Understanding the Antibiogram in the Long-Term Care Setting: What Is A 'Red Flag', How Much Resistance Is Too Much, and How Do I Address Resistance Trends Within My Institution?

Arizona Healthcare-Associated Infections (HAI) Advisory Committee Meeting
Created July 2015

Concern about increased risk of infection may account for the frequency of unnecessary antimicrobial use at long-term care facilities (LTCFs). Nationally, 25%–75% of antibiotic prescriptions for long- term care residents have been found to be inappropriate. Overuse of antimicrobials further selects for antimicrobial resistance, collateral colonization and subsequent infections with *Clostridium difficile* and other antibiotic-resistant pathogens, and increased adverse drug reactions.[1] Appropriate antibiotic use in LTCFs entails finding a middle road between their potent ability to reduce the mortality and morbidity of patients with infections and their potentially hazardous effects. Tools which assist clinicians in selecting an antibiotic targeted against the most likely pathogen(s) may improve outcomes through achieving early appropriate therapy which optimizes clinical outcomes, reduces overall antibiotic use, improves patient safety, and decreases healthcare costs. Optimizing outcomes while minimizing adverse consequences of antibiotic therapy is the hallmark of effective antimicrobial stewardship. Once a bacterial infection is highly suspected then the choice of antimicrobial is largely identified through the antibiogram which matches susceptibility results for specific bacterial species against first-line drugs proven to be effective against a susceptible isolate. The association of certain pathogens with a type of infection is well-documented and empiric therapy should not be delayed while awaiting final culture and susceptibility (C&S) results.

The institution's cumulative annual antibiogram, or annual summary of susceptibility rates, provides clinically and epidemiologically useful recommendations for selection of initial empiric antimicrobial therapy through analysis and presentation of data on antimicrobial susceptibility and susceptibility trends within the institution. Simply, an antibiogram consists of dozens of "one pathogen-one drug" single point matches (Table 1). In the example for 215 isolates of *E. coli* recovered in urine during calendar year 2013, the susceptibilities of several antibiotics is provided. Three of these agents are administered parenterally, and selection of an oral antibiotic must be evaluated based on the susceptibilities provided for that institution. In this case, oral amoxicillin may not be optimal (i.e., only 42% of isolates tested demonstrated susceptibility to ampicillin) whereas nitrofurantoin was associated with the highest susceptibility rate (96%). However, nitrofurantoin may not be safe in some elderly patients with renal insufficiency, and therefore other options may need to be prescribed for treatment of a symptomatic UTI.

Example Table 1. *Escherichia coli* – Urinary source, adults, Jan-Dec 2013 (n=215)

Antibiotic	Percent Susceptible
Ampicillin	42
Ceftriaxone	85
Ciprofloxacin	60
Gentamicin	95
Imipenem-cilastatin	94
Nitrofurantoin	96
Trimethoprim-sulfamethoxazole	77

An analysis of antibiograms over several years (also called a longitudinal analysis) establishes trends in bacterial resistance. Degradation of susceptibility over time may signify the loss of a previously effective antibiotic. Again, early appropriate therapy is more likely with the effective use of surveillance tools such as antibiograms.

The most frequent use of a cumulative antibiogram report is in guiding initial empirical antimicrobial therapy decisions for the management of infections in patients for whom microbiological test data to target treatment do not yet exist. The antibiogram has limitations. For example, the ongoing antimicrobial management of prolonged infections should rely on culture and susceptibility (C&S) test results. In addition, the cumulative antibiogram may not be useful for monitoring the emergence of antimicrobial resistance during therapy, guiding therapy choices for recurrent or relapsed infections, or identifying isolates with specific antimicrobial resistance patterns (also referred to as "resistance phenotypes"). This is because the cumulative annual antibiogram is based on first unique clinical isolate. Exposure to antibiotics may select for resistant bacterial subpopulations and these subsequent isolates are not counted. Antibiogram development is also limited by the diversity of calculation methods and the inherent tendency to over-estimate antimicrobial resistance in normally healthy individuals who are antibiotic naive while under-estimating resistance in the seriously ill patient with significant recent history of antibiotic exposure.

A word of advice to readers of this article: while it is not the intention of this document to describe the specific recommendations involved in preparation of antibiograms, the end-user should consult additional readings on the topic of selecting antibiotics, and clinicians should work with their microbiologists on addressing specific critical issues of susceptibility testing, data interpretation, and antibiogram presentation.

