"Is it This Time of Year Again?" How Oregon Laboratorians Can Generate a More Meaningful Antibiogram

OHA Webinar

December 18, 2017

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Today's Objectives

1. Learn about the OHA Antibiogram Project which aimed to take a "snapshot" of the adherence of Oregon clinical microbiology laboratories practices to CLSI M39-A4, understand perceptions of Oregon Infection Preventionists on facility Antibiogram distribution and use, and evaluate burden of antimicrobial resistance in Oregon statewide.

2. Understand current M39-A4 guidance *and apply it to improving your own facility's Antibiogram*.

Background

- The Antibiogram – a labor of love & sometimes used by clinical staff
- Guidelines exist regarding best practice for creation and dissemination. If guidelines were followed:
  - Local utility would likely improve
  - Cross-facility & regional comparison would be possible
- Guideline adherence not previously evaluated in our region
  - Duke study – found very poor guideline adherence in a community cohort (Moehring et al, J Clin Micro 2015)

What is possible?
UTI Empiric Treatment Examples

- IDSA UTI treatment guidelines: use TMP-SMX if local resistance <20%

- **Emergency Deptartment (ED) project - Ohio State University**
- **Methods-** all UA were sent for culture in 2009. Symptomatic, uncomplicated UTIs were included; ED-UTI antibiogram vs. hospital-wide Antibiogram compared
- **RESULTS:**
  - ***E. coli* susceptibility:** TMP-SMX - **80%** vs. 71%; cefazolin - **97%** vs. 87%; ciprofloxacin - **89%** vs. 73% ($p < 0.05$); nitrofurantoin (99% vs. 98%).
  - Empiric treatment effectiveness: **TMP-SMX – 92%;** ciprofloxacin: 89%.
- **CONCLUSIONS:** ED-specific Antibiogram has greater Abx susceptibility rates for uncomplicated cystitis than the hospital-wide Antibiogram.

What is Possible for UTI Empiric Rx?

- Transplant-specific Antibiogram (e.g., urinary Antibiogram for kidney transplant patients

RESULTS (study looking at 1st year post-transplant inpatient urinary isolates obtained for UTI – U. Arizona vs. hospital-wide):

- 299 kidney transplants
- 66 subjects included; 47% of these had ≥2 UTIs
- Urinary *E. coli* in kidney tx recipients **were significantly more resistanTMP/SMX (88%), ceftriaxone (20%), ciprofloxacin (37%)** ($p<0.0001$).

Korayem GB et al. J Glob AMR 2017

What's Possible & Useful?

- Meet with your clinicians – ask what's relavent!
- **Low hanging fruit for many labs: (outpatient) urinary Antibiogram:** include TMP-SMX, nitrofurantoin, amoxicillin, cephalexin, Cipro.
  - Even Consider: nudge your clinicians to preferred therapy → (e.g., "use TMP-SMX, nitrofurantoin, or fosfomycin as 1st- line agents for uncomplicated UTI based on our local Antibiogram & IDSA recommendations)

