bile AST

Isolate	Antimicrobial Drug	MIC	Interpretation
Escherichia coli	Amikacin	<= 4	Susceptible
Escherichia coli	Amoxicillin/Clavulanic Acid	4	Resistant
Escherichia coli	Ampicillin	2	Resistant
Escherichia coli	Cefazolin	2	Susceptible
Escherichia coli	Cefpodoxime	<= 1	Susceptible
Escherichia coli	Cephalexin	8	Resistant
Escherichia coli	Enrofloxacin	<= 0.12	Susceptible
Escherichia coli	Gentamicin	0.50	Susceptible
Escherichia coli	Marbofloxacin	<= 0.12	Susceptible
Escherichia coli	Orbifloxacin	<= 1	Susceptible
Escherichia coli	Pradofloxacin	<= 0.25	Susceptible
Escherichia coli	Trimethoprim/Sulfamethoxazole	<= 0.50	Susceptible

NUMBER VALUES = Micrograms/ml; Antimicrobial susceptibility results in veterinary medicine may include antimicrobials that are not approved for use in the host species. Please consider that the standards from the Clinical Laboratory Standards Institute (CLSI) may not exist for use of some antimicrobials in some species, and in vitro results may not predict in vivo efficacy. The client assumes responsibility for efficacy, safety, and residue avoidance with extra label uses of antimicrobials.

Down the rabbit hole….

Isolate	Antimicrobial Drug	MIC	Interpretation
Escherichia coli	Amikacin	<= 4	Susceptible
Escherichia coli	Amoxicillin/Clavulanic Acid	4	Resistant
Escherichia coli	Ampicillin	2	Resistant
Escherichia coli	Cefazolin	2	Susceptible
Escherichia coli	Cefpodoxime	<= 1	Susceptible
Escherichia coli	Cephalexin	8	Resistant
Escherichia coli	Enrofloxacin	<= 0.12	Susceptible
Escherichia coli	Gentamicin	0.50	Susceptible
Escherichia coli	Marbofloxacin	<= 0.12	Susceptible
Escherichia coli	Orbifloxacin	<= 1	Susceptible
Escherichia coli	Pradofloxacin	<= 0.25	Susceptible
Escherichia coli	Trimethoprim/Sulfamethoxazole	<= 0.50	Susceptible

Cat breakpoints:
S≤ 0.25 – but should **always be reported as R** which clinicians think means the E. coli is resistant – extreme frowny face

So really just fluoroquinolone breakpoints….

Where are the other interpretations coming from?

Is this ok?

Isolate	Antimicrobial Drug	MIC	Interpretation
Escherichia coli	Amikacin	<= 4	Susceptible
Escherichia coli	Amoxicillin/Clavulanic Acid	4	Resistant
Escherichia coli	Ampicillin	2	Resistant
Escherichia coli	Cefazolin	2	Susceptible
Escherichia coli	Cefpodoxime	<= 1	Susceptible
Escherichia coli	Cephalexin	8	Resistant
Escherichia coli	Enrofloxacin	<= 0.12	Susceptible
Escherichia coli	Gentamicin	0.50	Susceptible
Escherichia coli	Marbofloxacin	<= 0.12	Susceptible
Escherichia coli	Orbifloxacin	<= 1	Susceptible
Escherichia coli	Pradofloxacin	<= 0.25	Susceptible
Escherichia coli	Trimethoprim/Sulfamethoxazole	<= 0.50	Susceptible

Dog

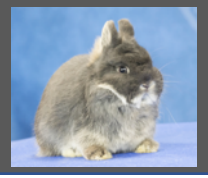
Human

Amikacin
Cat: Nada
Dog: S <=4
Human: S <=16

Cefazolin:
Cat: Nada
Dog: S <=2
Human: S <=2

Cefpodoxime
Cat: Nada
Dog: S <=2
Human: S <=2

Can we report the nuance?



Isolate: *E.coli*
Site: Bile

Feline-specific Interpretations

ß-Lactam and combination agents:

Antimicrobial Agent	MIC	Interpretation
Amoxicillin/Clavulanic Acid	4	Resistant
Ampicillin	2	Resistant
WARNING: Due to poor pharmacokinetics, the drugs reported above are unsuitable for use in treating *Enterobacterales* infection in any body site in cats. For acquired resistance monitoring, this isolate would be considered wild-type with no phenotypic resistance detected.		

Fluoroquinolones:

Enrofloxacin	<=0.12	Susceptible
Marbofloxacin	<=0.12	Susceptible
Orbifloxacin	<=1	Susceptible
Pradofloxacin	<=0.25	Susceptible

Canine-specific Interpretations

WARNING: Canine-specific breakpoints may be less accurate for predicting clinical efficacy in cats. Please review with caution.

Aminoglycosides:

Antimicrobial Agent	MIC	Interpretation
Amikacin	<=4	Susceptible

ß-Lactam agents:

Cefazolin	2	Susceptible
Cefpodoxime	<=1	Susceptible
Cephalexin	8	Resistant
WARNING: The resistance reported for cephalexin is due to poor pharmacokinetics in dogs and is unsuitable for use in treating *Enterobacterales* infection outside of the urinary tract. For acquired resistance monitoring, this isolate would be considered wild-type with no phenotypic resistance detected.		

Human-specific Interpretations

WARNING: Human-specific breakpoints may be less accurate for predicting clinical efficacy in cats. Please review with caution.

Aminoglycosides:

Antimicrobial Agent	MIC	Interpretation
Gentamicin	0.5	Susceptible

Folate pathway antagonists:

Trimethoprim/Sulfamethoxazole	<=0.5	Susceptible

Plus definitions….