What Do The Numbers Mean?

A sample antibiogram is provided below (Table 2). The structure is fairly common in acute care hospitals for *Staphylococcus aureus* but should include patient location. In the long-term care (LTC) setting, such breakouts may not be available. The number of isolates may also be much lower. However, similar to hospitals, patients in LTCs have diverse demographics and bacterial resistance is commonly imported from the acute care setting. Horizontal spread may then further increase the incidence of healthcare-associated and drug-resistant infections. For example, "location" could be wings of a ward, a grouping of patients chronically catheterized, or a special unit such as spinal cord injury or stroke. The format of an antibiogram for *S. aureus* in a LTC setting is often a single line, but segmenting antibiogram data by location and/or special patient demographics could provide additional direction to clinicians.

Example Table 2. *Staphylococcus aureus* by patient location, Jan-Dec 2014

Organism	Location [a]	No. Isolates	% Susceptible (%S)		
			CEF [b]	OXA [c]	VAN [d]
Staphylococcus aureus	OP	551	67	67	100
	IP	274	53	53	100
	ICU	183	42	42	100

a OP= outpatient; IP= inpatient; ICU= intensive care unit. Importantly, outpatient could include isolates from emergency department, outpatient clinics, or physician offices (reference laboratory). b CEF= cefazolin; also includes cephalexin and cephapirin. c OXA= oxacillin; also includes methicillin and nafcillin. d VAN= vancomycin

Therapy is empiric and susceptibility results are not known at the onset of a new infection. In the "limited antibiogram" represented by Table 2 (only three drugs represented in this example), 67% of all outpatient *S. aureus* isolates were susceptible to CEF and OXA and would represent methicillin-susceptible *S. aureus*, or MSSA. However, 33% of all outpatient *S. aureus* were represented by methicillin-resistance *S. aureus* (MRSA). For empiric therapy, drugs such as cefazolin and nafcillin are reasonable parenteral options if MSSA is suspected whereas only vancomycin is an option for MRSA. But an antibiogram which includes patient location may reveal that MRSA is exceedingly unusual in a specific area of the LTCF occupied by the infected patient in which case vancomycin may be unnecessary for a mild new skin infection. Once MSSA or MRSA is

identified from an adequately obtained clinical specimen, therapy should be reassessed and targeted according to antibiotic susceptibility results (i.e., pathogen-directed therapy). Vancomycin should be considered for empiric parenteral therapy in a seriously ill patient population at risk for MRSA, such as a recent history of MRSA infection or known colonization, but a switch to cefazolin or nafcillin is preferred if the isolate tests as MSSA, and for mild infections appropriate oral therapy can be instituted for either MRSA or MSSA (example not shown). The health department should be notified if a vancomycin-resistant isolate of *S. aureus* is identified.

A more informative antibiogram in the LTC setting is provided in Table 3. As opposed to patient location, the antibiogram lists susceptibilities as a single location but further divides susceptibilities according to resistance pattern or "phenotype", e.g., MRSA versus MSSA, and total isolates of bacterial species. Such an architecture is more instructive to healthcare practitioners in selecting antibiotics. For example, if a prescriber has a high index of suspicion that a new infection is due to MRSA then oxacillin would not be selected. For oral therapy against MRSA, a tetracycline may be preferred over clindamycin of trimethoprim-sulfamethoxazole.

Example Table 3. *Staphylococcus aureus*, Jan – Dec 2014

Organism	No. isolates	% Susceptible [a]							
		CLI	DOX	ERY	OXA	PEN	RIF	SXT	VAN
TOTAL *S. aureus*	126	86	96	48	67	4	95	90	100
MSSA	84	91	99	52	100	5	98	95	100
MRSA	42	76	90	40	0	4	89	80	100

