UNDERSTANDING YOUR DATA: THE ANTIBIOGRAM

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WHAT WE WILL COVER

- Describe the CLSI recommended guidelines for production of the antibiogram
- Discuss factors that influence antibiogram data
- Disclosure: antibiograms shown illustrate what not to do and contain errors

CLSI M39-A3: CUMULATIVE AST DATA

- Describes methods for recording and analysis of AST data, consisting of cumulative and ongoing summaries of susceptibility patterns of clinically significant organisms
- Commonly referred to as the antibiogram

CLSI M39-A4: CUMULATIVE AST DATA

	Recommendation
1	Analyze/present report annually
2	Include only final, verified results
3	Include only species with ≥30 isolates
4	Include only diagnostic isolates
5	Include only the first isolate of a species/patient/analysis period, irrespective of body site or antimicrobial profile
6	Include only agents routinely tested; do not report supplemental agents tested only on resistant isolates
7	Report %S and do not include %I in this statistic
8	*S. pneumoniae*: provide both meningitis and nonmeningitis %S; oral pen
9	Viridans strep: provide both %S and %I for penicillin
10	*S. aureus*: list %S for all and MRSA separately

FACTORS THAT INFLUENCE THE ANTIBIOGRAM (M39-A4)

- Patient population
- Culturing practices
- Laboratory AST and reporting practices
- Temporal outbreaks

WHERE TO PULL THE DATA

- Instrument
- LIS
- Other downstream system (e.g. EPIC, Decision Support System, other data repository, etc.)

Why does it matter?

EFFECT OF LABORATORY AST AND REPORTING PRACTICES

- A lab may use MicroScan for routine AST and have multiple "off-line" tests
  - Confirmation of results
  - Additional agents
  - Limitations of system
  - Determination of resistance mechanism
- Antibiogram is created directly from this instrument

EXAMPLE

E. coli has elevated MICs for multiple agents, namely cephalosporins and carbapenems

Isolate Details | Antimicrobic Results

Ø	**	Test	Result	System	Expert	Final
Ø		Ceftazidime/K Clavulanate	>2			
		Ceftriaxone	>32	R		R
		Cefuroxime	>16	R		R
		Ciprofloxacin	>2	R		R
		Doripenem	<=0.5	S		S
		Ertapenem	2	S		S
		Gentamicin	<=1	S		S

Current Alerts

Possible carbapenemase in Enterobacteriaceae - elevated ertapenem
Possible carbapenem resistant Enterobacteriaceae. Follow current CLSI or public health guidelines.
Save isolate. Verify isolate results by repeat testing unless patient had isolate previously.
Enterobacteriaceae resistant to three classes of antibiotics
Multidrug resistance. Check results.

POSSIBLE ESBL-UNABLE TO INTERPRET CONFIRMATION TEST
Possible ESBL. Organism has MICs greater than highest dilution or panel.
PERFORM THE 12 TEST 'R' PANEL

Alerts fire in instrument

EXAMPLE

- Ertapenem dilution range on GN panel (1-4µg/ml)
- Recommended breakpoints

	S	I	R
Ertapenem	≤0.5	1	≥2

- AST panels do not have dilution low enough to differentiate susceptible versus intermediate per current standard

WORKAROUND

- If isolate is resistant to a 3rd generation cephalosporin and carbapenem MIC ≥2, an alert fires instructing tech to perform carbapenem susceptibility by disk diffusion
  - Originally designed to capture carbapenemases, includes additional testing
  - Allows for confirmation and correct interpretation of carbapenems

RESULT

- Disk diffusion is 16mm, corresponds to MIC of ≥2: Interpretation Resistant

Current Interpretations (M100-S26)

	Zone Diameter			MIC		
	S	I	R	S	I	R
Ertapenem	≥22	19-21	≤18	≤0.5	1	≥2

RAMIFICATION

Instrument

Isolate Details | Antimicrobic Results

Ø	**	Test	Result	System	Expert	Final
Ø		Ceftazidime/K Clavulanate	>2			
		Ceftriaxone	>32	R		R
		Cefuroxime	>16	R		R
		Ciprofloxacin	>2	R		R
		Doripenem	<=0.5	S		S
		Ertapenem	2	S		S
		Gentamicin	<=4	S		S