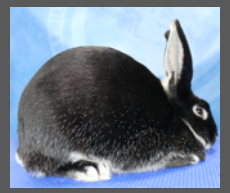
Definitions:

Susceptible: a category defined by a breakpoint that implies that isolates with an MIC at or below or zone diameters at or above the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

Intermediate: a category defined by a breakpoint that includes isolates with MICs or zone diameters within the intermediate range that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates; **NOTE:** The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher-than-normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

Resistant: a category defined by a breakpoint that implies that isolates with an MIC at or above or zone diameters at or below the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs or zone diameters that fall in the range in which specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

Or this?



Isolate: *E.coli*
Site: Bile

Aminoglycosides:

Antimicrobial Agent	MIC	Interpretation	Species Interpretation
Amikacin	<=4	Susceptible	Canine
Gentamicin	0.5	Susceptible	Human

ß-Lactam and combination agents:

Antimicrobial Agent	MIC	Interpretation	Species Interpretation
Amoxicillin/Clavulanic Acid	4	Resistant	Feline
Ampicillin	2	Resistant	Feline
Cefazolin	2	Susceptible	Canine
Cefpodoxime	<=1	Susceptible	Canine
Cephalexin	8	Resistant	Canine

WARNING: Due to poor pharmacokinetics, the drugs reported above as resistant are unsuitable for use in treating *Enterobacterales* infection in any body site. For acquired resistance monitoring, this isolate would be considered wild-type with no phenotypic resistance detected.

Fluoroquinolones:

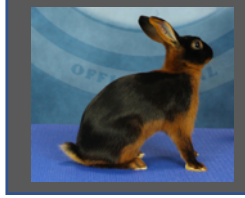
Enrofloxacin	<=0.12	Susceptible	Feline
Marbofloxacin	<=0.12	Susceptible	Feline
Orbifloxacin	<=1	Susceptible	Feline
Pradofloxacin	<=0.25	Susceptible	Feline

Folate pathway antagonists:

Trimethoprim/Sulfamethoxazole	<=0.5	Susceptible	Human

PLEASE NOTE: Unfortunately, we lack feline-specific clinical interpretations for some of antimicrobial agents reported. Canine-specific or human-specific breakpoints were used instead, which may aid in clinical decision-making. However, these interpretations may be less accurate for predicting clinical efficacy in cats. Please review with caution.

Or this?



Isolate: *E.coli*
Site: Bile

Aminoglycosides:

Antimicrobial Agent	MIC	Interpretation	Species Interpretation
Amikacin	<=4	No interpretation	None
Gentamicin	0.5	No interpretation	None

ß-Lactam and combination agents:

Antimicrobial Agent	MIC	Interpretation	Species Interpretation
Amoxicillin/Clavulanic Acid	4	Resistant	Feline
Ampicillin	2	Resistant	Feline
Cefazolin	2	No interpretation	None
Cefpodoxime	<=1	No interpretation	None
Cephalexin	8	No interpretation	None

WARNING: Due to poor pharmacokinetics, the drugs reported above as resistant are unsuitable for use in treating *Enterobacterales* infection in any body site. For acquired resistance monitoring, this isolate would be considered wild-type with no phenotypic resistance detected.

Fluoroquinolones:

Enrofloxacin	<=0.12	Susceptible	Feline
Marbofloxacin	<=0.12	Susceptible	Feline
Orbifloxacin	<=1	Susceptible	Feline
Pradofloxacin	<=0.25	Susceptible	Feline

Folate pathway antagonists:

Trimethoprim/Sulfamethoxazole	<=0.5	No interpretation	None

PLEASE NOTE: Unfortunately, we lack feline-specific clinical interpretations for some of antimicrobial agents reported. The MIC reported is an in vitro measure which may aid in clinical decision-making in conjunction with pharmacologic and efficacy information. Please review with caution.

Last one…promise

Isolate: ***E.coli***
Site: Bile

Aminoglycosides:

Antimicrobial Agent	MIC	Interpretation	Species Interpretation
Amikacin	<=4	Wild-type	None-ECOFF
Gentamicin	0.5	Wild-type	None-ECOFF

ß-Lactam and combination agents:

Antimicrobial Agent	MIC	Interpretation	Species Interpretation
Amoxicillin/Clavulanic Acid	4	Resistant	Feline
Ampicillin	2	Resistant	Feline
Cefazolin	2	Wild-type	None-ECOFF
Cefpodoxime	<=1	Wild-type	None-ECOFF
Cephalexin	8	Wild-type	None-ECOFF

WARNING: Due to poor pharmacokinetics, the drugs reported above as resistant are unsuitable for use in treating *Enterobacterales* infection in any body site. For acquired resistance monitoring, this isolate would be considered wild-type with no phenotypic resistance detected.

Fluoroquinolones:

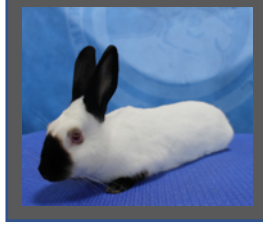
Enrofloxacin	<=0.12	Susceptible	Feline
Marbofloxacin	<=0.12	Susceptible	Feline
Orbifloxacin	<=1	Susceptible	Feline
Pradofloxacin	<=0.25	Susceptible	Feline

Folate pathway antagonists:

Trimethoprim/Sulfamethoxazole	<=0.5	No interpretation	Concentration range does not allow determination WT/NWT

PLEASE NOTE: Unfortunately, we lack feline-specific clinical interpretations for some of antimicrobial agents reported. The ECOFF reported is an in vitro measure which may aid in clinical decision-making in conjunction with pharmacologic and efficacy information. Please review with caution.

Few more definitions….



Definitions:

Susceptible: a category defined by a breakpoint that implies that isolates with an MIC at or below or zone diameters at or above the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

Intermediate: a category defined by a breakpoint that includes isolates with MICs or zone diameters within the intermediate range that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates; **NOTE:** The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher-than-normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

Resistant: a category defined by a breakpoint that implies that isolates with an MIC at or above or zone diameters at or below the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs or zone diameters that fall in the range in which specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

ECOFF: Distinguishes between organisms with and without phenotypic resistance.

