

Developing and Evaluating an Antibiogram

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- Examine the importance of developing and maintaining an antibiogram
- Identify important considerations when creating an antibiogram
- Recognize limitations of antibiograms
- Identify strategies to utilize information on antibiogram to improve antibiotic stewardship and patient care



- What is an antibiogram
- Applications and uses of antibiograms
- Limitations
- Antimicrobial stewardship



• What is an antibiogram?

- Tool displaying a periodic summary of microbiologic data from a defined patient population to estimate the prevalence of susceptibilities for common bacterial pathogens
- Used by clinicians as an aid in selecting empiric antibiotic therapy
- Important for monitoring trends in antimicrobial resistance within an institution over time

Benefits of antibiograms

- Encourage responsible use of antibiotics
- May be used to target inappropriate antibiotic use
- Supports infection-control measures
- May improve outcomes among patients with infections
- Detect changes in resistance patterns over time
- Inexpensive to develop and maintain

Steps for development

- Work with lab to create report
- Ensure compliance with guidelines
- Choose format and provide instructions for use
- Inform staff about antibiogram and provide training if needed
- Distribute antibiogram
- Update regularly

Working with your laboratory

- Identify the correct contact at the lab
 - Usually someone in the microbiology department
- Most labs have capability to create an antibiogram report
- Establish desired parameters and specifications for the antibiogram





Consensus guideline from the Clinical and Laboratory Standards Institute (CLSI) M39: "Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data"

Contains specific recommendations for:

- Collection
- Storage
- Analysis
- Presentation
- Preparation of reports
 - Routine and enhanced antibiograms
 - Guide selection of antimicrobial therapy

CLSI M39-A4 recommendations

- Analyze and present data at least annually
- Include only species with at least 30 isolates tested
- Include diagnostic, not surveillance, isolates
- Include results for drugs that are routinely tested and clinically useful
- Include the first isolate per patient in the period analyzed, irrespective of body site
- Calculate the percentage susceptible (%S), not including percentage with intermediate susceptibility (%I)

+ Isolates





- Isolate: pure culture of a bacteria
- Sufficient numbers of isolates to analyze can be concern for smaller facilities and infrequently isolated species
- Acceptable to include isolates collected over >1 year or to include data from multiple facilities in same geographic area if <30 isolates of a species
- Exclude isolates collected from surveillance or screening cultures from routine analysis

CLSI M39-A4 recommendations

- Data stratification: to encourage optimal antibiotic therapy, often useful to stratify results for select patient populations, medical services, an organism's resistance profile, or specimen types
- Presentation issues: susceptibility panels may differ for testing of isolates from different body sites or groups

Supplemental analyses by organism

- Streptococcus pneumonia: calculate and list the (%S) using meningitis, non-meningitis and oral penicillin breakpoints. Ceftriaxone, cefotaxime, cefepime: calculate and list (%S) using meningitis and non-meningitis breakpoints
- Viridans streptococci: for isolates from sterile sites, calculate and list both (%S) and (%I) for penicillin
- Staphylococcus aureus: consider including a separate analysis for MRSA, and indicate the percentage of S. aureus isolates that are MRSA
- Enterococcus spp: consider separating the analysis for *E. faecalis* and *E. faecium;* indicate the percentage that are VRE
- K pneumonia: consider reporting data by resistance mechanism (ESBL producing or KPC producing) and/or hospital unit

+ M39 5th Edition

- Published February 2022
- New information on:
 - Extracting data from various sources
 - Combining results from rapid diagnostics and resistance markers with the antibiogram
 - Developing antibiograms for long-term care facilities and veterinary practices
 - Preparation of multifacility antibiograms
 - Antibiogram percent susceptible trends and empiric therapy considerations



-Antibiogram construction

- Cover page
- Unit- or site-specific susceptibility tables
- Name and number of bacteria isolates
- Antibiotics tested against the organism consider including breakpoints
- Review complete antibiogram
 - Ensure all abbreviations are defined
 - Data are included only for antibiotics that are appropriate for the organism
 - Data are not included for antibiotics that are inappropriate for an organism despite in vitro susceptibility

Antibiogram formats

- Spreadsheet
- Word processing file
- Formatted PDF file which cannot accidentally be altered
- Consider providing in multiple formats
- Consider use of highlighting, different font sizes, and notes
- Comprehensive antibiogram template available from Agency for Healthcare Research and Quality (AHRQ) at: <u>www.ahrq.gov/sites/default/files/wysiwyg/nhguide/5 TK2 T5-</u> <u>Concise Antibiogram Toolkit Comprehensive Antibiogram Templat</u> <u>e.docx</u>

Example instructions

For each antibiotic listed, this antibiogram provides aggregated data for the percent susceptibility (%S) of bacteria isolated in patients from this hospital during the time period indicated, unless otherwise noted. This antibiogram has been prepared according to standards established by the Clinical and Laboratory Standards Institute.