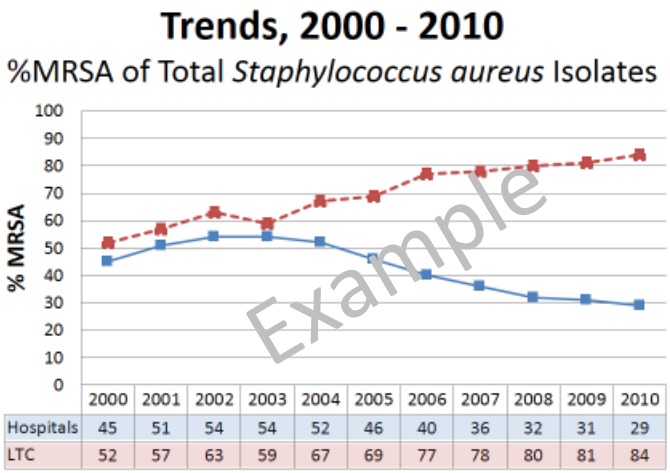
a CLI= clindamycin; DOX= doxycycline; ERY= erythromycin; OXA= oxacillin; PEN= penicillin; RIF= rifampin; SXT= trimethoprim/sulfamethoxazole; VAN= vancomycin

How Much Resistance Is Too Much?

There is no clear answer to this question. Assessing the status of resistance prevalence at an institution must consider several factors, including patient demographics, prescribing patterns of antibiotics in the community and nearby hospitals, colonization, hygiene, regional public health antibiograms, and horizontal and vertical transmission dynamics within the facility. Unfortunately, the U.S. has only recently moved towards defining bacterial resistance benchmarks. While these have been available in countries of the European Union they are starkly absent in the U.S. at this time. Probably the most practical way of assessing an excess frequency of antimicrobial resistance in a LTCF is to trend bacterial resistance for 3 to 5 of the most commonly encountered bacterial species recovered from clinical specimens and represented on the institution's antibiogram.

Another method is to define resistance patterns and trends within an institution or in a defined geographic area. For example, an LTCF could collect antibiograms of hospitals from which a high percentage of their patients are admitted. A combined antibiogram presents the weighted average of susceptibilities as a mix of community-acquired and hospital-acquired pathogens. For example, the MRSA trends in the graph below provide a regional or local benchmark of MRSA prevalence and trends. Therefore, trending resistance patterns may be helpful to assess the need for tighter controls on antibiotic use and improved infection prevention measures. Over several years, trending the prevalence of specific resistance patterns in a LTCF compared to local antibiograms may be a valuable indicator.

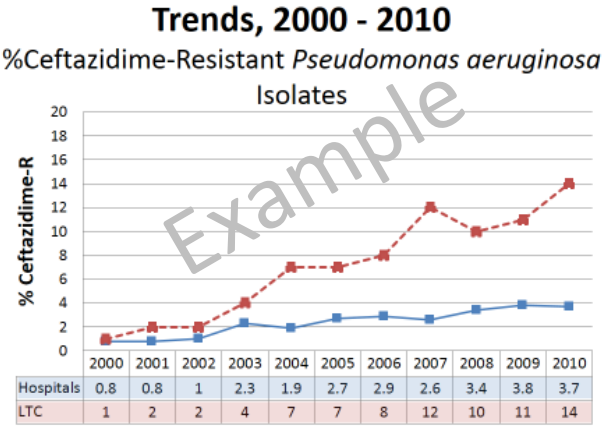
In this example, the LTC antibiogram was compared to a collection of 3 hospital antibiograms which were combined, and these acute care hospitals were within a 5 mile radius. The percent of methicillin resistance of all isolates of *S.aureus* were compared graphically. It is readily apparent that while MRSA was decreasing cumulatively in the hospital setting, the opposite was true in the LTCF. In fact, disparities became wider beginning in 2003-2004. It may be prudent to partner with nearby hospitals to assess measures for controlling MRSA as shared experiences could be beneficial to both institutional types.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Hospitals	45	51	54	54	52	46	40	36	32	31	29
LTC	52	57	63	59	67	69	77	78	80	81	84

Key patterns other than methicillin resistance in *S. aureus* should include fluoroquinolone resistance in *E. coli*, ESBL-producing *E. coli* and *K. pneumoniae,* carbapenem-resistant *K. pneumoniae*, and ceftazidime- and piperacillin-resistant *P.aeruginosa.*

In another example, ceftazidime-resistant *P. aeruginosa* increased in both settings, but rates rose more quickly in the LTC institution. It could be suggested that the source of these isolates could be investigated. For example, in the hospital setting ceftazidime resistance could be most prevalent in respiratory isolates whereas in the LTCF these isolates may constitute the majority of *P.aeruginosa* from the urinary tract. Regardless, the trend of resistance in the LTC setting is worrisome.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Hospitals	0.8	0.8	1	2.3	1.9	2.7	2.9	2.6	3.4	3.8	3.7
LTC	1	2	2	4	7	7	8	12	10	11	14

Trending and benchmarking in a geographic location, comparing antibiotic resistance between a single LTC and acute care hospitals in the common service area, may be useful although it has confounding factors which must be cautiously assessed. The single line represented by multiple hospitals (in blue) is an average and the range of susceptibilities amongst individual hospitals may be wide. Such analyses should always provide the range of susceptibilities amongst a cohort of hospitals. It was assumed, in these examples, that the resistance rates were similar between the hospitals.

