ANTIBIOGRAM TOOLKIT

Office of Healthcare-Associated Infections

ARIZONA DEPARTMENT OF HEALTH SERVICES

Updated 10/09/2023

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A Note to Our Readers

The objectives of the Arizona Department of Health Services (ADHS) Antimicrobial Stewardship (AS) Subcommittee are directed at education, presentation, and identification of resources for clinicians to create toolkits of strategies that will assist clinicians with understanding, implementing, measuring, and maintaining antimicrobial stewardship programs. The AS Subcommittee is a multidisciplinary committee representing various healthcare disciplines working to define and provide guidance for establishing and maintaining antimicrobial stewardship programs within a variety of healthcare settings across Arizona. Their work was guided by the best available evidence at the time although the subject matter encompassed over one hundred references. Accordingly, the Subcommittee selectively used examples from the published literature to provide guidance and evidenced-based criteria regarding optimizing use of the annual cumulative antibiogram and applications for antimicrobial stewardship programs.

The Antibiogram Toolkit reflects consensus on criteria which the Healthcare-Associated Infections (HAI) Advisory Committee deems to represent best practices in the interpretation and utilization of antibiogram data. The Toolkit was first developed by the AS Subcommittee of the HAI Advisory Committee in 2012–2013. This document reflects updates based on guidance provided by the Clinical and Laboratory Standards Institute (CLSI) 2022 M39-A5 consensus document entitled “Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data”. This Toolkit is intended to be used in conjunction with approved CLSI documents such as M39 and M100 and additional literature regarding microbial resistance.

Introduction

The Cumulative Antibiogram Susceptibility Data Report

The Clinical and Laboratory Standards Institute (CLSI) has published a series of guidelines to assist in the preparation of annual cumulative antimicrobial susceptibility test data, which are known as antibiograms. CLSI's 2022 M39 5th edition consensus document entitled "Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data" provides guidance to clinical laboratories and antimicrobial stewards in the collection of data for preparation of a single institution's annual cumulative antibiogram.[1] The guideline emphasizes presenting of antimicrobial susceptibility data in an accurate, reliable, consistent, transparent, and timely manner, distributing the antibiogram to clinicians and others who need access to the information, and presenting results in a manner that facilitates comparisons between healthcare institutions, public health laboratories, and other surveillance programs. The most frequent use of a cumulative antibiogram report is to guide initial empiric antimicrobial therapy decisions for the management of infections in patients for whom definitive identification and susceptibility are unavailable for the infecting pathogen(s). Empiric antimicrobial choice is guided by many considerations, but local antimicrobial susceptibility patterns of commonly isolated bacteria are paramount among them. Since antimicrobial resistance has increased steadily in many institutions, and because resistance rates vary by geographic location and patient demographics, readily available and up-to-date cumulative antimicrobial susceptibility data is crucial. These data are essential for monitoring emerging trends in resistance at the local level. In addition to informing clinical decision-making, antibiograms are used to evaluate infection prevention interventions and multidrug-resistant organism containment strategies to optimize microbiology susceptibility testing and reporting methods, and to guide Pharmacy and Therapeutics Committee formulary decisions. Other applications for the analysis of susceptibility test data may include methods discussed in the CLSI M39-A5 manual, such as identifying isolates with specific antimicrobial resistance phenotypes and resistance markers.

The most recent M39 guidance document expands the scope of the antibiogram to include several helpful sections: long-term care, multifacility antibiograms, incorporation of phenotypic and genotypic results, differentiation of community-onset versus hospital-onset infections, information systems design, communicating and distributing the antibiogram, antimicrobial stewardship programs, and preparation of multifacility reports and publications for submission to peer-reviewed journals.

Cumulative antibiogram reports have significant limitations. These should be noted as part of any educational program concerning antibiogram use. At the same time, these limitations provide opportunities for innovation and discussion with clinicians and

infectious diseases physicians and pharmacists on how to incorporate this data into future antibiogram editions. For example, a hospital antibiogram may be less valuable when selecting empiric therapy for a patient with a recurrent or persistent infection because the antibiogram uses the first isolate mean susceptibilities. Patients who have significant recent antibiotic exposure may have increased risk for infection due to resistant pathogens; such patients may harbor bacterial isolates that are resistant to empiric therapy suggested by the antibiogram. In these cases, empiric therapy suppression of the susceptible pathogen may also create an environment for the resistant pathogen (already present) to multiply and establish a new infection, perhaps in other patients. Also, antibiograms provide mean susceptibility data derived from large patient populations but do not reveal additional information concerning microbial isolates, such as time from admission to index culture. This is frequently used by the National Healthcare Safety Network (NHSN) to determine whether the infection (and subsequently identified pathogens) represents a community-acquired versus hospital-acquired infection. Again, specific information on a patient's recent exposure to antibiotic cannot be discerned from the antibiogram.

Antibiograms reveal qualitative measures of susceptibility (i.e., whether a pathogen is resistant or susceptible) but do not provide quantitative data, such as minimum inhibitory concentrations (MICs), and thereby cannot detect significant elevations in MICs even within a susceptible range, which might signal acquired mechanisms of resistance (e.g., “MIC creep”). A further limitation of antibiograms is the capture of only single-drug single-isolate susceptibility which does not provide data on the proportion of other antibiotics that are also active (i.e., cross-resistance to multiple antibiotics). Therefore, the antibiogram should be viewed as a compilation of data which provides both opportunities and challenges. By its inherent nature, antibiograms provide information which is valuable and vast but at the same time limited and easily misinterpreted. Antibiograms represent qualitative data on selected pathogen(s) and antibiotic susceptibility based on commonly used agents (based on product availability or formulary status). Therefore, an active and continuous educational program through an antimicrobial stewardship program is necessary.

This Antibiogram Toolkit is supported by ADHS to provide additional direction for clinicians involved in constructing the cumulative antibiogram susceptibility test report and educating their fellow clinicians. The Toolkit hopefully enriches discussions on the challenges and opportunities with susceptibility data reporting. While some specific scenarios are provided herein, a multidisciplinary antimicrobial stewardship team should find ways to implement some of these projects and further analyze their own antibiogram data to produce more accurate and fruitful educational activities.

The ADHS Antibiogram Toolkit contains two chapters: Introduction to Routine Antibiograms (Chapter 1) and Specific Antibiogram Scenarios and Solutions (Chapter 2). Chapter 2 includes several topics which should enhance the accuracy and clinical utility of the cumulative susceptibility report at an institution. These scenarios were selected by the authors from professional experience while involved with antimicrobial stewardship programs during their careers. However, many more examples can be identified from the literature. A short list of additional resources is supplied at the end of this Toolkit but falls short of the hundreds of examples published in the peer-reviewed literature. It is hoped that additional examples can be added in the future.