Antibiograms have been shown to improve the appropriate use of antibiotics by providing the actual susceptibilities of infection-causing organisms. The antibiogram should be used to guide empiric therapy. Selection of empiric therapy in a particular patient should not be based solely on an antibiogram. A patient's individual characteristics, including infection history, past antimicrobial use, and other risk factors must also be considered. Refer to microbiologic lab results for %S information for a specific patient.

> Adapted from Toolkit 1. Working With Your Lab To Improve Antibiotic Prescribing. Content last reviewed October 2016. Agency for Healthcare Research and Quality, Rockville, MD. https://www.ahrq.gov/nhguide/toolkits/help-clinicians-choose-theright-antibiotic/toolkit1-working-with-a-lab.html



		Amin	oglyco	sides		B-Lac	tams	с	ephalo	osporii	าร	Quinolones		Oth	ers			
Gram (–) Highlighted rows include less than 30 isolates; interpret these results with caution	# of residents	Amikacin	Gentamicin	Tobramycin	Ampicillin	Imipenem	Piperacillin- tazobactam	Cefazolin	Cefoxitin	Ceftriaxone	Ceftazidime	Ciprofloxacin	Nitrofurantoin		TMP/SMX			
Escherichia coli	37	100	100	100		100	100				100	75						
<i>Klebsiella</i> sp *	* 33		84.6	92.3	38.5	100	92.3	84.6	100	100	100	38.5	92.3		3 38.5			
<i>Proteus</i> sp	31	71.4	57.1	71.4		85.7	85.7			57.1	57.1		28.6		28.6		71.4	
Pseudomonas aeruginosa †	<u>† 23</u>	100	83.3	92.3	91.7		100		81.8	100	100	30.8			69	.2		
			Penio	cillins		Ceph	alosporins	Quinolones				Others						
Gram (+) Highlighted rows include less than 30 isolates; interpret these results with caution	# of residents	Penicillins	Ampicillin	Oxacillin	Nafcillin	Cephalothin	Ceftriaxone	Ciprofloxacin	Moxifloxacin	Gentamicin	Linezolid	Rifampin	Tetracycline	TMP/SMX	Vancomycin	Nitrofurantoin		
Staph aureus (all) †	† 17	0	0	0	0			0	0	<mark>87.5</mark>	100	100	<mark>100</mark>	<mark>100</mark>	<mark>100</mark>	<mark>100</mark>		
Methicillin Resistant (MRSA) Methicillin Susceptible (MSSA)	34 0	0	0	0	0			0	0	87.5	100	100	100	100	100	100		
Enterococcus sp *	* 30	100	100					50		75			25		100	100		

* This antibiogram uses 2 years of culture data for these organisms.
† Results based on fewer than 30 isolates are less reliable and should be interpreted with caution.

+ Examples

[Nursing Home Name] Antibiogram

January 2013–January 2014

The antibiogram provides an estimate of % susceptibilities for bacteria isolated in residents. Use this as a guideline in selecting empiric therapy. Refer to lab results for specific susceptibility of individual resident isolates.

G	RAM-POSITIVE	Staph aureus	Enterococcus sp	Streptococcus agalactiae		GRAM-NEGATIVE	Escherichia coli	Klebsiella sp	L Proteus sp	++ Pseudomonas 55 aeruginosa
	# of Residents	34	* 30	0		# of Residents	37	33	31	*† 23
	Penicillin	0	100		sides	Amikacin	100	100	71.4	100
Penicillins	Ampicillin	0	100		Aminoglycosides	Gentamicin	100	84.6	57.1	† 83.3
Penic	Oxacillin	0			Amin	Tobramycin	100	92.3	71.4	† 92.3
	Nafcillin	0			s	Ampicillin		38.5		†91.7
Quinolones	Ciprofloxacin	0	50		B-Lactams	Imipenem	100	100	85.7	
Quino	Moxifloxacin	0			Ġ	Piperacillin-tazobactam	100	92.3	85.7	†100
	Gentamicin	87	75			Cefazolin		84.6		
	Linezolid	100			sporins	Cefoxitin		100		† 81.8
	Rifampin	100			Cephalosporins	Ceftriaxone		100	57.1	† 100
Others	Tetracycline	100	25		Ū	Ceftazidime	100	100	57.1	†100
	TMP/SMX	100				Ciprofloxacin	75	38.5		† 30.8
	Vancomycin	100	100		Others	Nitrofurantoin		92.3	28.6	
	Nitrofurantoin	100	100			TMP/SMX		38.5	71.4	† 69.2

* Indicates when 2 years of resident data used.