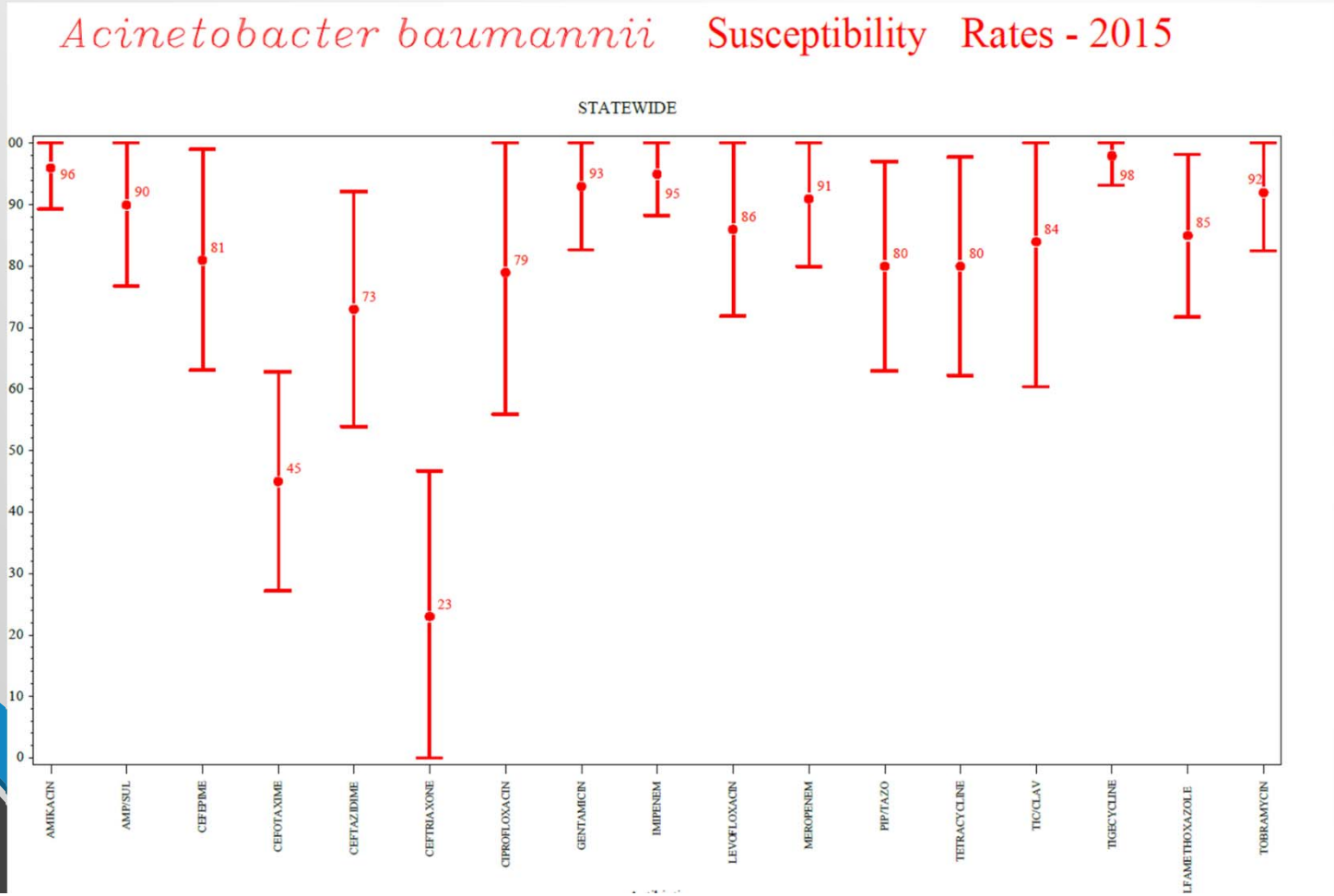
What's Possible on Regional Level: Statewide Antibiogram

- Could offer regional perspective of empiric treatment for UTI, community-acquired intraabdominal infection, community-acquired bloodstream infection
- Utility tailored to your labs' rapid diagnostic capacity (e.g., do you use Verigene? MALDI? BioFire?)

Bureau of Infectious Disease and Laboratory Sciences

2015 Statewide Antibiogram Report

In 2015, 55 (79%) acute-care hospitals reported their antibiogram data and are included in this statewide report. Each page of this eleven page report displays the average percent susceptibility (red dots) and standard deviation (red bars) of a bacterial pathogen to relevant antibiotics. This data is representative of antibiotic susceptibility data for 232,748 inpatient and outpatient bacterial infections from reporting Massachusetts acute-care hospitals, and does not represent the full extent of antibiotic resistant infections in Massachusetts.



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ANTIBIOGRAM FOR SELECTED BACTERIA OF PUBLIC HEALTH AND CLINICAL SIGNIFICANCE: ISOLATES COLLECTED BY CLINICAL LABORATORIES IN MONTANA

		aminoglycosides			b-lactam/b-lactamase inhibitor				cephems						
Gram Negative Isolates	# of isolates (all sources)	Gentamicin	Tobramycin	Amikacin	Amoxicillin-Clavulanic Acid	Ampicillin-Sulbactam	Piperacillin-Tazobactam	Ticarcillin-Clavulanic Acid	Cefazolin	Cefuroxime	Cefepime	Cefotetan	Cefoxitin	Cefotaxime or Ceftriaxone	
E. coli	15226	94%	94%	96%	88%	70%	97%	95%	92%	89%	96%	98%	96%	97%	
K. pneumoniae	2625	91%	89%	97%	83%	92%	84%	100%	86%	81%	90%	100%	86%	90%	
Enterobactor spp.	1246	99%	99%	98%	1%		91%	95%	78%	48%	98%	75%		98%	
Serratia spp.	178	100%	91%	100%							96%			100%	
P. aeruginosa	1636	93%	98%	99%			97%				95%				
Acinetobactor spp.	< 30														