Chapter 1: Introduction to Routine Antibiograms

Chapter 1.1: Recommendations for Preparation of the Cumulative Antibiogram

The terminology has evolved over time. 'Cumulative antimicrobial susceptibility test data report', or cumulative antibiogram, refers to the report generated (usually from a single healthcare facility) by analysis of antimicrobial susceptibility test results from a defined period that reflects the percentage of isolates of a given species or organism group that is susceptible to each of the antimicrobial agents tested, This includes antibiograms and other relevant analyses presented in tabular, graphic, or other types of formats. This report will be referred to as the 'Antibiogram' in this Toolkit.

Interpretation of minimal inhibitory concentration (MIC) or disk diffusion zone diameter values generated from antimicrobial susceptibility testing (AST) necessitates applying breakpoints specific for antimicrobial agents and microbial species. It is highly recommended that laboratories remain updated with the most current breakpoint revisions. Such revisions may affect patient safety and influence antimicrobial resistance reporting, which may make trending of susceptibilities over time challenging.

There are **EIGHT key recommendations** which should be followed during construction of the routine cumulative antibiogram:

1. Analyze and present the cumulative antibiogram report **at least annually**; consider multiple analyses within a rolling 12-month period only when critical trends in resistance are detected and require timely education of prescribers.
2. Only **diagnostic** (not surveillance) **isolates** should be included.
3. Only **final, verified test results** should be included.
4. Eliminate duplicates by including only the **first isolate of a species, patient, and/or analysis period**, regardless of specimen source or antimicrobial susceptibility profile.
5. Include **only species** with testing data for **≥ 30 isolates**.
6. Include only **antimicrobial agents routinely tested** against the population of isolates analyzed; %S (i.e., the percentage of isolates that are susceptible) should be calculated from the results reported and those that may be suppressed on patient reports with selective reporting rules applied.
7. **Refrain from** including results for **supplemental antimicrobial agents** selectively tested on resistant isolates only (see Chapter 2.5).
8. Report **percent susceptible (%S)** and do not include percent intermediate (%I) or

percent susceptible-dose dependent (%SDD) in the statistic.

Additional recommendations that should be considered for routine antibiogram development:

- *Streptococcus pneumoniae* and penicillin, cefotaxime, ceftriaxone, and/or cefepime: list %S using both meningitis and non-meningitis breakpoints; for penicillin, also indicate %S using oral breakpoint.
- *Staphylococcus aureus:* list %S for all and the methicillin-resistant *Staphylococcus aureus* (MRSA) subset.
- If specific agents are tested on isolates from a select specimen source (e.g., nitrofurantoin for urine isolates), preparing an antibiogram for urine isolates only should be considered.

Chapter 1.2: Education of Prescribers: Interpreting and Applying Antibiogram Data

Strongly Suggested Activities:

- Use clinical decision support tools to communicate antibiogram data.
  - Insert the antibiogram into the physician order entry computer program with links from the antibiotic ordering screens. The electronic health record (EHR) provides a resource for communicating antibiogram data and for building message alerts using clinical decision support tools.
  - Develop surveys and other questionnaires which convey updates to antimicrobial resistance. Surveys may be helpful in identifying 'myths' regarding antimicrobial use, knowledge of spectrum of activity, and common resistant phenotypes observed in the institution.
  - Consider topics on antimicrobial use and resistance for medical grand rounds and/or other staff education opportunities.
- Organize antimicrobial stewardship orientations and presentations at hospital events, healthcare seminars, employee health fairs, and other opportunities.
- Provide hard copy antibiograms to prescribers, fellows, residents, and students.
  - Consider educational tools which focus on appropriate antimicrobial use for common infection types and use these to create orientation programs for prescribers recently granted admitting privileges, and pharmacists and nurses in satellite and critical areas of the hospital (such as intensive care units [ICU]).
  - Demonstrate how use of the institution's antibiogram could facilitate early active antimicrobial therapy, especially when clinical examples are revealed such as on medical rounds.
  - Develop an antimicrobial resistance resource document for nurses which incorporates goals and objectives of the institution's antimicrobial stewardship

program.

- Implement antimicrobial recommendations based on the antibiogram.
  - Develop an “Empiric Antibiotic List” based upon common pathogens and susceptibilities reported in the antibiogram.
    - Alternative agents for patients with antibiotic allergies or organ dysfunction should be included.
  - Institutional antimicrobial prescribing policies and disease-state algorithms can be added to the backside of the antibiogram page accounting for allergies and organ function.
- Facilitate antibiogram-related projects, such as studying specific resistance patterns and patient outcomes.
  - Antimicrobial resistance causes delays in instituting pathogen-directed therapy. While challenging to study, risk factor analysis can improve early empiric antimicrobial therapy in specific patient populations with high mortality rates, such as hematology and oncology, transplant, and ventilator-associated pneumonia.
- Advertise antibiogram and bacterial resistance resources.
  - Use physician newsletters, electronic message alerts and other clinical decision support tools that can communicate effectively and timely important changes in antimicrobial resistance or public health concerns.
  - Provide clinicians contact information of the infectious diseases (ID) pharmacist, ID stewardship physician, microbiology laboratory, and infection prevention.
  - Contact information can be included on the antibiogram (printed or electronic) and placed at nursing stations.
- Work with the Medical Executive Committee and other departments to evaluate negative clinical outcomes which could benefit from additional antimicrobial prescribing education or related projects.

DO NOT perform the following activities:

- Mailing copies of antibiograms to prescribers as the only mechanism of dissemination and education. These are invariably disregarded.
- Educating clinicians on the antibiogram only once each year when a new edition is approved.
- Forgetting opportunities to use tools to educate clinicians throughout the year on appropriate empiric antibiotic therapy, such as newsletters, surveys, physician newsletters, and Pharmacy and Therapeutics Committee (P&T) agenda items.
- Hiding contact information for essential resources, such as the ID Pharmacist, Drug Information, Microbiology Laboratory, and Infection Prevention.
- Avoiding evaluation of mortality or significant morbidity events which are infection-related and result from inappropriate antibiotic use.