LIS Interpretation Table

EMR

Ertapenem	Resistant	2

RAMIFICATION

Organism	# Tested	Ampicillin	Piperacillin/Tazobactam	Ampicillin/Sulbactam	Cefazolin	Ceftriaxone	Ceftazidime	Cefepime	Aztreonam	Ertapenem	Meropenem	Gentamicin
Acinetobacter species	110			88		71	78	79			94	85
Citrobacter amalonaticus	30	13	93	47	33	53		90	63	97	97	87
Citrobacter freundii	233	23	91	64	5	79		99	81	100	100	97
Citrobacter koseri	81	0	99	6	95	96		98	98	100	100	98
Enterobacter aerogenes	188	12	93	53	5	90		99	93	98	99	99
Enterobacter agglomerans	37	57	100	89	86	97		100	100	100	100	97
Enterobacter cloacae	327	4	83	14	3	74		92	76	98	100	95
Escherichia coli	6124	57	98	60	92	99		99	99	100	100	92
Escherichia coli ESBL	247	0*	91	20	0*	0*		0*	0*	100	100	68
Klebsiella oxytoca	237	0	97	67	40	98		99	97	99	100	99

SOLUTION

- Confirm %S for this organism by using the LIS
  - Evaluate all rules in the LIS to see if they affect the antibiogram

Let's say that this is the only isolate that was a CRE for the year. What to do next??

SOLUTION

- If test 247 isolates, would need 2 resistant isolates to drop ertapenem to 99% susceptible
  - Either make it 99% so users know that carbapenem resistance is a possibility in your area
  - Or add footnote (comment) indicating number of CREs
  - Or combination of both

DISPLAYING THE DATA

Organism	# Tested	Ampicillin	Piperacillin/Tazobactam	Ampicillin/Sulbactam	Cefazolin	Ceftriaxone	Ceftazidime	Cefepime	Aztreonam	Ertapenem	Meropenem	Gentamicin
Acinetobacter species	110			88		71	78	79			94	85
Citrobacter amalonaticus	30	13	93	47	33	53		90	63	97	97	87
Citrobacter freundii	233	23	91	64	5	79		99	81	100	100	97
Citrobacter koseri	81	0	99	6	95	96		98	98	100	100	98
Enterobacter aerogenes	188	12	93	53	5	90		99	93	98	99	99
Enterobacter agglomerans	37	57	100	89	86	97		100	100	100	100	97
Enterobacter cloacae	327	4	83	14	3	74		92	76	98	100	95
Escherichia coli	6124	57	98	60	92	99		99	99	100	100	92
Escherichia coli ESBL	247	0*	91	20	0*	0*		0*	0*	99 [a]	99 [a]	68
Klebsiella oxytoca	237	0	97	67	40	98		99	97	99	100	99

a) 1 CRE isolated in 2015

FOOTNOTES

- Clarify (altering) the result
- Draw attention to indication or dosage (e.g. nitrofurantoin for UTI only)
- Provide information about how breakpoints derived (e.g. AHA, FDA, EUCAST)
- Provide information about testing mechanism (e.g. Etest, PCR)
- Provide information about surrogates or predicted susceptibilty

DIFFERENCES IN TESTING PRACTICES AND OFF-LINE TESTS

MULTIPLE LOCATIONS/MULTIPLE RULES

- Susceptibility testing on CoNS
- These locations pull antibiogram data from the LIS
- Location A: oxacillin resistance is reported routinely, but susceptibility is only reported if a physician requests this drug to be tested (*mecA* PCR)
- Location B: oxacillin susceptibility and resistance reported routinely
- Effect: skewing of %S

COMPARISON

- Location A: 38% S
- Location B: 42% S
- Result: Location A appears to have more resistance compared to location B; however this may simply be artifact
- Remember: LIS-generated antibiograms ONLY include data that were shipped from the instrument
  - Location A shipped over only resistant results automatically

RAMIFICATION

- Only releasing resistant and hiding susceptible results will artificially inflate % non-susceptible, making it look like a resistance problem

E. coli - % Susceptible

N	Amk	Amp	Cfaz	Cftrx	Gent	Mero	T-S	Notes
1356	48[1]	35	30	65	74	90[2]	55	Amk and Mero %S only from isolates where drugs were reported – SKEWED!
1356	86	35	30	65	74	96	55	Amk and Mero %S from all isolates tested – OK!