Wild-type: No phenotypic resistance

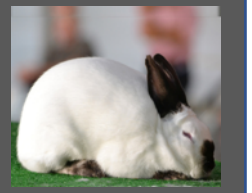
Non-wild-type: Phenotypic resistance

What about agricultural animals?

Case 2: Sick calves

- 2 month old Holstein calves
  - 8 dead
  - 25 affected
  - 500 in group
- Breathing hard
- Treatment with Tulathromycin and/or tetracycline
- Die within 1-2 days
- Evidence of septicemia on histo
- *Salmonella* Dublin cultured from lung

S. Dublin AST



Isolate	Antimicrobial Drug	MIC	Interpretation
Salmonella Dublin	Ampicillin	2	
Salmonella Dublin	Ceftiofur	0.5	
Salmonella Dublin	Clindamycin	>16	
Salmonella Dublin	Danofloxacin	<=0.12	
Salmonella Dublin	Enrofloxacin	<=0.12	
Salmonella Dublin	Florfenicol	>8	
Salmonella Dublin	Gentamicin	>16	
Salmonella Dublin	Neomycin	<=4	
Salmonella Dublin	Penicillin G	>8	😖😫😡😩
Salmonella Dublin	Spectinomycin	64	
Salmonella Dublin	Sulphadimethoxime	>256	
Salmonella Dublin	Tetracycline	>8	
Salmonella Dublin	Tiamulin	>32	
Salmonella Dublin	Tilmicosin	>64	
Salmonella Dublin	Trimethoprim-Sulfa	<=2	
Salmonella Dublin	Tulathromycin	32	
Salmonella Dublin	Tylosin	>32	

THE LAW?

The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) permits veterinarians to prescribe extralabel uses of certain approved new animal drugs and approved human drugs for animals under certain conditions. Extralabel use refers to the use of an approved drug in a manner that is not in accordance with the approved label directions.

The list

The following drugs, families of drugs, and substances are prohibited for extralabel animal and human drug uses in food-producing animals.

- (1) Chloramphenicol;
- (9) Sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine);
- (10) Fluoroquinolones
- (11) Glycopeptides.
- (13) Cephalosporins (not including cephapirin) in cattle, swine, chickens, or turkeys:
  - (i) For disease prevention purposes;
  - (ii) At unapproved doses, frequencies, durations, or routes of administration; or
  - (iii) If the drug is not approved for that species and production class.

THE LAW

Isolate	Antimicrobial Drug	MIC	Interpretation
Salmonella Dublin	Ampicillin	2	
Salmonella Dublin	Ceftiofur	0.5	
Salmonella Dublin	Clindamycin	>16	
Salmonella Dublin	Danofloxacin	<=0.12	
Salmonella Dublin	Enrofloxacin	<=0.12	
Salmonella Dublin	Florfenicol	>8	
Salmonella Dublin	Gentamicin	>16	
Salmonella Dublin	Neomycin	<=4	
Salmonella Dublin	Penicillin G	>8	
Salmonella Dublin	Spectinomycin	64	
Salmonella Dublin	Sulphadimethoxime	>256	
Salmonella Dublin	Tetracycline	>8	
Salmonella Dublin	Tiamulin	>32	
Salmonella Dublin	Tilmicosin	>64	
Salmonella Dublin	Trimethoprim-Sulfa	<=2	
Salmonella Dublin	Tulathromycin	32	
Salmonella Dublin	Tylosin	>32	

The shorter list…

Isolate	Antimicrobial Drug	MIC	Interpretation
Salmonella Dublin	Ampicillin	2	
Salmonella Dublin	Ceftiofur	0.5	
Salmonella Dublin	Florfenicol	>8	
Salmonella Dublin	Trimethoprim-Sulfa	<=2	

Interpretations and Comments

Isolate	Antimicrobial Drug	MIC	Interpretation
Salmonella Dublin	Ampicillin	2	Resistant
Salmonella Dublin	Ceftiofur	0.5	Susceptible
Salmonella Dublin	Florfenicol	>8	Resistant
Salmonella Dublin	Trimethoprim-Sulfa	<=2	NA

Please Note: Bovine breakpoints are derived from Bovine Pasteurellaceae breakpoints and may not provide as accurate clinical efficacy information. Unfortunately, we also lack bovine-specific clinical interpretations for one of antimicrobial agents reported. The MIC reported is an in vitro measure which may aid in clinical decision-making in conjunction with pharmacologic and efficacy information. Please review with caution.

An alternative…

Isolate	Antimicrobial Drug	MIC	Interpretation
Salmonella Dublin	Ampicillin	2	Susceptible
Salmonella Dublin	Ceftiofur	0.5	NA
Salmonella Dublin	Florfenicol	>8	NA
Salmonella Dublin	Trimethoprim-Sulfa	<=2	Susceptible

Please Note: Interpretaions provided are derived from human Enterobacteriaceae breakpoints and may not provide as accurate clinical efficacy information. Unfortunately, we also lack bovine-specific and human clinical interpretations for antimicrobial agents reported for this isolate. The MIC reported is an in vitro measure which may aid in clinical decision-making in conjunction with pharmacologic and efficacy information. Please review with caution.