Chapter 1.3: Antibiogram Pitfalls: Addressing Challenges in Susceptibility Testing and Reporting

There are many pitfalls to antibiograms. These can result in confusion and potential misinterpretation of susceptibility data. A well-developed and validated antibiogram still can be cumbersome for clinicians to interpret and to apply in clinical practice. The following situations could be considered as quality improvement projects during antibiogram development and subsequent educational plans. While not all examples below apply to every institution, they may provide valuable assistance to developers and educators of antibiogram reports as well as end-users.

Specific examples of each are provided in Chapter 2:

- Avoid reporting antimicrobial susceptibilities on the antibiogram using cascade algorithms regardless of formulary status or restrictions of use.
- Use the first isolate per patient in a reporting period and note the method used to eliminate duplicate isolates (e.g., manually, or by altering an automated default exclusivity date, such as 1 month).
- Segregate bacterial species into additional antibiogram analyses, such as patient demographics, specimen source, and hospital location when possible. Supplemental analyses provide clinicians with important data relative to specific infections and patients treated with antimicrobials.
    - ICU versus non-ICU
    - Adult versus pediatric (especially when there are different hospital locations for each)
    - Urinary tract isolates versus non-urinary (systemic) isolates
    - Hospital-onset versus community-onset infections and identified pathogens, especially pneumonias such as community-acquired versus hospital-onset versus ventilator-associated
    - Isolates from patients admitted from long-term care facilities, especially if these patients represent a significant proportion of your facility's inpatient population
    - Bloodstream isolates (mortality rates are higher in immunocompromised patients)
    - Bacterial isolates obtained from cystic fibrosis patients
    - Patients who frequently travel to other countries where multidrug-resistant pathogens or mechanisms of resistance are endemic and not commonly identified in the U.S.
- Develop a combination antibiogram against multidrug-resistant and problematic bacterial pathogens, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.
    - Empiric therapy of these pathogens, when suspected, may need combination therapy to provide broader coverage pending susceptibility results

- Exclude results obtained during surveillance studies (e.g., nasopharyngeal colonization studies for MRSA and rectal swabs for vancomycin-resistant *Enterococcus* [VRE]).
- Antibiograms provide data for a single reporting period and typically lack any resistance trending analyses. During reporting of antibiogram data, it may be helpful to provide trending of resistance and a statistical analysis of significance. Examples include:
  - % of *S. aureus* which is methicillin-resistant
  - Ceftazidime or cefepime resistance in *P. aeruginosa*
  - % Enterobacterales which are carbapenem-resistant (see definitions from the CDC)
  - Pathogens not normally included in the antibiogram but are medically important, such as *Clostridioides difficile*, should be communicated as part of the antibiogram in a separate section reserved for educational value (see Template examples section).
- 'Enhanced antibiograms' include regional, state, or national antibiogram reports which aggregate results from several separate institutional cumulative antibiograms.
  - While typically used for benchmarking, these antibiograms include demographics of hospitals and patients not common the institutional or single-center antibiogram.
  - Aggregated susceptibility data generated by combining multiple institutional antibiograms can include ranges, pooled arithmetic means, medians and/or interquartile ranges but should be interpreted with respect to patient demographics and medical services provided.
- Single-center antibiograms do not provide information on how antibiotic use can be epidemiologically linked to resistance rates.
  - Further study requires analysis of antibiotic use data in terms of defined daily doses (DDD), total duration of therapy (DOT) and total length of therapy (LOT) for all antibiotics used in an institution. Recently, some of these metrics have been included in the National Healthcare Safety Network (NHSN) reporting recommendations.
  - Trending resistance patterns with changes in antibiotic utilization can be correlated using time series analysis statistics.
- The availability of rapid diagnostic testing (RDT) and molecular genomics provides additional information of the use of these methods to identify genetic markers of antibiotic resistance and may guide clinicians towards earlier active antimicrobial therapy. To enhance the value of rapid tests for antimicrobial therapy decisions, a summary of these results from diagnostic (not surveillance) specimens or isolates can be added to antibiograms.

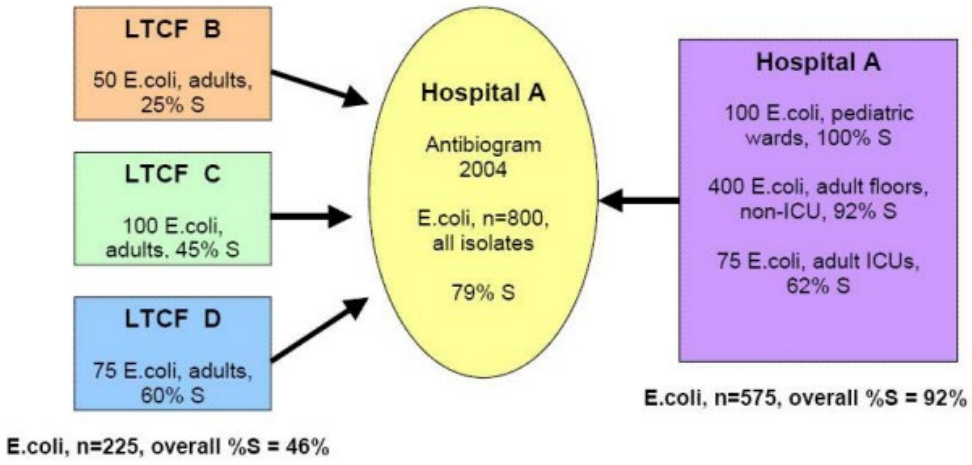
- Results from testing for antimicrobial resistance markers can be incorporated into the antibiogram as a separate line listing or combined with phenotypical AST results.
- Improving on the delay of susceptibility testing and reporting, which typically takes 48 to 72 hours, relies heavily on an effective notification system, real-time testing and reporting (as opposed to batch testing), and immediate action created by the antimicrobial stewardship program.
- For example, %S exceeds 90% for ceftriaxone and cefepime when resistance markers for *bla*$_{\text{CTX-M}}$ and carbapenemase genes are absent in *K. pneumoniae*.
- Results and stewardship actions taken based on RDT should be validated against final in vitro susceptibility results to assess predictive value (accuracy) of the presence and/or absence of the resistance markers.
- There are multiple limitations to incorporating antimicrobial resistance marker test results into the antibiogram. For example, the presence of an antibiotic resistance gene does not always correlate with expression of the resistance gene. Also, many other mechanisms of resistance can lead to resistance besides the genetic marker.

Chapter 2. Specific Antibiogram Scenarios and Solutions

The following examples expand on the "antibiogram pitfalls" listed in Chapter 1.3. These scenarios and associated solutions underpin the challenges of interpreting susceptibility data and applications in clinical practice.