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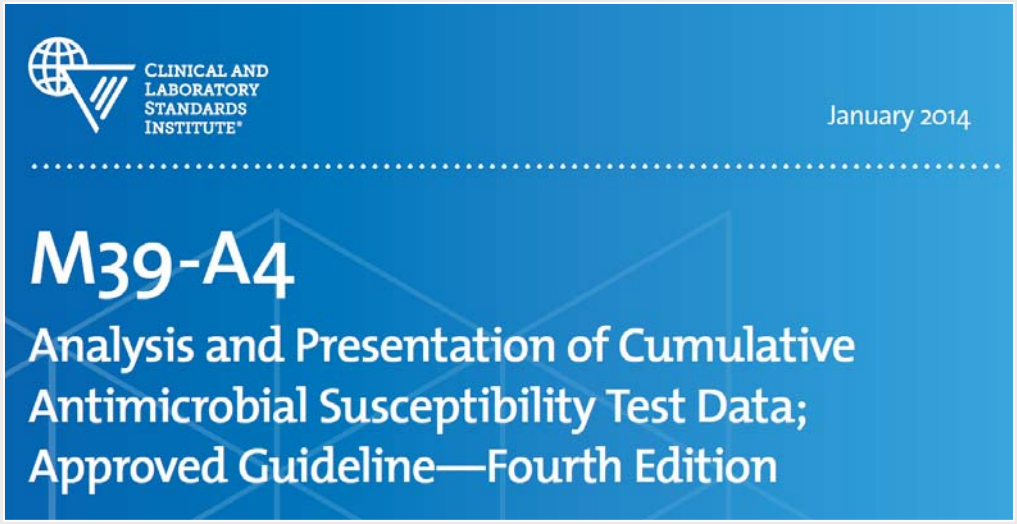
	quinolones		carbapenems			sulfona-mide	penicillins			single agents				
Gram Negative Isolates	Ciprofloxacin	Levoflaxicin	Ertapenem	Imipenem	Meropenem	Trimethoprim-Sulfamethoxazole	Piperacillin	Ampicillin	# of isolates urine only	Cephalothin	Norfloxacin	Nitrofurantoin	Sulfisoxazole	Trimethoprim
E. coli	79%	82%	99%	100%	91%	84%	58%	62%	9846	86%	82%	94%		85%
K. pneumoniae	88%	95%	100%	99%	100%	86%	47%	3%	754	56%	100%	43%		
Enterobactor spp.	96%	98%	87%	97%	98%	94%	77%	78%	515			24%		
Serratia spp.		100%			100%	100%								
P. aeruginosa	80%	78%		92%	96%		100%							
Acinetobactor spp.														

So, where do we start in Oregon?

- Create an accurate, standardized Antibiogram!

What are the CLSI M39-A4 Guidelines?



- "Recommendations for the collection, analysis, and presentation of cumulative antimicrobial susceptibility test data."

One "idealized" example (from CLSI)

Appendix E2. Cumulative Antimicrobial Susceptibility Report Example – Antimicrobial Agents Listed by Class (Hypothetical Data)

Memorial Medical Center
1 January – 31 December 2012 Cumulative Antimicrobial Susceptibility Report*
Percent Susceptible

Gram-Negative Organisms	No. Strains	β-lactams						Aminoglycosides			FQs	Other	
		Ampicillin	Cefazolin	Cefotaxime	Ceftazidime	Meropenem	Piperacillin-tazobactam	Amikacin	Gentamicin	Tobramycin	Ciprofloxacin	Nitrofurantoin†	Trimethoprim-sulfamethoxazole
Acinetobacter baumannii	32	R	R	34	52	80	46	80	60	59	51	–‡	58
Citrobacter freundii	49	R	R	72	67	99	67	100	100	100	90	78	67
Enterobacter aerogenes	31	R	R	68	69	99	74	100	91	91	92	85	95
Enterobacter cloacae	76	R	R	61	62	99	77	99	90	90	92	81	84
Escherichia coli	1433	36	68	96	94	99	51	99	91	92	72	98	65
Klebsiella pneumoniae	543	R	72	91	92	99	86	99	94	94	84	74	81
Morganella morganii	44	R	R	85	81	99	64	100	100	100	99	R	75
Proteus mirabilis	88	87	80	99	99	100	70	100	90	93	89	R	73
Pseudomonas aeruginosa	397	R	R	R	76	80	85	97	80	83	75	R	R
Salmonella spp.	32	88	–	97	97	100	91	–	–	–	90	–	86
Serratia marcescens	50	R	R	82	94	99	94	100	94	89	95	R	91
Shigella spp.	33	64	–	100	100	100	84	–	–	–	95	–	69
Stenotrophomonas maltophilia	72	R	R	R	63	R	R	R	R	R	6	R	98

* The percent susceptible for each organism/antimicrobial combination was generated by including the first isolate of that organism encountered on a given patient.
† Nitrofurantoin data from testing urine isolates only.
‡ (–) drug not tested or drug not indicated.
Abbreviations: FQ, fluoroquinolone; R, intrinsic resistance.