An alternative…

Isolate	Antimicrobial Drug	MIC	Interpretation
Salmonella Dublin	Ampicillin	2	Wild-type
Salmonella Dublin	Ceftiofur	0.5	Wild-type
Salmonella Dublin	Florfenicol	>8	Non-WT
Salmonella Dublin	Trimethoprim-Sulfa	<=2	Wild-type

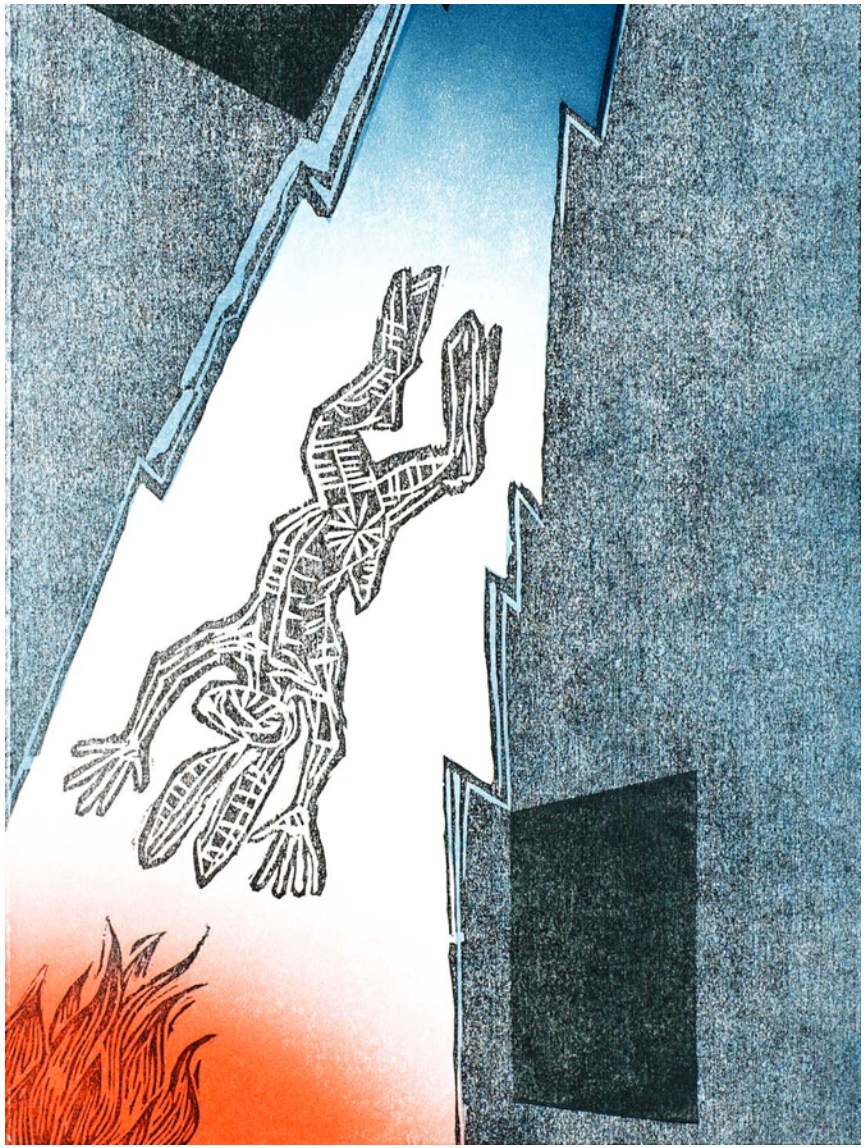
Please Note: Interpretations provided are derived from ECOFFs and are not a clinical parameter. However, the MIC reported is an in vitro measure which may aid in clinical decision-making in conjunction with pharmacologic and efficacy information. Please review with caution.

Last try!

Isolate	Antimicrobial Drug	MIC	Interpretation	Species	Interpretation
Salmonella Dublin	Ampicillin	2	Resistant	Bovine	
Salmonella Dublin	Ceftiofur	0.5	Susceptible	Bovine	
Salmonella Dublin	Florfenicol	>8	Resistant	Bovine	
Salmonella Dublin	Trimethoprim-Sulfa	<=2	Susceptible	Human	

Please Note: Both Bovine breakpoints, derived from Bovine Pasteurellaceae breakpoints, and Human breakpoints, which are Enterobacteriaceae specific, were used which may not provide as accurate clinical efficacy information. Please review with caution. For acquired resistance monitoring, this isolate would be considered wild-type with no phenotypic resistance detected to Ampicillin.

It’s complicated for us and we need help to reach that escape door….



Where do we want to go?

- Education on many levels
- Promotion of technical resources
- **Species-specific breakpoints**
- Consistent reporting of interpretations
- More funding for veterinary stewardship across all species
- Small steps toward informative communication in reporting

Acknowledgements

- CLSI VAST
  - Dubra Diaz
- WSU
  - Dale Moore

Beyond Susceptible/Intermediate/ Resistant (SIR): Enhancing Laboratory Communication with Reporting Comments

Antifungal SC Perspective

Tanis Dingle, Ph.D., FCCM, D(ABMM)
CLSI Educational Workshop
January 25, 2019

DISCLOSURES

Financial Interests or Benefits: Served as an investigator/received grant support from bioMérieux, Amplyx, AVIR Pharma, F2G, and JMI Laboratories.

CLSI M60, 1st Edition – Published Breakpoints

Table 1. Minimal Inhibitory Concentration Breakpoints for *In Vitro* Broth Dilution Susceptibility Testing of *Candida* spp. and Select Antifungal Agents After 24-Hour Incubation