How Do I Inform Healthcare Practitioners and Prescribers About Antimicrobial Resistance and Antibiotic Prescribing?

There is a dire need to educate prescribers on antibiotic resistance. Empiric antibiotic prescribing can be more accurate and appropriate using institutional antibiograms when combined with the patient's recent history of infections and antibiotic exposure. Assessment of an institution's resistance rates can identify underlying deficits in hygiene, room cleaning, isolation procedures, and admission of high-risk patients with a history of antibiotic resistance infections. Overuse of antibiotics applies selective pressure to resistant pathogens already present in the environment and establishes a background exposure which facilitates their selection and potential spread. The manner in which education on antibiograms and bacterial resistance is planned and executed must be multifaceted. Consideration should be given to a combination of measures and strategies, including institutional campaigns, educational meetings, feedback and reinforcement, written reminders, computer alerts, innovations in technology, financial incentives, and revision of professional roles and policies. While educating prescribers on the use of antibiograms in an effort to prescribe antibiotics sparingly and

appropriately is necessary, these efforts underscore the need to differentiate viral from bacterial infection, asymptomatic bacteriuria from symptomatic UTI, and appreciation of forces which drive antimicrobial resistance.

What Is The Role of Various Healthcare Personnel? A Case Study

Patient A is a 79yo female resident of LTCF B for the last 2 months. She has been active at the LTCF. She is allergic to sulfa. All labs have been normal, and serum creatinine is 0.7 mg/dL. Upon awakening, she complains of suprapubic discomfort. Her vitals: Temp 96.9F, BP 160/82, HR 77, RR 16. She appears anxious in mild discomfort. Upon urination, she complains of dysuria and foul-smelling urine which is cloudy. The nurse obtains a mid-void urine sample and places it on ice and then calls the attending physician. The prescriber orders Keflex 250 milligram TID x 10 days with an IM injection of ceftriaxone 500mg IM x 1 now. The nurse informs the physician that the LTCF had 149 urine culture results in the past 12 months and the antibiogram shows that *E.coli shows* a 20% susceptibility rate to cefazolin, ceftriaxone, and cephalexin. The nurse asks whether the ceftriaxone IM and Keflex prescription could be changed to another agent based on the antibiogram results. The nurse states that susceptibilities for the institution's urinary *E. coli* isolates were: nitrofurantoin 92%, ciprofloxacin 88%, and trimeth/sulfa 86%. The nurse also notes that the patient is allergic to sulfa drugs. Other urinary pathogens were minor, the second most prevalent pathogen as *K. pneumoniae* with 12 isolates. The prescriber changes the antibiotic orders to nitrofurantoin 50mg BID x 7 days and asks that a urine C&S be sent to the lab.

Summary

Changing antibiotic prescribing and instituting effective antimicrobial stewardship measures is a challenge of formidable complexity.[2] Many social, cultural, and behavioral determinants must be considered so that the measures or strategies undertaken to improve antibiotic use need to be equally diverse. The excessive and indiscriminate use of these so-called miracle drugs has led to the emergence and dissemination of resistant organisms that endanger their efficacy. Antimicrobial resistance has a significant adverse impact on clinical outcomes and leads to higher costs due to consumption of health-care resources. Resources which can improve the accuracy of empiric antibiotic therapy is consistent with exercising prudent antimicrobial stewardship. The Healthcare-Associated Infections Program at the Arizona State Health Department website provides several resources to improve stewardship practices. Included is a self-learning program on the cumulative annual antibiogram.

Healthcare-Associated Infections (HAI) Antimicrobial Stewardship Subcommittee
http://www.azdhs.gov/phs/oids/hai/advisory-committee/antimicrobial-stewardship.htm

HAI Program
www.preventHAIaz.gov

Questions or comments? Please contact
HAIProgram@azdhs.gov

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