† Indicates fewer than 30 isolates used; interpret these results with caution.

https://www.ahrq.gov/nhguide/toolkits/help-clinicians-choose-the-rightantibiotic/toolkit1-working-with-a-lab.html





CUMULATIVE ANTIMICROBIAL SUSCEPTIBILITY TEST DATA SUMMARY January 1, 2021 - December 31, 2021

	Amoxicillin	Amox/Clav	Ampicillin	Amp/Sulbactam	Azithromycin	Aztreonam	Cefazolin	Cefepime	Cefuroxime	Ceftriaxone	Ciprofloxacin	Clindamycin^	Daptomy cin	Doxycycline	Ertapenem	Gentamicin	Levofloxacin	Linezolid	Meropenem	Nitrofurantoin ++	Oxacillin	Penicillin G	Piperacillin/Tazobactam	Tetracycline	Trimethoprim/Sulfa	Vancomycin
Citrobacter freundii *		0	0	0		100	0	100	0	100	96				100	100	100		100	100			100	91	100	
Citrobacter koseri		100	0	96		100	92	100	81	100	100				100	100	100		100	50			100	96	100	
E. coli		84	51	56		93	87	94	90	93	81				100	92	84		100	97			98	79	78	
Enterobacter cloacae		0	0	0		86	0	94	0	86	91				87	98	92		100	29			87	91	92	
Klebsiella (Enterobacter) aerogenes		0	0	0		96	0	100	27	93	100				96	100	100		100	34			96	100	100	
Klebsiella oxytoca		88	0	42		92	75	92	83	92	88				100	92	96		100	86			96	83	79	
Klebsiella pneumoniae		97	0	83		97	95	97	93	97	96				99	99	98		99	56			94	87	93	
Proteus mirabilis		97	86	90		99	78	98	96	98	93				99	79	93						100		88	
Pseudomonas aeruginosa		0	0	0		84	0	95	0	0	80					96	81		97				89			
Enterococcus faecalis			100										100	41	8	2 (SYN	96	99		100		100		27		98
Enterococcus faecium *			23										92	77	1	00(SYN	30	85				31		0		46
Strep agalactiae (GBS)	100							100		100		40					98	100				100		12		100
MSSA												86	100	99		100	86	100			100				95	100
MRSA							R					80	100	97		100	21	99			R				95	100
Staph epidermidis							66					65	100	97		100	91	96		100	60			86		99

GENERAL NOTES:

a. Percent susceptible for each organism/antimicrobial combination was generated by including the first isolate

of that organism recovered from a given patient per year.

- b. E. coli and Klebsiella pneumoniae that are ESBL producers (resistant to 3rd gen. cephalosporins) are also resistant to all penicillins, cephalosporins, and aztreonam.
- c. Worldwide, there have been no penicillin resistant Beta-hemolytic Streptococcus, Group A (Strep pyogenes) reported to date.
- d. Vancomycin-resistent Streptococcus pneumoniae isolates have not been reported in the United States
- e. Pip/tazo has reliable coverage for Bacteroides fragilis; adding metronidazole is unnecessary.
- f. Organisms susceptible to tetracycline are also susceptible to minocycline and doxycycline.

KEY/DEFINITIONS:

- (↓ or ↑): Indicates a ≥10% change from previous year
- (R): Indicates intrinsic resistance to this antibiotic; inappropriate for use
- (Gray Cell): Antimicrobial agent is either not tested, known to be clinically ineffective, and/or suppressed per CLSI limitations
- (*): Statistical validity of estimates of percent susceptible may be low, as <30 isolates were obtained during this time period
- (++): Nitrofurantoin should be used only for treatment of uncomplicated urinary tract infections in patients with creatinine clearance > 40.
- (^): Isolates with inducible clindamycin resistance (+ D test) are considered resistant for the purposes of antibiogram reporting
- (##): Enterobacteriaceae cefazolin interpretation is for urine source only

+ Frequency of data analysis

- Most commonly data collected during one calendar year
- Depending on number of isolates, may consider more frequent analyses if there is a perceived change in susceptibility throughout year