Chapter 2.1: Contributions to Antibiotic Resistance: The Importance of Patient Demographics

In the antibiogram data presented below, an institution (Hospital A) shows a % susceptible value of 79% for *E. coli* (n=800 isolates) to Drug X. However, various sources of data contribute to this institution's susceptibility report. The number of isolates contributed by inpatients at Hospital A consists of pediatric inpatients and adult inpatients (both non-ICU and ICU). When the sources of inpatient isolates (n=575) are considered alone, the overall %S to Drug X is 92%, which contrasts sharply from the overall antibiogram results of 79% S. Where is the disparity?



During a pilot project, it is noted that *E. coli* isolates in patients from 3 local long-term care facilities (LTCF) exhibited high resistance rates to Drug X. The issue was discussed during ICU rounds during which 3 patients from LTCF B were discussed. All 3 patients were admitted for urosepsis and *E. coli* was isolated later from blood and urine cultures; all were resistant to Drug X.

The Antibiotic Stewardship Team (AST) approached the Microbiology laboratory to retrieve all test results from the current antibiogram year for patients admitted from these LTC facilities with positive cultures of *E. coli.* The laboratory confirmed that all 225 isolates contributed to the antibiogram with %S results of 46% to Drug X.

The high resistance rate of *E. coli* to Drug X was largely driven by patient isolates from these long-term care facilities, especially LTCF B and LTCF C, but not from other inpatients.

As a quality improvement project, the AST approached the Medical Directors of all 3 LTCFs and asked if they could assist the hospital in determining a root cause for resistance to Drug X. As a result, recommendations for use of Drug X and related agents from the same class were implemented at each facility. Further tracking of resistance in *E. coli* and use of alternative appropriate antibiotics were implemented. Results generated from the hospital's Microbiology Laboratory each quarter were tracked and, with cooperation from the medical and nursing staff and a consultant pharmacist for the LTCFs, susceptibilities gradually improved and were in line with Hospital A's ICU inpatients.

Since many patients in long-term care facilities transition back-and-forth between the hospital and the nursing home, it may be difficult to determine the precise moment or location of acquisition of resistant pathogens.

Chapter 2.2: "Values" Represent Single Pathogen-Drug Resistance ("Resistant Phenotypes")

Grid values for a specific antibiotic and pathogen species represent percent susceptibility (%S), or "bug-drug" susceptibility. However, there may be clinical situations in which drug combinations may be necessary, at least empirically and for brief periods pending susceptibility results. These situations usually involve the spectrum of drugs for which none are single drugs of choice (defined as any bug-drug combination with %S >90%).

A common pathogen in which this frequently occurs is hospital-acquired infection with *Pseudomonas aeruginosa*, especially bloodstream infection, pneumonia, and/or sepsis. In the antibiogram below, only the susceptibility of amikacin exceeds 90%. While aminoglycosides are not typically utilized as monotherapy agents for serious infections, the beta-lactams and ciprofloxacin would generally not be considered as reliably active in vitro as single agents either according to the %S values presented below, especially if a threshold of 90% S or greater defines "best therapy". In such cases, combination empiric therapy may provide the best chance that at least one of the two agents might test as susceptible.

One valuable calculation would be the construction of a cross-susceptibility table. It is generally agreed that beta-lactams in combination with tobramycin or amikacin or ciprofloxacin may satisfy the condition that one agent might demonstrate susceptibility. Arguments regarding penetration of drugs into pulmonary tissues is beyond the scope of this report.

Pathogen	# Isolates	% Susceptible (2012 Antibiogram, respiratory tract, ICU adults)			
		Piperacillin-tazobactam	Ciprofloxacin	Amikacin	Ceftazidime
Pseudomonas aeruginosa	100	84	70	92	78

In the table above, the susceptibilities of 100 isolates of *P. aeruginosa* are provided to four commonly used agents. This data is also reflected in the cross-susceptibility table below. Cross-susceptibility tables are not included in antibiograms, but the data can be valuable when this pathogen is responsible for severe infections, such as those encountered in the ICU. To construct such a table isolates which are susceptible to both agents must be determined (manually or with a computer program). The piperacillin-tazobactam/amikacin combination provides a higher chance that *P. aeruginosa* isolates test susceptible to BOTH agents (S-S, 76%) compared to the piperacillin-tazobactam/ciprofloxacin combination (S-S, 60%). Another view of this table is to determine the chance that AT LEAST one agent of the 2-drug combination will demonstrate susceptibility. This is calculated by adding the values for S-S, R-S, and S-R. For example, 100% of the isolates would be predicted to be susceptible to either piperacillin-tazobactam or amikacin if these agents are combined. The chances that at least one of the agents of the beta-lactam plus ciprofloxacin combination is susceptible to a group of 100 isolates is 94%.

Piperacillin-tazobactam S/R (in combination with either Drug #1 or Drug #2)							
Drug #1		S	R	Drug #2		S	R
Amikacin	S	76	16	Ciprofloxacin	S	60	10
	R	8	0		R	24	6

While combination susceptibilities do not need to be calculated for all pathogens, there are several problematic ones, including carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant *Enterobacterales*. The antibiogram data used to construct

combination antibiograms should be derived from the unit-specific antibiograms as opposed to the overall single-facility report, which would dilute and misrepresent the predictive values.

Chapter 2.3: Pediatric Antibiogram Considerations

Antimicrobial stewardship is important in helping avoid antibiotic overuse and this consideration is particularly important in the pediatric population. When comparing classes of medications by usage in the pediatric age group, children are prescribed antibiotics most commonly. It has been reported that approximately 20% of outpatient pediatric visits result in an antibiotic prescription, with over 40 million pediatric antibiotic prescriptions filled annually.[2] Parental insistence on a medicinal remedy resulting in unwarranted antibiotic prescriptions, as well as differing prescriber patterns regarding duration and choice of antibiotic, can lead to antibiotic resistance in this vulnerable population.

First-line antibiotic therapies and durations of therapy often vary between pediatric and adult groups, therefore development of a pediatric-specific antibiogram should be considered. Common infectious etiologies for specific types of infections also often vary between age groups. For example, community-acquired pneumonia in young children is often caused by *Streptococcus pneumoniae* and first-line therapies should be tailored to treat this pathogen. For adults, the atypical pathogen *Mycoplasma pneumoniae* is a common causative pathogen, so empiric coverage of the typical pathogens alone would be insufficient. Empiric antibiotic therapy choices would thus differ between the age groups.

