UNDERSTANDING 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
  - Outpatient versus inpatient
  - Specialty populations (e.g. CF, SNF)
- Culturing practices
- Laboratory AST and reporting practices
- Temporal outbreaks

HOW DO YOU PREPARE YOUR ANTIBIOGRAM?

A. Data directly from instrument
B. LIS
C. Other downstream system (e.g. EPIC, Decision Support System, other data repository, etc.)

Why does it matter?

OFF-LINE TESTING

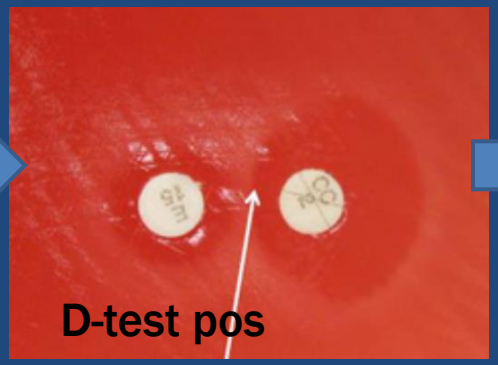
EFFECT OF LABORATORY AST AND REPORTING PRACTICES

- A lab may use automated instrument 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

Instrument

Agent	Interp
Clindamycin	S
Erythromycin	R



LIS and EMR

Agent	Interp
Clindamycin	R
Erythromycin	R

- Perform D-test for streptococci because it is not available on the AST panel
- Lab uses LIS data to prepare antibiogram: capture inducible resistance
- Lab uses instrument data to prepare antibiogram: will not capture inducible resistance (falsely elevated %S)

IF USING INSTRUMENT IN THIS SCENARIO, WHAT CAN YOU DO?

- Use LIS data for this drug/bug combination
- Add a comment to each report that “inducible clindamycin resistance detected” and then use LIS to determine the number of times the comment was added
- Override the clindamycin result in AST instrument when this testing performed
- Add comment to antibiogram that inducible resistance not captured

MAY ALSO BE TRUE WITH CRE

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

- Rare event: confirm %S for these drug/bug combinations by using the LIS (query for R isolates instead of all)

Let's say that we had one *E. coli* 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
  - Make it 99% so users know that carbapenem resistance is a possibility in your area
  - 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
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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 2016

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 susceptibility

TIERED OR CASCADE REPORTING

DO YOU HAVE SOME FORM OF TIERED OR CASCADE REPORTING?

- Yes
- No
- Not sure

- Encourage cascade reporting to assist with antimicrobial stewardship as a way for the lab to show your worth.

TIERED REPORTING

- CLSI recommends not reporting cumulative susceptibility data for “supplemental agents”
- Issue for any antibiogram produced using data downstream of the instrument (e.g. LIS) – may still affect antibiogram created by the instrument (manufacturer dependent)
- However, pharmacists (stewardship) likely want this information

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 in *S. aureus* 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 hidden agent

TIERED REPORTING

- Beware of the denominator

Organism	No. isolates	Vanc %S	Dapto %S
All MRSA	125	100	20
MRSA (vanc MIC 2)	10	100	20

- Appearance the daptomycin is poor agent, but more accurately, it may not be a good choice for MRSA isolates with elevated vancomycin MICs

*Daptomycin NEVER reported on pulmonary MRSA isolates

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, l]	81	82			57	79			51	85			0	0	77	78	84	98	54	95	65	90

- Limitation: Using only ABCC in 2015 created the apparent decrease in susceptibility for some agents

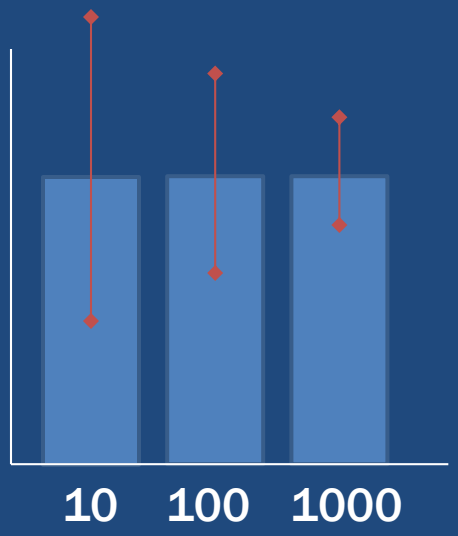
IDENTIFICATION BIAS

- Problematic if change ID systems
  - Complexes, groups, sub-species
  - "Coagulase-negative staph"
  - Split identifications (e.g. *K. oxytoca/R. ornithinolytica*)

BEWARE OF NUMBERS!

- Recommendation:
  - Include only species with at least 30 isolates

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!

- If <30 isolates available for a species, consider the following
  - Is it essential? If yes, consider
    - Footnote “Calculated with fewer than the recommended 30 isolates; %S may not be statistically valid”
    - Combine several years of data with footnote “Calculated using isolates from 2013-2016”
    - Combine species into the appropriate complex (e.g. Enterobacter cloacae complex) if intrinsic resistance is consistent within the group

AFFECT OF DUPLICATES

ELIMINATING DUPLICATES

- CLSI recommends:
  - First patient isolate per date range
- No single "correct" way to estimate susceptibility and resistance rates
  - Variations in calculation approaches may be more or less appropriate for certain applications

ELIMINATING DUPLICATES

- 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

ELIMINATING DUPLICATES

- Excluding duplicates
  - Pro – limits bias introduced by “difficult to treat” pathogens which in theory could reduce the %S
  - Con – may not capture some resistance mechanisms (e.g. AmpC) where the first isolate may be susceptible but resistance emerges on therapy

STRATIFICATION OF RESULTS

WHEN TO SPLIT OUT GROUPS

- Stratification by:
  - Unit or patient location
  - Body site
  - Population difference (e.g. CF)
  - Resistance phenotype (e.g. MSSA vs MRSA)
- 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	Cfaz	Cftrx	Cip	Gent	Imi	Levo *	P-T	T-S
E. coli (All)	3636	92	99	92	93	100	80	96	76
E. coli (nonurine)	292	82	96	80	87	100	80	93	62
E. coli (urine)	3417	93	99	93	94	100	–	97	77

*Tested on nonurine isolates only (N=292)

- Ciprofloxacin artificially appears to have higher %S than levofloxacin due to more restricted testing of levofloxacin against nonurine isolates
- Ciprofloxacin % S is different between urine and nonurine isolates

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
- Other units? (e.g. ICU)

GENERAL RULES

- No less than 30 isolates - otherwise add footnote
- Pilot locations, patient populations, sources, etc.
- Verify that results make sense
  - Compare to previous year
  - Compare to intrinsic table
  - Compare results amongst drug class
  - Compare against similar organisms
- Review rules and identify limitations
- Spot check – pull an epidemiology report or use a different method to see if you get a similar number
- Pay attention identification and AST procedural changes
- Communicate intent of antibiogram with limitations
- Use the antibiogram as a tool to identify AST issues

CONCLUSION

- Antibiogram easily biased
  - Understand the biases in your data
- Data differs by method of extraction
  - Know your limitations and minimize the 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