Antifungal Agent	Species	MIC Breakpoints and Interpretive Categories, µg/mL			
		S	I*	SDD†	R
Anidulafungin[1,‡]	*C. albicans*	≤0.25	0.5	–	≥1
	C. glabrata	≤0.12	0.25	–	≥0.5
	C. guilliermondii	≤2	4	–	≥8
	C. krusei	≤0.25	0.5	–	≥1
	C. parapsilosis	≤2	4	–	≥8
	C. tropicalis	≤0.25	0.5	–	≥1
Caspofungin[1,‡,§]	*C. albicans*	≤0.25	0.5	–	≥1
	C. glabrata	≤0.12	0.25	–	≥0.5
	C. guilliermondii	≤2	4	–	≥8
	C. krusei	≤0.25	0.5	–	≥1
	C. parapsilosis	≤2	4	–	≥8
	C. tropicalis	≤0.25	0.5	–	≥1
Micafungin[1,‡]	*C. albicans*	≤0.25	0.5	–	≥1
	C. glabrata	≤0.06	0.12	–	≥0.25
	C. guilliermondii	≤2	4	–	≥8
	C. krusei	≤0.25	0.5	–	≥1
	C. parapsilosis	≤2	4	–	≥8
	C. tropicalis	≤0.25	0.5	–	≥1
Voriconazole[2,‡,¶]	*C. albicans*	≤0.12	**0.25–0.5**	–	≥1
	C. glabrata#	–	–	–	–
	C. krusei	≤0.5	**1**	–	≥2
	C. parapsilosis	≤0.12	**0.25–0.5**	–	≥1
	C. tropicalis	≤0.12	**0.25–0.5**	–	≥1
Fluconazole[3,†]	*C. albicans*	≤2	–	4	≥8
	*C. glabrata***	–	–	≤32	≥64
	C. krusei††	–	–	–	–
	C. parapsilosis	≤2	–	4	≥8
	C. tropicalis	≤2	–	4	≥8

SDD?

Intrinsic Resistance?

Site-specific Reporting?

Susceptibility Prediction Rules?

UNIVERSITY OF ALBERTA

Things you may want to convey using susceptibility comments…

- Interpretation Definitions
  - Susceptible-Dose Dependent (SDD)
  - Epidemiologic Cutoff Values (ECV)
- Intrinsic resistance
- Site-specific drug penetration
- Susceptibility prediction
- Age-related antifungal use
- Use of alternative breakpoints
- Empiric therapy options

Susceptible Dose Dependent (SDD)

Yeast	Fluconazole SDD Breakpoint
C. albicans, C. parapsilosis, C. tropicalis	4 µg/mL
C. glabrata	≤32 µg/mL

- Reporting out SDD with no context is confusing for the end user
- Susceptibility depends on achieving the maximum possible blood levels
- For fluconazole dosing in normal adults, higher doses may be required above the standard 6mg/kg/day

Susceptibility

	Candida glabrata
	MIC
Fluconazole	**S-DD** [1]
Micafungin	**S**

[1] Susceptibility is dependent upon achieving the maximum possible blood level and may be used in select clinical situations. Consult Medical Microbiologist on call, if required.

S - Susceptible **S-DD** - Susceptible-dose dependent

- Consider:

Information on dosing

- Be cognizant of adult vs pediatric patients*

Appropriate stakeholders

*Nielsen, L.E., et al. 2019. One size fits all? Application of susceptible-dose-dependent breakpoints to pediatric patients and laboratory reporting. J Clin Microbiol, 58(1), e01446-19.

UNIVERSITY OF ALBERTA

Epidemiologic Cutoff Values (ECV)

ECV's available for:

- A number of *Candida* species without clinical breakpoints
- *Cryptococcus* species (specific molecular types)
- A number of *Aspergillus* species

ECV Comment Guidance: CLSI M57, 1st Ed.

Table 1. Example Report Explaining the Significance of ECVs for Filamentous Fungi

Isolate	Antifungal Agent	MIC	ECV	Suggested Comment for Discussion and for the Report
Aspergillus fumigatus	XYZ	2 µg/mL	0.5 µg/mL	There are currently no breakpoints or interpretive criteria for *A. fumigatus* and antifungal agent "XYZ." The "XYZ" MIC/MEC is above the WT MIC, which suggests that this isolate may have an acquired mechanism of resistance and could be considered NWT. The clinical implication of finding an NWT MIC/MEC is currently unknown. When the agent in question is being used for treatment, the patient should undergo clinical review, and in consultation with an infectious diseases physician or pharmacist, the decision should be made to continue the agent at the current dose, increase the dose of the agent, or switch to an alternative agent.

Abbreviations: ECV, epidemiological cutoff value; MEC, minimal effective concentration; MIC, minimal inhibitory concentration; NWT, non-wild-type; WT, wild-type.

UNIVERSITY OF ALBERTA

Referral Specimen/Isolate (Final result)

Culture	**Isolate submitted as:**
	Aspergillus fumigatus (A)

Susceptibility

	Aspergillus fumigatus
	MIC
Itraconazole	**WT** [1]

[1] There are no established clinical breakpoints for this antifungal. Results suggest that SUSCEPTIBILITY IS LIKELY (wild type) but may not reliably predict response in all clinical situations. For the treatment of critical infection, consult the microbiologist on-call or infectious desease physician, if required.

WT - Wild-type

Non-wild-type (NWT) – Results suggest RESISTANCE IS LIKELY (non-wild-type)…

Another option:

"Results distinguish between wild-type (WT) strains (no resistance mechanism) and those with a resistance mechanism (non-wild-type, NWT). The results do not predict clinical outcome."

Intrinsic Resistance and Site-Specific Drug Penetration

MIC.42700 **Antifungal Agents to Test/Report** **Phase II**

There are written policies to ensure that only antifungal agents appropriate for the organism and body site are routinely tested and reported.

NOTE: The microbiology department should consult with the medical staff and pharmacy to develop a list of antifungal agents to be reported for specific organisms isolated from certain body sites, instead of indiscriminant susceptibility testing and reporting of all fungal isolates or reporting of all antifungal agents that might be included on a test panel. Isolates from body sites for which susceptibility might be routinely tested and reported include Candida spp. isolates from blood cultures.

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.