In addition, because viral infections can cause symptoms that are like bacterial infections, diagnostic stewardship is an important part of pediatric antimicrobial stewardship and the development of a precise antibiogram. Utilizing laboratory and point-of-care tests to ascertain the presence of a treatable bacterial infection, rather than clinical assumption, would further reduce antibiotic overuse and therefore emerging resistance patterns. The American Academy of Pediatrics recommends that pediatric clinical pharmacists, infectious disease physicians, and/or other antimicrobial stewardship expert clinicians work together to guide their institution and clinics in formulating and establishing standardized approaches for pediatric antibiotic prescribing, including the development of a pediatric-specific antibiogram to assist clinicians with empiric therapy choices.[3]

Chapter 2.4: Detecting Excessive Influence of Repeat (Duplicate) Isolates on %S

The cumulative antibiogram should reflect “first isolate” only. This represents the first isolate of a particular species collected from one patient during the data reporting period (e.g., one year), regardless of body site or susceptibility profile (phenotype). This allows the antibiogram to be applied as a guide for selecting empiric antibiotic therapy. However, previous susceptibilities from past patient admissions should be considered when selecting empiric therapy although they should not be included in antibiograms.

Susceptibilities may be biased if more than one isolate is collected from a patient. Culturing practices become important in this case. Some clinicians may empirically select an antimicrobial agent against a likely pathogen without culturing the patient, such as with symptomatic urinary tract infections (UTIs) in otherwise healthy younger women. Unfortunately, repeated culturing of the same site is common practice with institutionalized patients and may not always be due to antibiotic failure or lack of anticipated clinical response. Therefore, a cumulative antibiogram report with many repeat isolates from a single patient will generally bias the results towards greater resistance and limit the selection of antibiotics.

Note: There may be instances in which the resistance phenotype may differ; for example, E. coli #1 from blood has a different phenotypic resistance pattern than E. coli #2 from urine. These may be counted as a single E. coli isolate as long as the more resistant strain is counted.

One mechanism to calculate the potential influence of repeat isolates is to divide the number of isolates of a particular species by the number of unique patients during the antibiogram reporting period from whom a specific bacterial pathogen (e.g., *E. coli*) is obtained. Ideally, the ratio should be 1.00. However, it is not uncommon to find ratios of 2 to 3, or more.

As the ratio increases, there is greater likelihood that the cumulative antibiogram report will have greater percent resistance than if only first isolates were counted. If the ratio far exceeds 1.00, it is recommended that the microbiology laboratory eliminate repeat isolates from the calculation prior to publishing the antibiogram. Also, many of the currently available software programs (e.g., Vitek, Microscan, etc) can be manually reset to a longer period for eliminating duplicate isolates, such as 3 months or longer if the default exclusion time is shorter.

An example is provided below to demonstrate the potential influence of duplicate isolates on the %R (i.e., the percentage of isolates that are resistant) of an antibiogram:

SCENARIO: You are examining the %R of *E.coli* from urinary sources in both inpatients and patients living in an attached spinal cord injury (SCI) unit. Ceftriaxone resistance is studied.					
Institutionalized Population	**# Urinary *E.coli* Isolates**	**# Unique Patients**	**Ratio: Isolate-to-Patient**	**%R, ceftriaxone (raw data)**	**%R, ceftriaxone (elimination of duplicate isolates)**
Hospital (400 adult beds)	2,000	1,500	1.3	4%	3%
SCI unit (100 adult beds)	1,000	200	5.0	27%	9%
EXPLANATION: Ceftriaxone may be an option more frequently, even in the SCI, once the isolate-to-patient ratio is corrected. This may allow sparing of carbapenems in patients not felt to be bacteremic. ESBLs may be more prevalent in populations with chronic indwelling Foley catheters and frequent antibiotic exposures.					

The opportunities to interact with microbiologists and clinicians are set in the following example:
Patient A is admitted for urosepsis. The admitting clinician enters orders for antibiotic therapy and orders urine culture with susceptibilities daily. Repeat cultures should be restricted to specific scenarios since the patient's urine will likely have a suppressive amount of antibiotic (if renally excreted) and cultures taken while on antibiotic therapy will often be negative if the original bacterial isolate is susceptible.

Chapter 2.5: Cascade Testing and Reporting May Introduce Bias

Suppression of results obtained during routine AST may be performed to encourage certain patterns of antimicrobial agent use. Suppression involves withholding (e.g., not releasing) certain antimicrobial susceptibility test results from the final report provided to clinical end users. Specific suppression rules are usually developed by the antimicrobial stewardship team together with the medical microbiology laboratory. "Selective reporting" and "cascade reporting" are two types of antimicrobial test result suppression strategies. Cascade reporting is a strategy of reporting antimicrobial susceptibility test results on an individual patient's isolate in which secondary (e.g., broader spectrum, more toxic, sometimes more costly) agents may only be reported if an organism is resistant to primary agents within a particular drug class. For example, if an *E. coli* isolate from urine is susceptible to all 10 antimicrobial agents tested, only a limited set of recommended first-line agents are reported (e.g., ampicillin, ciprofloxacin, gentamicin, nitrofurantoin, and trimethoprim-sulfamethoxazole), and the results of

broader-spectrum agents if susceptible are suppressed (e.g., ertapenem and cefepime). Cascade reporting should be differentiated from selective reporting, which is the strategy of reporting of certain antimicrobial susceptibility test results on an individual patient's isolate based on defined criteria, such as organism identification, body site, resistance mechanism, and overall susceptibility profile. For example, results for first- and second-generation cephalosporins are not reported on *Salmonella* spp. because of their ineffectiveness in treating patients with *Salmonella* infections. Aminoglycosides and first and second generation cephalosporins are not reported on isolates from cerebrospinal fluid (CSF) specimens because they do not readily cross the blood-brain barrier.

The practice of cascade reporting results in bias of the resistance pattern to second-line and other antibiotics. Susceptibility results are frequently available for antibiotic agents included in FDA-approved automated panels (e.g., Vitek, Microscan, Phoenix, others). The antimicrobial stewardship team should discuss reporting susceptibilities of restricted drugs on the antibiogram in certain situations, such as when problem pathogens, such as CRE or very drug-resistant *P. aeruginosa* or *Acinetobacter* species, is increasing. However, since reporting would be specific to resistant bacterial isolates, the chances of multi-drug resistance inherently skews towards greater %R.