- ✓ Facility (and Lab) Name
- ✓ Isolate Dates
- ✓ De-duplication strategy noted

A Non-Ideal, but real, example

January to December 2015 Antimicrobial Susceptibility Profile					
FACILITY NAME XXXXXX					
Inpatient & Outpatient Isolates					
ORGANISMS		Acinetobacter baumannii complex	Acinetobacter lwoffii	Pseudomonas aeruginosa	Pseudomonas fluorescens
TOTAL ISOLATES	1129	7	1	60	1
		S	S	S	S
Amikacin			100%		
Amoxicillin/Clavulanic Acid		0%		2%	0%
Ampicillin		0%	100%	0%	0%
Aztreonam		0%	100%	100%	
Benzylpenicillin					
Beta-Lactamase					
Caspofungin					
Cefaclor					
Cefazolin		0%	100%	2%	0%
Cefepime		100%		93%	100%
Cefotaxime			100%		
Cefoxitin			100%		
Cefoxitin Screen					
Ceftriaxone		14%		2%	0%
Cefuroxime					
Ciprofloxacin		100%	100%	62%	100%
Clarithromycin					
Clindamycin					

✓ Recommended Frequency

- ***At least annually*** **-** provides up to date information for clinicians, infection control, pharmacy, etc.

✓ Isolates

- <u>Only include species with testing data for ≥30 isolates</u>
  - If <30 isolates are available, it should be noted to inform user of less stastitical validity; or combine data from multiple calendar years.
- Only include diagnostic (not surveillance) isolates.
- <u>Only include 1st isolate of a given species per patient per analysis period</u>
  - E.g. Don't include all 10 MRSA+ blood cultures from a patient w/ endocarditis

Example of potential Bias

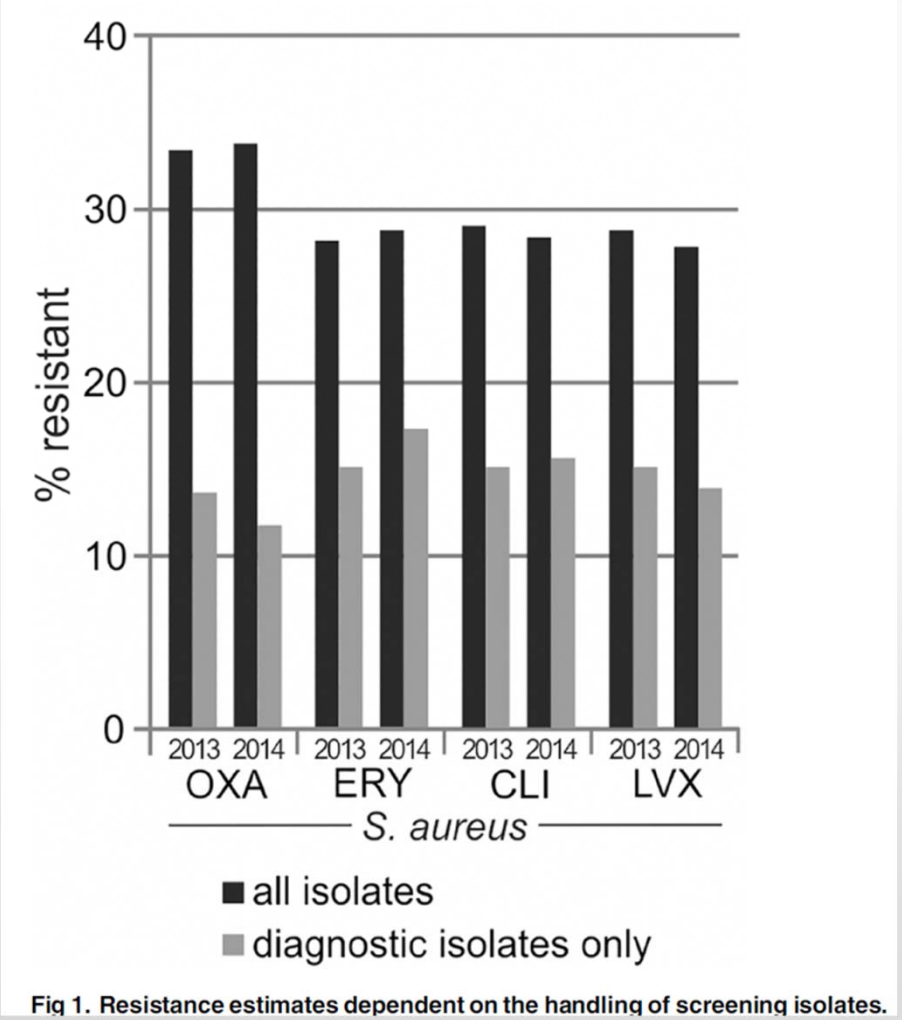


Fig 1. Resistance estimates dependent on the handling of screening isolates.