Repeat isolates

- Controversial aspect of cumulative antibiogram preparation
- Interpretation and presentation of multiple isolates of a given bacterial species from an individual patient
- Patients with complicated clinical courses, long hospital stays, and infections with multidrug-resistant organisms frequently have specimens cultured on multiple occasions

-Example

	Hospitalization	Specimen		Ant	imicrol	bial tes	ted	
Isolate	day	source	Clin	Ery	Gen	Pen	Ox	Van
1	1	Wound (toe)	S	S	S	R	S	S
2	7	Blood	R	R	R	R	R	S
3	20	Wound (foot)	R	R	S	R	R	S
4	32	Wound (foot)	R	R	R	R	R	S

NOTE. Clin, clindamycin; Ery, erythromycin; Gen, gentamicin; Ox, Oxacillin; Pen, penicillin; R, resistant; S, susceptible; Van, vancomycin.

Algorithms for repeat isolates

- Patient-based algorithms
- Episode-based algorithms
- Resistance phenotype-based algorithms



- Each patient contributes equally to the estimate of isolates susceptible
- Clinically and epidemiologically relevant
- Practical

+ Episode-based

- Focus is on "episodes" of infection
- No agreed upon consensus definition of episode
 - Interval of time between episodes
 - Phenotypic characteristics of isolates
 - Site of infection

Resistance-phenotype based

- Data analyst focuses on particular bacterial strains defined by phenotypic characteristics
- Challenge is defining the features to be used to discriminate between isolates

Isolates included according to various algorithms

Algorithm	Isolates included in the analysis ^a
Isolate based (all isolates)	1, 2, 3, 4
Patient based (first isolate per patient)	1
Episode based (first isolate per episode)	
7-Day interval from initial isolate	1, 3, 4
7-Day interval from previous isolate	1, 3, 4
30-Day interval from initial isolate	1, 4
30-Day interval from previous isolate	1
Resistance phenotype based (first isolate per phenotype)	
Major difference in any antimicrobial result	
Consecutive isolates	1, 2, 3, 4
Nonconsecutive isolates	1, 2, 3
Major difference in oxacillin result	
Consecutive isolates	1, 2
Nonconsecutive isolates	1, 2

^a Isolates are numbered as in table 2.

Antimicrobial agents to analyze

- Only present agents that are routinely tested and clinically useful
- Avoid biases that may be introduced by selective reporting practices by including results from all antimicrobials tested in analysis database
- Antimicrobials tested only against drug-resistant strains as part of reserve or second-line testing panels generally biased towards higher rates of resistance



- Cumulative report should represent data as percentage of isolates susceptible
- Representative of likelihood of successful therapeutic response

(# of isolates susceptible to antibiotic/# isolates tested) x 100



- Clinical and Laboratory Standards Institute (CLSI)
- European Committee on Antimicrobial Susceptibility Testing (EUCAST)
- Food and Drug Administration (FDA)

Determination of susceptibility

- Usually achieved through dilution in microbiology labs
- Through directly applying antibiotic at defined concentrations uniformly to growth media
 - Broth dilution

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- Agar dilution
- Diffusion gradient through media
 - Kirby-Bauer Disk Diffusion





- Breakpoint: concentration (mg/L) at which bacteria are susceptible or resistant to an antibiotic
- Minimum inhibitory concentration (MIC): lowest concentration of antibiotic required to inhibit growth of an organism
- MIC ≤ breakpoint indicates bacterial susceptibility
- Predicts likelihood of clinical success of treatment with antibiotic



- Defined antibiotic concentration or zone of inhibition diameter
- Antimicrobial's *in vitro* activity against organism
- Do not account for:
 - Host responses
 - Site of infection
 - Pharmacokinetics/pharmacodynamics
 - Dosing





+ Breakpoints



- Pharmacokinetic (PK) and pharmacodynamic (PD) properties are key to assessing clinical applicability
- Indices used to determine optimal drug target concentrations
 - % time free drug concentration remains above MIC
 - Ratio of free drug max concentration (peak) to MIC
 - Ratio of free drug (area under the curve/AUC) over 24 hours (AUC/MIC)
- Antimicrobial exposure in relation to MIC is often based on blood concentrations of antimicrobial – not always the site of infection
- Same bug-drug combination can have multiple breakpoints specific to site of infection

Breakpoint guidance documents

- CLSI M100: Performance Standards for Antimicrobial Susceptibility Testing
- FDA website
- Breakpoints may differ between regulatory agencies for various reasons
- different databases
- different interpretations of data
- differences in doses used in different parts of the world
- different public health policies
Guidance on reading EUCAST Breakpoint Tables