In the example below, susceptibility results are provided for 4 drugs tested against isolates of *Streptococcus pneumoniae*. In this example, levofloxacin susceptibility is reported only for isolates testing resistant to ceftriaxone, although this antibiogram 'suggests' it was tested against all isolates. However, if susceptibility results for levofloxacin are tested and reported against all 100 isolates of *S. pneumoniae,* the results are notably different.

Pathogen	# Isolates	% Susceptible			
		Penicillin	Azithromycin	Ceftriaxone	Levofloxacin
Streptococcus pneumoniae **(respiratory)**	**100**	**87**	**63**	**91**	**90**

In the table above, the antibiogram user interprets this data as "90 of 100 isolates test susceptible to levofloxacin (10 isolates [10%]) test resistant)." A 10% resistance rate for levofloxacin for *S. pneumoniae* would be very unexpected and should alert clinicians to a bias in testing and/or reporting.

In the above case it is discovered that the microbiology laboratory tests all 100 *S. pneumoniae* isolates to all the antimicrobials listed (penicillin, azithromycin, and ceftriaxone), but reports levofloxacin results only when the isolate is multidrug-resistant (MDR), such as resistant to penicillin and azithromycin. The denominator is no longer

100 isolates as in the table above but rather it is only 10. A simple investigation reveals that of the 10 isolates of *S. pneumoniae* tested against levofloxacin only 1 is resistant. While this is still 10%, this refers only to MDR isolates. When the microbiologist accesses levofloxacin data for all 100 isolates it is found that only 1 isolate tested resistant, and clearly that isolate was a MDR *S. pneumoniae.*

There are two potential solutions in accurately reporting such data:

- Solution #1: For the antibiogram, insert a note at the bottom of the table warning clinicians that only a limited number of isolate susceptibilities were reported against levofloxacin, such as: "Levofloxacin is tested and reported for *S. pneumoniae* isolates which are resistant to both penicillin and azithromycin; there were 10 such isolates in this antibiogram period with one testing resistant." Inclusion of levofloxacin should be highlighted within the table using an asterisk.
- Solution #2: Only report antimicrobial susceptibilities for all the same 100 isolates as with all the antimicrobials listed in the table. In this case, the antibiogram would appear as shown below. Only 1 isolate was resistant to levofloxacin of the 100 tested.

Pathogen	# Isolates	% Susceptible			
		Penicillin	Azithromycin	Ceftriaxone	Levofloxacin
Streptococcus pneumoniae **(respiratory)**	**100**	**87**	**63**	**91**	**99**

Reporting should be performed for the same antimicrobials against the same isolates so that accurate antibiogram susceptibilities are unbiased and can accurately be reported. Otherwise, footnotes should be prominently displayed to account for alternative strategies of reporting, and these should be clearly stated.

Chapter 2.6: Presenting Multi-Institutional Cumulative Antibiogram Data

While constructing the antibiogram from a single institution is a key activity of an antimicrobial stewardship program, there may be opportunities to construct an antibiogram representing multiple institutions within a healthcare system. These may provide both local and single health-system susceptibilities for common bacteria.

There have been many difficulties associated with compiling such antibiograms, including quality assurance and data verification of susceptibility results. The greatest challenge has been to 'risk-stratify' the reporting institutions because multi-institutional antibiograms represent a large array of hospital services. For example, antibiogram data from a large academic hospital which performs solid organ and hematopoietic stem cell transplants might be expected to have higher resistance rates compared to a small

community non-teaching hospital or one which provides obstetric/gynecology services. Inclusion of isolates from patients in long-term care settings should remain separate.

While many examples are provided in the literature, a multi-institutional antibiogram should contain the following elements and efforts should ensure that certain data can be acquired from each participating hospital:

- Antibiotic susceptibility testing methodology, including disk diffusion, MIC gradient strips, and automated hardware devices and software versions.
- MIC breakpoints used to interpret S, I, and R.
- Representation of key pathogens of interest between hospitals, such as *E. coli*, *K. pneumoniae*, *Enterobacter spp*., *P. aeruginosa*, *S. aureus* (including MRSA), *S. pneumoniae*, and *Enterococcus spp*.
- Risk score for each institution, such as case-mix index or demographic categorization of each hospital which can be stated in a multi-facility antibiogram report.
- Displays for each bacterial species the interquartile ranges (IQR, for use with median %S values) or high-low ranges (for use with mean %S values).

Interquartile ranges are useful to identify outlier hospitals and to compare hospital susceptibilities, which provides more comparative data on the overall hospital cohort. For example, in the table below, considering all 2,888 *K. pneumoniae* isolates from 20 hospitals, 25% of hospitals fell below a %S rate of 75% while 75% of hospitals had %S rate of 95% or less. Institutions with more resistance (%S below the mean or median) deserve attention to analyze reasons accounting for higher resistance rates. Reporting inaccuracies should be identified and removed prior to discussing any action plan. For top performing institutions, these should be analyzed for efficiency of the antimicrobial stewardship program. These best practice centers can be targeted for duplicating antibiotic prescribing which might reduce resistance in other institutions.

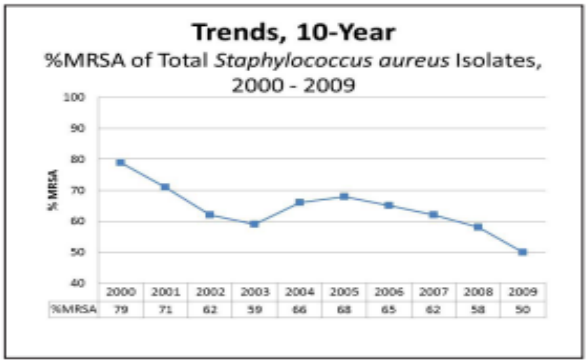
Pathogen	# Isolates	# Institutions Reporting	%S, ceftriaxone		Percentile of hospitals (%S ceftriaxone)				
			Pooled mean	Range (low, high)	10%	25%	50% (median)	75%	90%
Klebsiella pneumoniae	2,888	20	85	61, 94	n/a	75	90	95	n/a

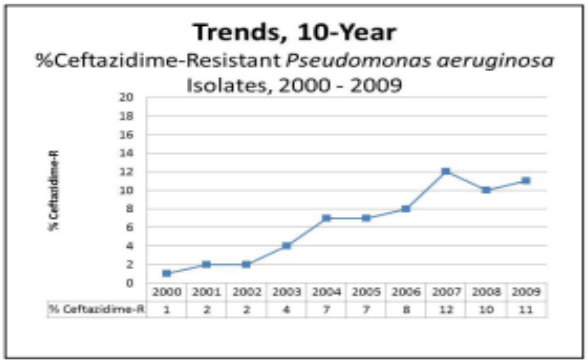
Chapter 2.7: Presenting Trends in Resistance