Kohlmann R, Gatermann SG. PLosOne 2016

✓ Data Verification

- Include only final, verified results.
  - Examples to verify: Vancomycin-resistance in *S. pneumoniae;* Meropenem-resistance in *E. coli*

✓ Facility vs. System

- Ideally each hospital has its own Antibiogram.
- Compile data if low number of isolates provided the population is similar
- Some systems compile both facility-specific & system-wide

URINE CULTURE WITH MIC

* SOURCE:	URINE-CYSTO
STATUS:	FINAL

COMPLETED CULTURE RESULTS

ESCHERICHIA COLI - GREATER THAN 100,000 ORGANISMS PER ML

SUSCEPTIBILITY RESULTS:

S = Susceptibility I = Intermediate R = Resistant

Minimum Inhibitory Concentration (MIC) expressed in ug/mL

ORGANISM(S): ECOLI

AMIKACIN	*S	<=2
AMPICILLIN	*R	>=32
AUGMENTIN	*R	>=32
CARBENICILLIN	*R	>=512
CEFOTAXIME	S	<=4
CEFTAZIDIME	*S	<=8
CEFTIOFUR	*S	<=1
CEFTRIAXONE	S	<=8
CEPHALOTHIN	*R	>=32
CHLORAMPHENICOL	*S	4
CIPROFLOXACIN	*R	>=4
DOXYCYLINE	R	>=16
ENROFLOXACIN	*R	>=2
GENTAMICIN	*R	>=16
IMIPENEM	S	<=4
NITROFURANTOIN	*S	<=32
OFLOXACIN	R	>=8
PIPERACILLIN	*R	>=256
TETRACYCLINE	*R	>=16
TICARCILLEN	*R	>=256
TOBRAMYCIN	*S	2
TRIBRISSEN	*R	>=320

“Selective” or “cascade” reporting

- Antimicrobial susceptibility results of second-line antimicrobial agents (broader spectrum, more toxicity, more costly) are reported *only if* the organism is resistant to first line agents.

- **This is a useful antimicrobial stewardship tool:** again, nudge the clinician towards first-line, narrower-spectrum (and less costly) agents.

However, Beware of Reporting Bias

- All results including those suppressed by "selective" or "cascade" reporting MUST BE ANALYZED
- If suppressed results are excluded, drug-bug combinations based on incomplete denominator data (suppressed results excluded) will appear MORE resistant than they truly are.