[1] Amikacin only reported on gentamicin-I or -R isolates (n=353)

[2] Meropenem only reported on ceftriaxone-I or –R isolates (n=475)

TIERED REPORTING

- If this, then that rule
- Example:
  - If MRSA with vancomycin MIC ≥2 µg/ml, then release daptomycin (**otherwise remains hidden**)
- Daptomycin non-susceptibility often tracks with elevated vancomycin MICs
- Only releasing results on a population that is already more resistant than the wild-type population might skew data
- Artificially decrease %S for the sequestered agent

TIERED REPORTING

- Issue for any antibiogram produced using data downstream of the instrument – may still affect antibiogram created by the instrument (manufacturer dependent)
- CLSI recommends not reporting cumulative susceptibility data for "supplemental agents"

TIERED REPORTING

- Beware of the denominator
- For example: you may only report linezolid susceptibility on MRSA from pulmonary sources

Organism	No. isolates	% S - LZD
All MRSA	125	14
MRSA - Pulmonary	20	90
MRSA – Non-pulmonary	105	—

– Susceptibility not reported on non-pulmonary MRSA isolates

DOCUMENTING CONFIRMED RESULTS

- Back to the example: performing *mecA* PCR on oxacillin-susceptible coagulase negative staphylococci
- Off-line testing results may or may not be entered into the instrument
  - Confirmation of result
  - Supplemental test

DOCUMENTING CONFIRMED RESULTS

- CLSI recommends confirmation of certain susceptibility results (M100-Appendix A)
  - Not reported or only rarely reported to date
  - Uncommon in most institutions
  - May be common, but it is generally considered of epidemiological concern
- All roads lead to confirm ID and susceptibility if uncommon in institution

WHICH ORGANISMS TO INCLUDE IN ANTIBIOGRAM

RECOMMENDED ORGANISMS

- CLSI: Include only species with ≥30 isolates

Gram Negative		*Gram Positive*	*Others*
A. baumannii	*Providencia* spp.	*E. faecium*	Yeast
C. freundii	*Salmonella* spp.	*E. faecalis*	Anaerobes – *B. fragilis and C. perfringens*
E. aerogenes	*S. marcescens*	*S. aureus* (separate MSSA and MRSA)	
E. cloacae	*Shigella* spp.		
E. coli	*S. maltophilia*		
H. influenzae		Coag neg staph	
K. pneumoniae		*S. pneumoniae*	
M. morganii		*Viridans* strep	
P. mirabils			

Recommend sharing published CLSI version

IDENTIFICATION OF *A. BAUMANNII*

- How does your lab report an identification of *A. baumannii*?
  - *A. baumannii* vs *A. baumannii/calcoaceticus* complex
- Or does your system struggle and you call it *Acinetobacter* species?
- Do you do it the same way every time?

ACINETOBACTER SPECIES VS *A. BAUMANNII/CALCOACETICUS* COMPLEX

2014 Organism (% susceptible)	Cefepime		Cefotetan		Ceftazidime		Ceftriaxone		Ciprofloxacin		Doxycycline		Ertapenem		Gentamicin		Imipenem		Levofloxacin		Meropenem	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Acinetobacter spp. [g,h]	87	94			79	88			76	85			0	0	79	94	89	97	77	85	85	97

2015 Organism - % susceptible	Cefepime [a]		Cefotetan		Ceftazidime		Ceftriaxone		Ciprofloxacin [a]		Doxycycline		Ertapenem		Gentamicin		Imipenem		Levofloxacin [a]		Meropenem	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Acinetobacter baumannii/calcoaceticus complex [h, i]	81	82			57	79			51	85			0	0	77	78	84	98	54	95	65	90