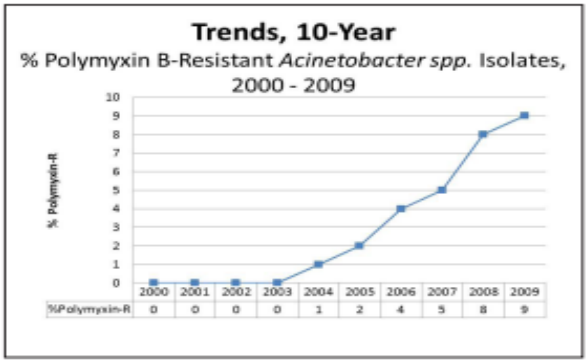
Antibiograms present susceptibility data over a discrete period, usually one calendar year. This creates a lack of perspective regarding trends in resistance rates over multiple years or the rise and decline of the number of pathogens of epidemiologic and medical importance.

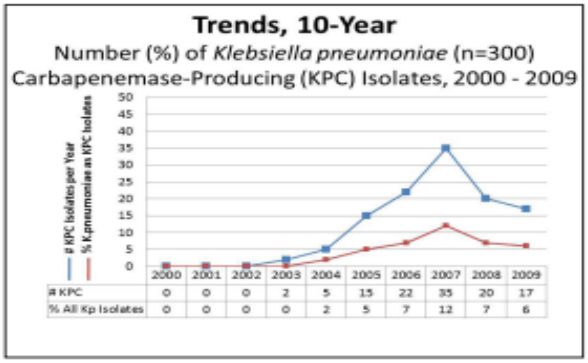
Education of resistance trends or pathogen distribution can be reserved for sections of the antibiogram report outside of the susceptibility data template, namely the margin or footnotes. Some helpful rules in presenting resistance trends follow:

- Due to space limitations, the number of graphs and tables should be minimized.
- Alternatively, these may be presented as part of an extended and ongoing educational program aimed at providing perspective in resistance through trending over 5-year (or greater) periods.
- Also, the rise of medically important pathogens which have not been observed in past years is valuable for observing infection prevention practices, impacts on patient safety (e.g., national patient safety goals), and trends which make selection of appropriate antibiotics challenging. An example can be carbapenem resistance in *Enterobacterales*, *Pseudomonas,* or *Acinetobacter*.
- Pathogens of epidemiologic importance should also be presented, such as incidence of *Clostridioides difficile* infection and isoniazid-R and rifampin-R strains of *Mycobacterium tuberculosis.* While not included in the antibiogram template, this information may be communicated in the margins or footnotes.









Chapter 2.8: Institutional Antibiograms and Antibiotic Use

In general, increased antimicrobial resistance is related to the density of use. The foundation for this correlation has been established by a plethora of literature and has become dogma. However, cumulative antibiogram reports do not provide details as to the density of antimicrobial use and the impact on resistance. Likewise, the emergence of new MDR pathogens cannot be easily linked to the hospital or local use of specific agents or antimicrobial classes. Similarly, antibiograms do not provide data on clinical or microbiologic outcomes although patients infected with resistant pathogens frequently receive inadequate empiric therapy and fail to achieve bacterial eradication and clinical cure. Using trends in institutional resistance, members of the antimicrobial stewardship program may study antibiotic use over time (e.g., days of therapy [DOT] or length of therapy [LOT]). The threshold of antimicrobial use above which increasing resistance is observed has not been quantified. Therefore, trending resistance with antimicrobial use can provide valuable information. Conversely, there is little data to guide clinicians on how resistance trends can be reversed once they become established or endemic. There are several limitations to consider which highlight the complexity between antimicrobial use and microorganism resistance even when both are studied over time and attempts are made to correlate these parameters.

- Resistance and high antibiotic density may not occur in parallel even when the same medical units are compared across institutions.
- Changes must be studied over a period of several years; a change in resistance should not be assumed to result from changes in antibiotic pressures. More sophisticated methods should be employed, such as interrupted time-series analyses.
- Outside influences, such as imported resistance, is not accounted for in an antibiogram without tedious investigation.
- Antibiograms do not assess the changes in MICs (essential data) since S, I, and R (categorical data) are determined by breakpoints. Migration of MICs towards the breakpoint may be a signal of resistance, but not always and can be multifactorial.
- Hospital-wide antibiogram reports do not provide detailed analysis of specialized areas of the hospital or patient subpopulations. Therefore, emerging pockets of resistance may be missed. The overall pathogen-drug susceptibility values may dilute the effect of an emerging resistance problem in a specific location or in specific patient demographics.
- Antibiograms constructed using a “first isolate” method underestimates true resistance since susceptible isolates may be replaced by resistant ones during therapy. However, the “first isolate” rule holds to be the most practical for assessing empiric antibiotic use.

- Antibiograms do not capture multidrug-resistant organisms; only single pathogen-drug combinations are represented.
- Resistance may be curtailed through other measures, such as infection prevention and control measures, including improvements in hand hygiene and patient isolation and patient movement protocols, improved technology for insertion and maintenance of anatomic entry sites for medical devices, and updated room cleaning procedures.
- Changes in antibiotic policies frequently result in “squeezing the balloon” whereby restriction of one antibiotic class results in over-utilization of another. This collateral type of resistance should be considered.

The deficiencies of antibiograms based on their static nature of analysis over a short period should not discourage clinicians involved with ASP activities from further development of innovative and useful analyses of antimicrobial resistance.

Chapter 2.9: Assessing Resistance Trends Using Statistical Analysis Tools

Cumulative antibiogram data can be an invaluable tool to help track trends in resistance and can identify a need for further investigation and potential action. Additionally, comparisons can be made from within institutions or externally, such as from one institution compared to regional or national data. Generally, this is determined by evaluating changes in %S estimates between different data sets for specific organisms and antimicrobials. A crucial part of the analysis is determining the precision of a %S estimate and the significance of an increase or decrease in susceptibility over time.

A confidence interval table is used to provide an estimate of the precision of the observed susceptibilities which make up a trend. The sample sizes (number of isolates tested) influence the precision of the estimate and the subsequent confidence interval. The larger the sample size, the more precise the resulting observed change in %S. Conversely, the smaller the sample size, the less precision. This serves to validate the %S value and allows a data analyst to determine the confidence of the observed %S changes which represents the statistical significance of the susceptibility change.