Published example of this Bias

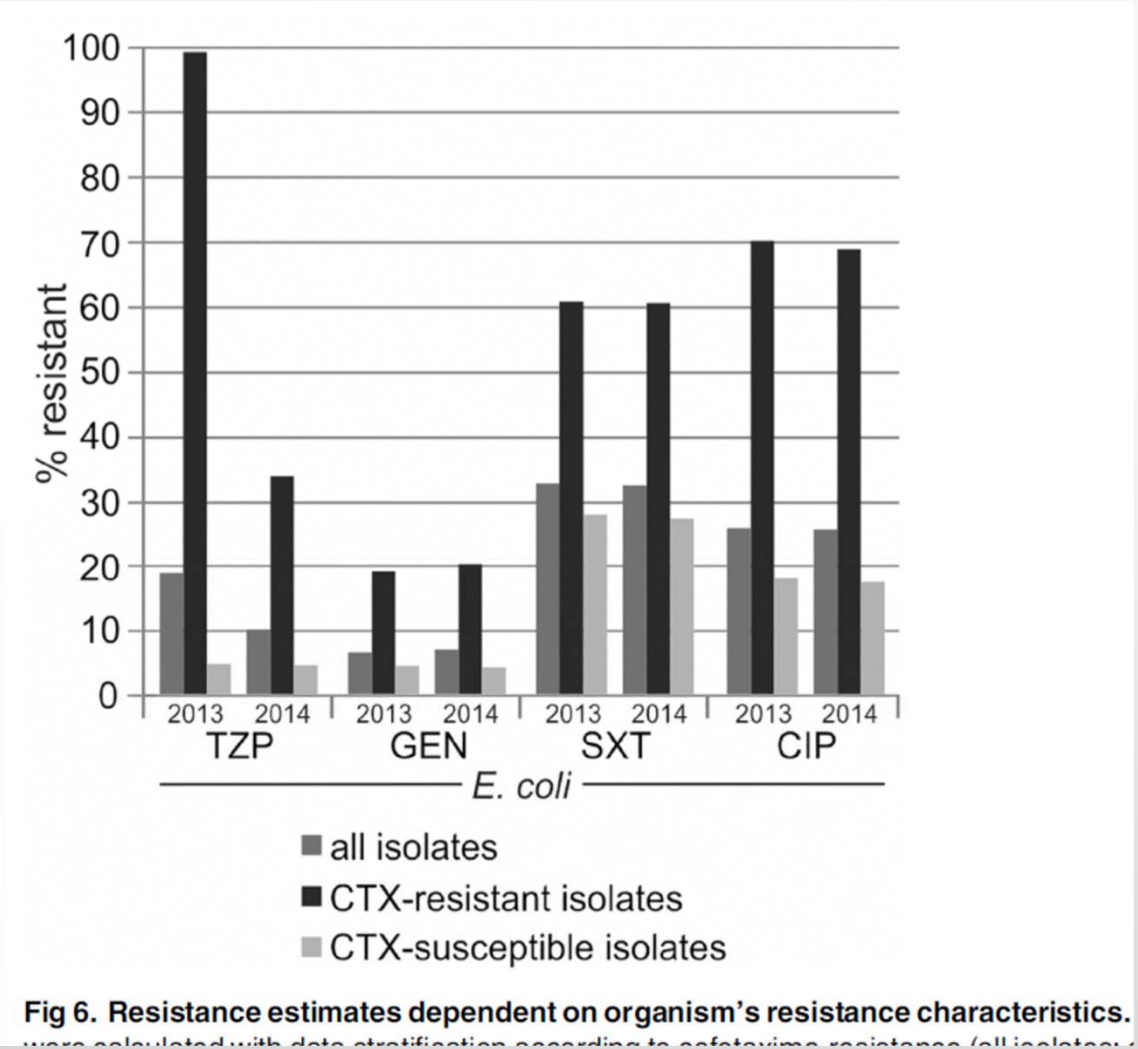


Fig 6. Resistance estimates dependent on organism's resistance characteristics.

- TZP = pip-tazo

Kohlmann R, Gatermann SG. PLosOne 2016

✓ Report Only *Recommended* Drug-Bug Combinations

- CLSI M100-S27 Table 1 outlines drug-bug combinations that *should* and *should NOT* be tested & reported.
- E.g., **do NOT report** *Pseudomonas aeruginosa* + ceftriaxone and *Enterococcus* + cephalexin.

Table 1A. Suggested Groupings of Antimicrobial Agents Approved by the US Food and Drug Administration for Clinical Use That Should Be Considered for Testing and Reporting on Nonfastidious Organisms by Microbiology Laboratories in the United States

	Enterobacteriaceae	*Pseudomonas aeruginosa*	*Staphylococcus* spp.	*Enterococcus* spp.[m]
P A / TEST / PORT	Ampicillin[c]	Ceftazidime	Azithromycin[b] or clarithromycin[b] or erythromycin[b]	Ampicillin[n]
	Cefazolin[d]	Gentamicin Tobramycin		Penicillin[o]
	Gentamicin[c]	Piperacillin-tazobactam	Clindamycin[b]	

Penicillin (PCN) Susceptibility Testing of *S. pneumo*

- When calculating *S. pneumo* PCN susceptibilities, must differentiate CSF vs. other sites
  - Lower breakpoints in CSF
  - Clumping the data risks inaccurate interpretation, underestimating PCN resistance in *S. pneumo* meningitis

CLSI Breakpoints: Are you Up To Date??

- Antibiogram calculated based on %"Susceptible" (not MICs)
- While updated breakpoints aren't *required*, they are **"best practice"-** optimize patient care & enable apple-to-apples comparison w/ others!
- Note- interpretation of resistance trends during the update may temporarily be complicated

VA Portland Antibiogram	*M. morganii* – imipenem-S
2009 & 2010	100% & 100%
Breakpoint updated	
2011 & 2012	20% & 30%

Recommended Distribution

- "Pocket" guides, Websites
- Available to clinicians, infection control personnel, epidemiologist, pharmacists, clinical microbiology laboratory personnel
- No specific recommendation on sharing with outside facilities

Pocket Antibiogram

“Enhanced Antibiogram”

- Stratifying or segregating Antibiogram by various parameters
  - Take into account clinical needs
  - Need sufficient isolate numbers to make subgroups meaningful

IDSA Antibiotic Stewardship Guidelines, 2016

Microbiology and Laboratory Diagnostics

XIV. Should ASPs Work With the Microbiology Laboratory to Develop Stratified Antibiograms, Compared With Nonstratified Antibiograms?

Recommendation

15. We suggest development of stratified antibiograms over solely relying on nonstratified antibiograms to assist ASPs in developing guidelines for empiric therapy *(weak recommendation, low-quality evidence)*.