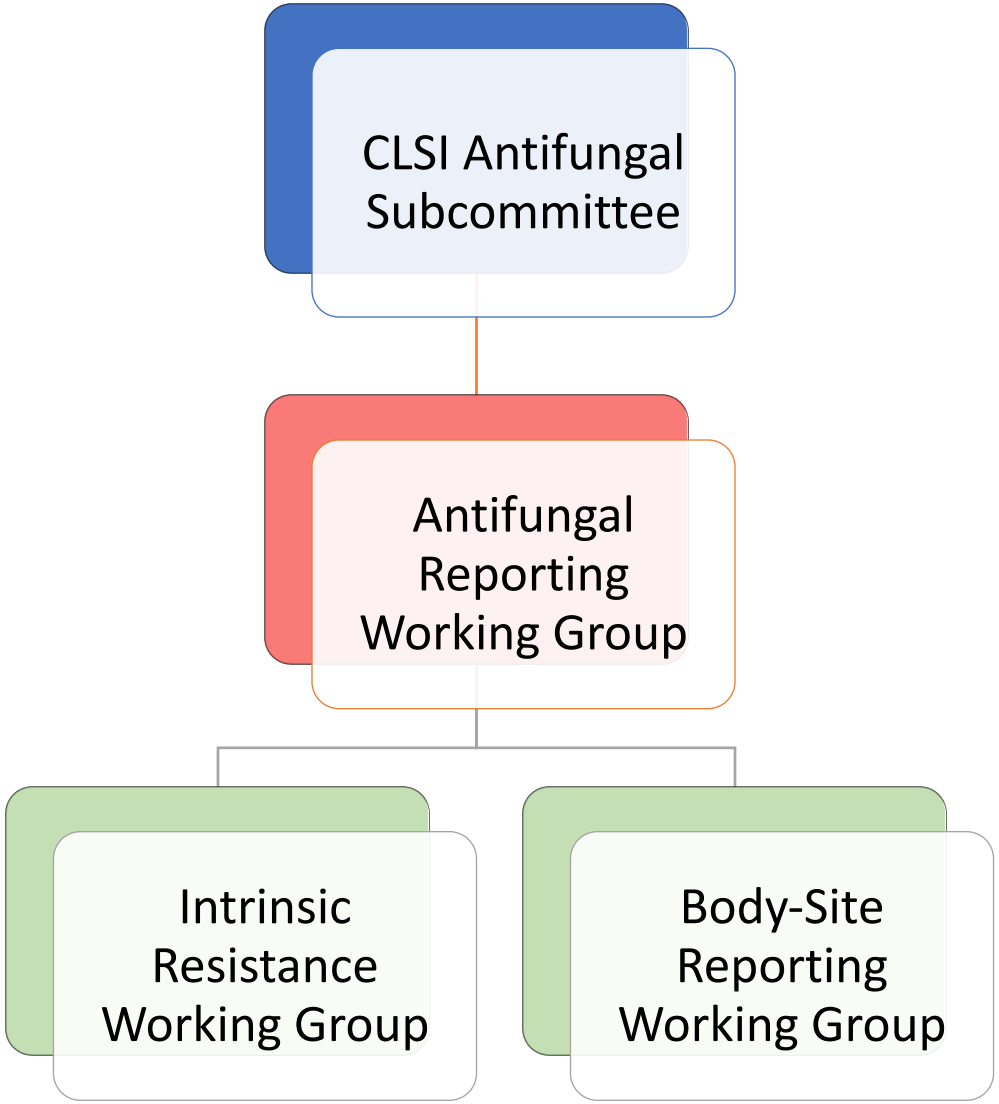
These tables can be helpful in at least three ways: 1) they provide a way to evaluate the accuracy of testing methods; 2) they aid in the recognition of common phenotypes; and 3) they can assist with verification of cumulative antimicrobial susceptibility test data. In the tables, an "R" occurring with 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."

Appendix B. (Continued)

B1. *Enterobacteriaceae*

Organism \ Antimicrobial Agent	Ampicillin	Amoxicillin-clavulanate	Ampicillin-sulbactam	Piperacillin	Ticarcillin	Cephalosporins I: Cefazolin, Cephalothin	Cephamycins: Cefoxitin, Cefotetan	Cephalosporin II: Cefuroxime	Imipenem	Tetracyclines	Tigecycline	Nitrofurantoin	Polymyxin B Colistin	Aminoglycosides
Citrobacter freundii	R	R	R			R	R	R						
Citrobacter koseri, ***Citrobacter amalonaticus* group**[a]	R				R									
Enterobacter cloacae complex[b]	R	R	R			R	R							
Escherichia coli	There is no intrinsic resistance to β-lactams in this organism.													
Escherichia hermannii	R				R									
Hafnia alvei	R	R	R			R	R							
Klebsiella (*formerly Enterobacter*) *aerogenes*	R	R	R			R	R							
Klebsiella pneumoniae, ***Klebsiella oxytoca, Klebsiella variicola***	R				R									
Morganella morganii	R	R				R		R	[c]		R	R	R	
Proteus mirabilis	There is no intrinsic resistance to penicillins and cephalosporins in this organism.								[c]	R	R	R	R	
Proteus penneri	R					R		R	[c]	R	R	R	R	
Proteus vulgaris	R					R		R	[c]	R	R	R	R	
Providencia rettgeri	R	R				R			[c]	R	R	R	R	
Providencia stuartii	R	R				R			[c]	R	R	R	R	[d]
***Raoultella* spp.**[e]	**R**				**R**									



Antifungal Intrinsic Resistance

CLSI M60, 1st Ed: "Isolates of *C. krusei* are assumed to be intrinsically resistant to fluconazole, so their MICs should not be interpreted using this scale."

CLSI recommendations to come for:

Organism	Antifungal
Cryptococcus spp., *Rhodotorula* spp. and *Trichosporon* spp.	Echinocandins
Mucorales	Fluconazole Voriconazole

Referral Specimen/Isolate (Final result)

Culture	**Isolate submitted has been identified as:**
	Cryptococcus neoformans (A)

Susceptibility

	Cryptococcus neoformans [Iso1]	
	MIC	
5-Fluorocytosine	4.	ug/mL
Amphotericin B	0.06	ug/mL
Fluconazole	2.	ug/mL

Iso1 - Cryptococcus neoformans:
Clinical breakpoint not available. The current data is insufficient to demonstrate a correlation between in vitro susceptibility testing and clinical outcome.