Changing breakpoints

- Common reasons for revisions:
 - New PK/PD data
 - Identification of novel resistance mechanisms
 - New clinical data suggesting poor correlation of clinical response with established breakpoint
- Microbiological methods may also be refined over time affecting quantification of MIC
- CLSI and EUCAST continually monitor and update information in recommendations

Susceptibility testing categories

- Susceptible (S): isolates inhibited by usually achievable concentrations
- Susceptible-dose dependent (SDD): susceptibility depends on dosing regimen
- Intermediate (I): implies clinical efficacy in body sites where the drugs are physiologically concentrated or when higher-than-normal dose can be used thereby increasing exposure to the agent
- Resistant (R): isolates not inhibited by usual achievable concentrations

FDA-cleared automated identification & susceptibility testing platforms

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Automated System	Organisms Detected
Sensititre System (TREK Diagnostic Systems)	Gram +; Gram -; <i>Streptococcus</i> ; ESBL; yeast
BD Phoenix [™] Automated Microbiology System Becton, Dickinson	Gram +; Gram -; <i>Streptococcus</i>
VITEK [®] System bioMérieux	Gram +; Gram-; <i>S. pneumoniae</i> ; yeast
MicroScan WalkAway [®] (Siemens Medical Solutions Diagnostics)	<i>Streptococcus</i> ; ESBL; Rapid; Synergies plus

Distribution of antibiogram

- Should be available to all prescribers of antibiotics, pharmacists, infection prevention and control, and microbiology department
 - Pocket guide
 - Electronic medical record or institutional website
 - Posted at nursing station, order entry terminals, medical team rooms
- Reviewed and distributed at local pharmacy and therapeutics committee, antimicrobial stewardship committee, medical executive committee meetings

Statistical applications

- CLSI M39 includes tables to help users assess the statistical confidence that they should have in observed estimates of the (%S) for different sample sizes
- Statistically significant differences may not always be clinically important
- Patient population, culturing practices, and/or laboratory methodology may influence changes

Supplemental messages

- Can improve communication to front-line staff about data or processes
- Emphasize the importance of microbiology laboratory involvement as an antimicrobial stewardship strategy

Examples:

- 'Staphylococcus aureus bacteriuria is associated with Staphylococcus aureus bacteremia. Blood cultures are recommended'
- *Clostridioides difficile* organism present but toxin not detected via EIA.
 Consider *C.difficile* colonization or early infection'



Combination

(n=423)	Aztreonam	Cefepime	Meropenem
Monotherapy (%)	74.0	74.8	77.2
Amikacin (%)	95.9	94.2	94.2
Tobramycin (%)	92.7	90.2	90.2
Ciprofloxacin (%)	82.9	79.7	80.5
Colistin (%)	88.2	85.3	79.4

Escalating *biggenerative constrained of the second of t*

Syndrome-Specific

E. coli	Urine, % S (n=463)	Intraabdominal, % S (n=308)
Ampicillin/sulbactam	75	47
Ciprofloxacin	82	68
Ceftriaxone	94	92
TMP/SMX	91	88

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Important considerations

- Not generalizable between institutions
- Empiric therapy selection should not be based solely on antibiogram
- Capture aggregate proportion of susceptible isolates for a given organism-antibiotic combination
- FDA must ensure antibiotic labels contain up-to-date breakpoints
- Lab must continuously update and validate FDA approved automated testing systems





- MICs not included on antibiograms
- Data may not be generalizable to specific patient populations or locations of a healthcare facility if compiled using system-wide data
- Changing breakpoints
- Inability to track emergence of resistance during therapy

Antimicrobial stewardship applications

- Assess local susceptibility rates
- Aid in recommending empiric antibiotic therapy
- Develop guideline based quick orders using local data
- Monitor resistance trends over time
- Influence anti-infective selection on drug formulary
- Professional societies and national agencies recommend monitoring resistance





Should multiple cultures from the same patient for the same organism be included in a cumulative antibiogram?





Should multiple cultures from the same patient for the same organism be included in a cumulative antibiogram?

NO





How many isolates are needed to make the data valid enough to include the organism in the antibiogram according to CLSI M39?





How many isolates are needed to make the data valid enough to include the organism in the antibiogram according to CLSI M39?

30





True or False?

You should always choose the antibiotic with the lowest MIC value to empirically treat your patient's infection, since it indicates the most effective treatment against a given organism.



True or False?

You should always choose the antibiotic with the lowest MIC value to empirically treat your patient's infection, since it indicates the most effective treatment against a given organism.

FALSE





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