Comment: Although there is limited evidence at this time that stratified antibiograms (eg, by location or age) lead to improved empiric antibiotic therapy, stratification can expose important differences in susceptibility, which can help ASPs develop optimized treatment recommendations and guidelines.

"Enhanced Antibiogram" Stratification by…

- By nursing unit or site of care (e.g. ICU, Outpatient, Inpatient)
- By organism's resistance characteristics (e.g. MRSA, VRE, resistant Gram-negative)
- By specimen type or infection site (e.g. urine, blood isolates)
- By clinical service or patient population (e.g. surgical, pediatric, cystic fibrosis)

"Enhanced Antibiogram"- Combination of Antimicrobial Agents

- Assist with empirical therapy or therapy for an organism when only the ID is known
- Idea is to examine the % isolates susceptible to one or both drugs in relevant combination
- Example: *P. aeruginosa* susceptibility to cefepime plus ciprofloxacin, meropenem plus tobramycin

OHA Antibiogram Survey
Materials & Methods

- In January 2016, we distributed electronic self-administered, surveys via Survey Monkey to microbiology laboratories and IP programs serving Oregon acute care facilities
- We collected the facilities' 2015 Antibiograms
- Email reminders and calls encouraged participation.
- Follow up phone calls to surveyed laboratories confirmed the certain responses (see Appendix 1)
- We performed a descriptive analysis of creation practices and utilization of Antibiograms via Microsoft Excel

Inclusion Criteria

- Laboratories that create cumulative Antibiograms for Oregon hospitals with available contact information via the Oregon Health Authority
- Infection Prevention Programs of Oregon hospitals with available contact information via the Oregon Health Authority

Definition of "CLSI-adherence"

- Had ≥30 isolates of each species (or noted that <30 isolates affects validity)
- Removed duplicates (only included the first isolate per species per patient per analysis period)
- Only included finalized, verified results
- Created Antibiogram at least once a year
- Included only appropriate drug-bug combinations based on CLSI M100-S27
- Only included diagnostic (not surveillance) cultures
- Did not exclude "suppressed results" from Antibiogram calculations if cascade reporting was utilized.
- Include meningeal and non-meningeal breakpoints for *S. pneumoniae* PCN susceptibility

Results

Response Rates Lab Survey: 25/25 (100%)

Response of Confirmatory Phone calls: 25/25 (100%)

Antibiogram Collection Rate: 22/25 (88%)

Response Rates Infection Prevention Survey: 53/62 (85%)

Demographics of Laboratories

- Median *E. coli* 1272
- Median *Enterococcus* 287
- Median *Staph Aureus* 761

Lab Survey Data

Lab Survey Data			n=25
CLSI guidelines	Refer to CLSI M39-A4 (2014)	16	64.00%
	Refer to CLSI M39-A3 (2009)	2	8.00%
	Did not refer to CLSI guidelines	10	40.00%
Frequency of Antibiogram	Published once a year	23	92.00%
	Published more than once a year	1	4.00%
	Published less than once a year	1	4.00%
Only included first isolate from each patient		18	72.00%
Remove isolates obtained for surveillance purposes (i.e. pre-surgical cx)		19	76.00%
Consistently confirm unexpected results during their resistance testing		21	84.00%
Utilize Cascade Reporting		14	56.00%
	If yes, suppressed results included in Antibiogram calculations	10 (of 14)	71.43%
Used the most recent CLSI break points for susceptibility of Enterobacteraciae to Ertapenem*		14 (of19)	73.68%
*Not all facilities perform ertapenem testing of Enterobacteraciae			

Antibiogram Accuracy

Antibiogram Accuracy:			
Minimum # isolates per species	≥30 isolates or included a disclaimer*	8	36.4%
	≥10 isolates	9	40.9%
	≥5 isolates	2	9.1%
	No minimum # isolates required	3	13.6%
Either differentiated S. pneumoniae meningeal and non-meningeal penicillin susceptibilities or did publish S. pneumoniae penicillin susceptibilities		7	31.8%
Published only appropriate bug-drug combinations per Table 1A & 1B in CLSI M100-27		14	63.6%

Labeling of Antibiograms

Antibiogram Labeling:	(n=22)	
Facility name(s)	17	77.3%
Dates of the included isolates	17	77.3%
If duplicate patient isolates removed	3	13.6%
Type of isolates included (e.g., all vs. inpatient and/or outpatient specimens)	7	31.8%

Use of Enhanced Antibiogram Strategies:

Stratified by any of the below enhanced Antibiogram technique	16	72.7%
Stratify by Organisms' Resistance Characteristics	13	59.1%
MRSA isolates:	13	59.1%
VRE isolates:	2	9.1%
Drug resistant gram negatives:	4	18.2%
Relative antibiotic cost included	3	13.6%
Stratify by Location	3	13.6%
Inpatient and/or Outpatient	2	9.1%
ICU	1	4.5%
Stratify by Body Site (i.e. urine)	2	9.1%
Stratify by susceptibility to empirical two drug combinations	0	0.0%