One common statistical test utilized to determine statistically significant differences in resistance rates is the Chi-squared test. Generally, a *P* value of ≤ 0.05 suggests that the observed differences are not likely due to chance. Information about Chi-squared calculations can be found in biostatistics textbooks, however, the CLSI M39-A5 guidance contains appendices that may be used as guides to determine statistical significance.[1] Keep in mind, the tables provided in the CLSI guidance can only be used if the two populations being compared have a similar sample size.

While analysis of resistance trends can identify “statistically significant” differences, this

should not be confused with or imply a “clinically or epidemiologically important” difference. In the case of a large sample size of isolates, small changes in %S (e.g., a decrease from 63.2% to 61.9%) may be statistically significant but deemed unimportant when evaluating the clinical implications. Conversely, in the case of a small number of isolates, a change in %S from 80% to 55% may not be statistically significant, however it is clinically significant since it could alert the institution of the potential emergence of resistance. In both cases, the institution should determine whether the results are due to true changes in susceptibility or confounded by other factors, including changes in the patient population, sample collection practices, laboratory testing, or data reporting.

Regardless of the method used, critical analysis of changes in antimicrobial resistance patterns using antibiogram data can help identify areas of improvement related to antimicrobial prescribing and provide a focus for stewardship activities.

For example, in the 3-year trend shown in the table below, %S data can be compared between 2004 and 2005, 2005 and 2006, and 2004 and 2006 for inpatients and outpatients. Only inpatient (IP) *E. coli* isolate susceptibilities compared between 2004 and 2006 achieve a statistically significant *P* value of ≤0.05 for a sample size of 200 and an initial susceptibility of 70% in 2004. Therefore, a decrease in susceptibility from 70% to 54% is statistically significant, while a change from 70% (2004) to 65% (2005) or a change from 65% (2005) to 54% (2006) are not statistically significant.

None of the trending comparisons for outpatient (OP) isolates of *E. coli* are statistically significant since the minimum %S value does not achieve a value of 76% or lower for 2005 or 2006 compared to 2004.

Confidence Intervals and Statistical Significance with *E. coli* versus Drug A

	2004		2005		2006		Statistical Thresholds (compared to 2004)*	
	% S (drug A)	No. of Isolates	% S (drug A)	No. of Isolates	% S (drug A)	No. of Isolates	% S	Based on No. of Isolates
IP	70%	180	65%	207	54%	197	60%	200
OP	80%	990	78%	1097	77%	1001	76%	1000

The number of isolates used to calculate the %S change threshold approximate 200 or 1,000. More complex calculations would be needed for final precision in comparing resistance trends between periods

Chapter 2.10: The Antibiogram and Antimicrobial Stewardship Initiatives

Antibiograms have a variety of applications to clinical practice and data gathered can help identify potential opportunities for improved antimicrobial prescribing. While practitioner education plays a key role in improving antimicrobial prescribing practices, improvement can also be realized through targeted initiatives. This goal can be achieved through several different antimicrobial stewardship efforts which vary in complexity when considering implementation and impact.

The following are some select examples of how antibiogram data can be incorporated into stewardship-related activities:

Formulary Considerations:

- In response to increasing resistance trends, institutions may consider formulary changes using antibiogram data as a guide. Often these involve changing agents within the same medication class.
- A study by Empey et al. described a significant decrease in the observed rates of ceftazidime-resistant *Pseudomonas aeruginosa*, ceftazidime-resistant *Klebsiella pneumoniae,* and piperacillin-resistant *Pseudomonas aeruginosa* infections in patients after changing their cephalosporin formulary from ceftazidime and cefotaxime to cefepime.[4]

Antibiotic Restriction:

- Based on antibiogram susceptibility trends, use of specific agents or classes of agents may be restricted or controlled. Traditionally this has applied to broad-spectrum newer agents but could be individualized based on local antibiogram data. Prescribers should obtain prior approval from an infectious diseases consult service or the antimicrobial stewardship team to use the restricted agent.

Prospective Review:

- Similar to antimicrobial restriction, this intervention identifies targeted agents based on resistance trends and aims to decrease use. However, the method employed here utilizes a back-end approach which requires an infectious diseases expert to review all uses of the prescribed agent and make recommendations to decrease inappropriate use and impact resistance rates. These reviews usually occur within the first 72 hours of therapy initiation with specific antibiotics. There may be advantages to this approach in contrast to restrictive formularies.

Order Set/Clinical Pathway Design:

- Antibiogram data and trends can be incorporated into the design of hospital-specific order sets, guidelines, and clinical pathways to increase or decrease empiric use of specific agents based on susceptibility.
- Example: develop empiric antibiotic selections as part of a severe sepsis admission order set. Based on the hospital antibiogram, cefepime, piperacillin/tazobactam, and tobramycin may have consistently high susceptibilities to many Gram-negative organisms, including *Pseudomonas aeruginosa*. Comparatively, fluoroquinolones may demonstrate lower susceptibilities overall. Using this information, the order set could be built to include only cefepime and piperacillin/tazobactam as primary or first-line beta-lactam agents for Gram-negative organisms. While fluoroquinolones may be excluded from the selection list, tobramycin can be included as an adjunct agent. Again, empiric first-choice antibiotics will be based upon the most recent antibiogram (with attention to any negative trends), but a more focused examination of previous cultures obtained from patients may be warranted.

Computer-assisted decision support services (CDSS):

- Some institutions may be able to embed predefined pathways and restrictions on antimicrobial selection electronically as part of the ordering process.
- A study by Pestotnik et al found that a computer-assisted decision support program resulted in an overall reduction in antibiotic use of 22.8% over the study period. The institution's antibiogram remained stable over the 7-year period.[5]

It should be noted that these antimicrobial stewardship initiatives are established with the two-pronged goal of improving patient outcomes and improving susceptibility rates. While specific patient outcomes can be measured, it is more difficult to assess the true impact of a specific stewardship initiative on changes in rates of resistance, as these may not appear for months or years after an intervention is established and can be influenced by several factors. The over-reliance on a specific antibiotic is frequently met with increased resistance over time as a result of selection and these susceptibility trends should be closely followed.

Additional Resources

Agency for Healthcare Research and Quality. The Nursing Home Antibiogram Program Toolkit: How to Develop and Implement an Antibiogram Program. Page last reviewed November 2016. https://www.ahrq.gov/nhguide/toolkits/help-clinicians-choose-the-right-antibiotic/toolkit3-develop-implement-antibiogram-program.html.

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