Cryptococcus species are intrinsically resistant to echinocandins.

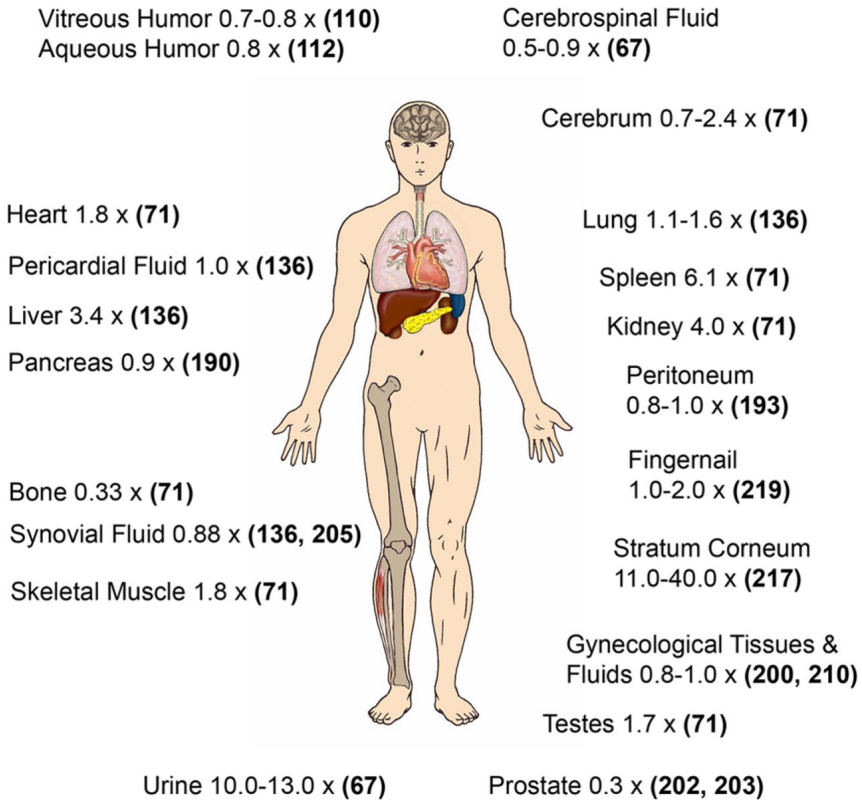
UNIVERSITY OF ALBERTA

Site-Specific Drug Penetration

CLSI recommendations to come for:

- Polyenes
- Flucytosine (5-FC)
- Echinocandins
  - CNS, eye, urine
- Azoles
  - CNS, eye, urine

Fluconazole tissue and fluid concentrations



Felton et al. 2014. Clinical Microbiology Reviews, 27(1): 68-88.

UNIVERSITY OF ALBERTA

Site-Specific Drug Penetration

Compound	Eye			Skin			Vagina		Heart		Liver	Pancreas	Kidney	Bone		Prostate		Brain		Lung			Spleen	Muscle	Reference
	Aqueous	Vitreous	Cornea	Tissue	Interstitial fluid	Nail	Tissue	Fluid	Tissue	Pericardial fluid				Tissue	Synovial fluid	Tissue	Fluid	Tissue	CSF	Tissue	Alveolar cells	ELF			
Fluconazole	X	X	O	X	X	X	X	X	X	X	X	X	X	X O	X	X X	X	X	X	X		O	X	X	(67, 70, 72, 120, 137, 200-203, 205, 219, 237, 238)
Itraconazole	O X	O[2] X	O	X X	X	X	X X	X X	O		X	O	X	X	X	X	X	O	X	X X[5]	X	X	X	X	(25, 56, 73, 74, 120, 121, 140, 220, 221, 239-242)
Voriconazole	X	X		O	O				X X[◇]		X X		X X	X	X			X	X	X X	X	X X[•]	X X	O	(58, 80, 81, 83, 114, 142, 153, 154, 208, 224, 243, 252, 253)
Posaconazole		X		X		X												O	X		X	X			(57, 59, 85-89, 223, 244)
AmBd	X X	X							O X[◇]		X	X X	X	O	X			X X	X	O O[4]		X[3] O	X		(37, 52, 53, 91, 115, 123, 148, 151, 156, 210, 245-247, 249)
ABLC	O[2]	O[2]							X		X		X	O				O	X	X[◇]		X[•] X	X[◇]		(90, 92, 117, 125, 147, 155, 210, 246, 249)
L-AMB	O[2]	O[2]	O[2]	X[□]					O X		X[◇]		X[◇]	O				X	X	X		X[•] X	X[◇]		(34, 53, 60, 90, 125, 147, 155, 210, 248, 249)
5-FC	O	X		O					O		O		O O	O	O			O	X X	O[4]		O[3]	O	O	(91, 96, 115, 116, 151, 156, 174, 250)
Anidulafungin	O	O		O					O		O		O	O				O	O	O O	X	X	O O		(58, 100, 102, 175, 251)
Caspofungin	X O[2]	X	O[2]						O		O		O					O	X	O	X		O	O	(44, 103, 105, 113, 126, 130, 149)
Micafungin	O[2]	O[2]		X[◇]							O O	X[•]	O O					X	X X	O O	X	X X[•]	O		(61, 62, 106-108, 127, 150, 252)

X- human data
O- animal data

0 to ≤0.5X plasma [ ]
>0.5X to ≤5X plasma [ ]
>5X plasma [ ]

Felton et al. 2014. Clinical Microbiology Reviews, 27(1): 68-88.

UNIVERSITY OF ALBERTA

Body Site Reporting Options

- Report susceptibility result with comment
- Restrict reporting with/without comment

e.g. “<1% of active echinocandin drug is excreted into the urine and echinocandins are generally not recommended for treating candiduria.”