Infection Prevention Survey

Table 1: Infection Prevention Survey of Antibiogram Methodology	
	# Hospitals (n=53)
Developed an antibiogram	50 (94%)
Shared Antibiogram with	
Pharmacy	44 (83%)
Facility Clinical Staff	38 (72%)
Infection Prevention & Control	38 (72%)
Quality Committee	24 (45%)
Providers/Hospitals WITHIN the Health Care System	19 (36%)
Executive Leadership	13 (25%)
Providers/Hospitals OUTSIDE the Health Care System	7 (13%)
Communication of Antibiograms to Providers	
Via the intranet	33 (62%)
During educational meetings (e.g. grand rounds)	20 (38%)
Email to providers	19 (36%)
Other	7 (13%)

Infection Prevention Survey

The antibiogram is used in the facility to	
Impact clinical decision algorithms	30 (57%)
Guide pharmacy decisions	28 (53%)
Impact antibiotic stewardship (ASP) activities	26 (49%)
Guide empiric antibiotic treatment	26 (49%)
Guide Laboratory Practice	18 (34%)
Guide Infection Control Activities	18 (34%)
Compare with other facilities or sources	11 (21%)
Unsure	5 (9%)
Other	1 (2%)

Discussion

- In 2015 , Oregon laboratories reported & demonstrated inconsistent adherence to CLSI M39A4 as well as partial adoption of updated Gram-negative CLSI M100-27 breakpoints
  - Each issue compounds to complicate cross-facility comparison
- ~75% of laboratories employed Enhanced Antibiogram
  - ~50% of those ONLY stratified MSSA vs. MRSA.
  - 32% (n-7) used additional Enhanced Antibiogram techniques, indicating a slow adoption of these practices

Discussion (cont.)

- IP survey: only 50-60% of hospitals used the Antibiogram to impact relevant clinical operations such as clinical decision pathways, antibiotic stewardship.

- Hospitals commonly shared Antibiogram data within the facility but infrequently outside the facility (either within or outside of their system).

Focus Group

Methods: Antibiogram study data presented to 3 Oregon microbiologists via teleconference. Drs. Kirsch and Pfeiffer recorded feedback based on group responses to pre-determined questions. Notes were compared for accuracy.

Results:

- Antibiogram data often comes from many sources; de-duplication & avoiding cascade reporting bias is *not* straightforward.

- Barriers to Adopting:
  - M100-S27 breakpoints include: LARGER - need for verification study, lack of time, lack of clinical microbiologist, need for clinical isolates- particularly a resistant Gram-negative training set.
  - M39A4 recommendations: MINIMAL- need to purchase, education.

- Data-sharing barriers: perceived issues with publicly sharing potentially high resistance rates, but little to no issue re: data sharing with colleagues.

Recommendations

- **To create accurate and standardized Antibiograms, all facilities should adopt updated CLSI-recommended guidelines.**
  - ✓ Adhere to "routine Antibiogram" recommendations in M39A4
  - ✓ Employ "enhanced Antibiogram" techniques as appropriate for the clinical needs of the facility/health system
    - ✓ E.g., syndromic (outpatient UTI, ICU sepsis), by organism (MRSA vs MSSA)
  - ✓ Adopt updated CLSI breakpoints
- **Facilities should publicize the Antibiogram in ways that impact clinical operations (locally and regionally)**

Current Steps to Address Perceived Barriers

- Statewide Education to improve diffusion of best practices
- **OHA – providing M39A4 Quick Guide to all Oregon Labs**

Future Directions

- Feedback "best practices" to individual facilities & understand facility-level barriers in particular to slow adoption of M27-100 breakpoints – OHA to facilitate adoption as is feasible
- Create a "statewide" Antibiogram with potential for stratification using large datasets, e.g.
  - % susceptible *E. coli* and *Klebsiella* spp. to CTX.
  - % outpatient E.coli, Klebsiella, and Proteus susceptible to TMP-SMX
- Collect (new & improved) facility 2017 Antibiograms & re-survey to evaluate impact.

Special Thanks

- **Oregon Microbiology Laboratorians and IPs!!!**
  - **And special thanks/congrats to Sue!**
- **Denise Kirsch, MD**
- Alex Perry MD
- OHA DROP-CRE Group (current & former) including:
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  - Genevieve Buser MDCM, MSHP
  - Katherine Ellingson PhD
  - Dat Tran MD, MS
  - Zintars Beldavs MS
  - Etc.