- Limitation: Using only ABCC in 2015 likely contributed to perceived decrease in susceptibility for some agents

IDENTIFICATION BIAS

- Same is true of coagulase negative staphylococci
  - If prepare antibiogram looking for coagulase negative staphylococci, but report to the species level on significant isolates, it could falsely skew antibiogram toward susceptibility
  - Remember to adjust antibiogram organisms with updates in testing and/or reporting, as well as with nomenclature changes

BEWARE OF NUMBERS!

Recommendation:

Include only species with at least 30 isolates tested

E. coli susceptibility to meropenem

Organism	# isolates	% susceptible	95% CI*
E. coli	10	80	48 - 95
	100	80	71 - 87
	1000	80	77 - 82

*confidence interval

95% certainty that the true %S lies somewhere in this range

BEWARE OF NUMBERS!

Alternative:

If <30 isolates available for a species, consider the following:

- Is it essential to include? If yes, include footnote

  "Calculated from fewer than the standard recommendation of 30 isolates; %S may not be statistically valid"

- Combine several years of data, include a footnote

  "Calculated from 2012-2015 data"

- Combine species (e.g. *Citrobacter* spp.) where acceptable

AFFECT OF DUPLICATES

ELIMINATING DUPLICATES

- No single "correct" way to estimate susceptibility and resistance rates
  - Variations in calculation approaches may be more or less appropriate for certain applications
- Examples:
  - First isolate per patient - ignoring all subsequent isolates
  - Episode-based – first isolate in 7- or 30- day interval
  - Phenotype-based – first isolate, major or minor differences in one or any antimicrobial agent

STRATIFICATION OF RESULTS

WHEN TO SPLIT OUT GROUPS

- Stratification occurs to look at:
  - Unit or patient location
  - Body site
  - Population difference (e.g. CF)
  - MDR phenotype
- Do you have enough isolates?
- Is it expected to be different from the standard antibiogram?
- Does it make sense?
  - If data isn't being used, don't bother!

URINE SUBSET ANTIBIOGRAM

E.coli - % Susceptible

Organism	No. isolates	Amp	Cfaz	Cftrx	Cip	Gent	Imi	Levo*	P-T	T-S
E. coli (All)	3636	61	92	99	92	93	100	80	96	76
E. coli (nonurine)	292	44	82	96	80	87	100	80	93	62
E. coli (urine)	3417	63	93	99	93	94	100	–	97	77

*Tested on nonurine isolates only (N=292). Results should not be compared to those of other antimicrobial agents, all of which were tested against both urine & nonurine isolates

- Cipro appears to have higher %S than levofloxacin in all-isolate view due to more restricted testing of levofloxacin against nonurine isolates
  - %S is identical when nonurine isolates evaluated separately

GROUPS THAT MATTER

- Cystic Fibrosis
- Populations on prolonged therapy, especially if it is the same empiric therapy (e.g. HemOnc)
- ED (maybe) and outpatient clinics
- Populations that may be different are specific to the location

GENERAL RULES

- Preferably, no less than 30 isolates - otherwise add footnote
- Pilot locations, patient populations, sources, to see if makes sense to pursue
- Verify that results make sense
  - Compare to previous year
  - Compare to intrinsic table
  - Compare results amongst drug class
  - Compare against similar organisms
- Confirm where “rules” are built and identify limitations
- Spot check – pull an epidemiology report or use a different method to see if you get a similar number
- Pay attention to how organism identifications change
- Communicate intent of antibiogram with limitations, if necessary
- Use the antibiogram as a tool to identify AST issues

CONCLUSION

- Antibiogram easily biased
  - Know what is represented in your data
- Data differs by method of extraction
  - Know your limitations and minimize their impact
- Antibiogram should not be used to monitor year to year trends if changes are made
  - E.g. breakpoints, testing practices, reporting rules, etc. – all of these will affect the data