Susceptibility Prediction

Caspofungin* - susceptibility testing is highly variable for *Candida* spp. and false resistance has been reported.

If Caspofungin tests:	Report:
Susceptible →	Susceptible
Resistant →	1) Use micafungin or anidulafungin to predict susceptibility. 2) Perform FKS sequencing. 3) Send to a referral laboratory for confirmation.

*As outlined in CLSI M60, 1st Ed.

Susceptibility Prediction

- An option for reporting of caspofungin for *Candida* species could be via comment:

  "The result of micafungin susceptibility predicts caspofungin susceptibility."

- Alternatively, the caspofungin result could be automatically compiled in the LIS based on the micafungin result.

Age Related Antifungal Use

- Certain antifungal agents may not be appropriate for certain age groups (e.g. pediatric patients).
- Work with your stewardship and infectious disease colleagues to determine if commenting on susceptibility reports may be appropriate.

e.g. “Echinocandin use in neonates and infants (< 2 months of age) may not be appropriate.”

2016 IDSA Practice Guidelines, *Clinical Infectious Diseases*, Volume 62, Issue 4, 15 February 2016, Pages e1–e50.

UNIVERSITY OF ALBERTA

Use of Alternate Breakpoints

- Informs provider when not using your typical breakpoint standards

Antifungal	Interpretation	Participants No.	%
Amphotericin B	Susceptible	81	38.0
	Resistant	1	0.5
	No Interpretation	131	61.5

CAP F-C 2019, *C. glabrata*

"Interpretation of Amphotericin B based on EUCAST clinical breakpoints."

Use of Alternate Breakpoints

TEST: Culture **COLLECTED: 2020/01/01 13:01**
SPECIMEN TYPE: Swab **RECEIVED: 2020/01/01 15:30**
SPECIMEN SOURCE: Ear, Right **ACCESSION: EA-20-0012345**

FINAL REPORT
Candida auris isolated

	Candida auris **Interpretation**
Amphotericin B	S
Fluconazole	S
Micafungin	S

Tentative interpretive breakpoints for *Candida auris* defined by the Centers for Disease Control and Prevention: https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html.

UNIVERSITY OF ALBERTA

Empiric Therapy

- Comments regarding empiric therapy may be useful:
  - if using a rapid identification system
  - if not routinely performing susceptibility testing

Randomized Trial of Rapid Multiplex Polymerase Chain Reaction–Based Blood Culture Identification and Susceptibility Testing

Ritu Banerjee,[1,a] Christine B. Teng,[2,a] Scott A. Cunningham,[3] Sherry M. Ihde,[3] James M. Steckelberg,[4] James P. Moriarty,[5] Nilay D. Shah,[5] Jayawant N. Mandrekar,[6] and Robin Patel[3,4]

[1]Division of Pediatric Infectious Diseases, Mayo Clinic, Rochester, Minnesota; [2]Department of Pharmacy, National University of Singapore and Tan Tock Seng Hospital, Singapore; [3]Division of Laboratory Medicine and Pathology, [4]Division of Infectious Diseases, [5]Division of Health Care Policy and Research, and [6]Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

Rapid Multiplex PCR Result	Reporting Comments
Candida albicans +	"Preferred empiric therapy, pending antimicrobial susceptibility results, is fluconazole unless there is QTc prolongation or other clinical contraindication. If the patient is unstable, consider empiric caspofungin."
Candida parapsilosis +	
Candida tropicalis +	
Candida glabrata +	"Preferred empiric therapy, pending antimicrobial susceptibility results, is caspofungin or an amphotericin preparation, unless clinically contraindicated."

CID 2015, 61: 1071-1080

Additional options for conveying antifungal susceptibility information

- Links to websites/literature
- Links to annual antibiograms

YEAST (ALL AGES, STERILE SITES)	n	Amphotericin B[a]	Fluconazole	Micafungin
Candida albicans	95	100	100	100
Candida glabrata	55	98	96[b]	95

[a]Using interpretive breakpoints from EUCAST.
[b]This number represents % susceptible dose-dependent isolates.

UNIVERSITY OF ALBERTA

Comments: Tips and Tricks

Keep it simple

- DO NOT over comment!

Engage your stakeholders

Be mindful of the clinical impact of the comment

Keep your IT colleagues close

Review final reports

UNIVERSITY OF ALBERTA

Or else you may end up in this scenario…

Referral Specimen/Isolate (Final result)

Culture	**Isolate submitted as:**
	Candida dubliniensis (A)

Susceptibility

	Candida dubliniensis
	MIC
Amphotericin B	**WT** [1]
Fluconazole	**WT** [2]
Micafungin	**WT** [3]
Voriconazole	**WT** [4]

[1] There are no established clinical breakpoints for this antifungal. Results suggest that SUSCEPTIBILITY IS LIKELY (wild type) but may not reliably predict response in all clinical situations. For the treatment of critical infection, consult the microbiologist on-call or infectious desease physician, if required.

[2] There are no established clinical breakpoints for this antifungal. Results suggest that SUSCEPTIBILITY IS LIKELY (wild type) but may not reliably predict response in all clinical situations. For the treatment of critical infection, consult the microbiologist on-call or infectious desease physician, if required.

[3] There are no established clinical breakpoints for this antifungal. Results suggest that SUSCEPTIBILITY IS LIKELY (wild type) but may not reliably predict response in all clinical situations. For the treatment of critical infection, consult the microbiologist on-call or infectious desease physician, if required.

[4] There are no established clinical breakpoints for this antifungal. Results suggest that SUSCEPTIBILITY IS LIKELY (wild type) but may not reliably predict response in all clinical situations. For the treatment of critical infection, consult the microbiologist on-call or infectious desease physician, if required.

WT - Wild-type

UNIVERSITY OF ALBERTA

Thank you! Questions?