



Update on Improving Antimicrobial Use and Research Developments in Antimicrobial Stewardship

Antimicrobial stewardship programs were the subject of one of four CE in the Mornings continuing education activities presented in early December 2009 at the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada. The presenter was Debra A. Goff, Pharm.D., Clinical Associate Professor, The Ohio State University College of Pharmacy, and Infectious Diseases Specialist, The Ohio State University Medical Center (OSUMC), Columbus, Ohio. Attendees submitted questions about the implementation of antimicrobial stewardship programs and emerging research related to antimicrobial stewardship that were later addressed by Dr. Goff in a live webinar conducted on February 25, 2010. Some of the highlights of the webinar pertaining to overcoming barriers to the implementation of antimicrobial stewardship programs were described in an e-newsletter released in March and available for download from the web portal for this educational initiative at www.ashpadvantage.com/cemornings. Highlights of the webinar pertaining to ways that pharmacists can improve the quality of antimicrobial therapy in their institutions and emerging research related to antimicrobial stewardship are described in this newsletter.

Antimicrobial stewardship is defined as an activity that includes the appropriate selection, dosing, route, and duration of antimicrobial therapy.¹ The goals of antimicrobial stewardship programs should be clear, and program requirements should be evidence-based.

“ Prescribing restrictions, clinical practice guidelines, pathways, protocols, and other antimicrobial stewardship program guidelines should be easy to follow. ”
—Debra A. Goff, Pharm.D., FCCP

Faculty

Debra A. Goff, Pharm.D., FCCP
Clinical Associate Professor
The Ohio State University College of Pharmacy
Infectious Diseases Specialist
The Ohio State University Medical Center
Columbus, Ohio

Staff Concerns

Stakeholders in antimicrobial stewardship programs are multidisciplinary and include infectious diseases (ID) physicians, residents, and fellows; emergency department physicians; surgeons; critical care physicians; hospitalists (i.e., physicians specializing in the delivery of comprehensive medical care to hospitalized patients); pharmacists; infection control practitioners, microbiologists, and nurses. These staff may have concerns about antimicrobial stewardship programs that need to be addressed to ensure program success. For example, extended or continuous infusions of certain antibiotics have been used as part of dose-optimization protocols (i.e., optimization of dosing based on individual patient characteristics, the causative organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics) to improve outcomes in patients with infections caused by pathogens with limited susceptibility to the antibiotic. Reductions in 14-day mortality and length of hospital stay were observed in a study comparing extended infusions (i.e., infusion for 4 hours every 8 hours) and intermittent infusions of piperacillin-tazobactam in critically-ill patients with *Pseudomonas aeruginosa* (*P. aeruginosa*) infections that were susceptible to the drug.²

The use of protocols for extended antibiotic infusions may raise concerns among nurses about inconvenience or potential problems such as limiting the patient's intravenous (i.v.) access for several hours. Table 1 lists a step-wise approach to overcoming objections to the implementation of i.v. antibiotic dose-optimization protocols in hospitals. Personnel who might object to such protocols should be identified, and the reasons for their objections should be addressed or defused through education about the potential benefits of using the protocol. As front-line providers of i.v. therapy at the bedside, nurses may view protocols as problematic because of concerns about drug incompatibilities in i.v. tubing (i.e., the need to interrupt administration of one drug because of incompatibility with another). The use of extended infusion antibiotic protocols may have important implications for pharmacists involved in i.v. admixture preparation because of the impact on logistics and workload and infusion pump-related issues. Staff education should be provided about the rationale for the protocol, using support from the published literature. Steps should be taken to prevent or minimize problems associated with protocols. For example, policies and procedures for i.v. admixture preparation could be revised to minimize pharmacist workload.

Table 1. Step-wise Approach to Overcoming Potential Objections to Implementation of Intravenous Antibiotic Dose-Optimization Protocols in Hospitals

- Identify personnel who might object to the protocol and reasons for objection
 - Nursing staff who administer i.v. therapy
 - Pharmacists involved in i.v. admixture preparation
- Provide staff education
 - Rationale for protocol
 - Support for protocol from published literature
- Address objections to protocol
- Resolve or minimize potential problems with protocol

i.v. = intravenous

Antibiogram Controversy

Monitoring antimicrobial resistance at the local (i.e., institutional) level is crucial to support clinical decision making because resistance patterns vary widely among institutions, even within the same geographic region. Antibiograms are reports prepared by the institutional microbiology laboratory that indicate the susceptibility of various pathogens to different antibiotics. These reports should be obtained annually for the institution to guide antibiotic use. Antibiograms with susceptibility data for pathogens isolated in specific locations within the institution where unique resistance patterns often develop (e.g., intensive care units with high rates of resistance among gram-negative pathogens) can be particularly helpful. Antibiograms with susceptibility data for pathogens associated with skin and skin structure infections in the emergency department at OSUMC have been developed in response to an increasing prevalence of community acquired methicillin-resistant *Staphylococcus aureus* (*S. aureus*).³

The handling of multiple isolates of a given bacterial species from an individual patient (referred to as repeat isolates) when preparing antibiograms is controversial. Using an isolate-based approach in which all isolates are considered equally can exaggerate resistance because this approach includes specimens cultured on multiple occasions from patients with complex clinical courses, long hospital stays, and infections caused by multidrug-resistant organisms. Therefore, a new consensus guideline from the Clinical and Laboratory Standards Institute (CLSI) recommends using one of three algorithms for handling repeat isolates (Table 2).⁴ Only the first isolate from a patient, episode, or phenotype is used instead of all isolates when these algorithms are used. Each patient contributes equally to the susceptibility estimates provided in antibiograms when a patient-based algorithm is used, and this information has direct clinical and epidemiologic relevance. When an episode-based algorithm is used, the focus is on an episode, although there is a lack of consensus about the definition of an episode. When a resistance phenotype-based algorithm is used, the focus is on bacterial strains defined by certain phenotypic characteristics (e.g., antimicrobial susceptibility pattern). The susceptibility data in antibiograms may vary depending on the choice among these algorithms (Table 2). In developing an antimicrobial stewardship program, it is important to determine and communicate to the microbiology laboratory which type of algorithm should be used to avoid repeat isolates in antibiogram preparation to provide the susceptibility information that is most useful to clinicians for clinical decision making.

Table 2. Estimated Susceptibility of *Staphylococcus aureus* Based on All Isolates and 3 Types of Algorithms for Handling Repeat Isolates in Antibiogram Preparation^{4,*}

Method	Estimated Susceptibility (% of isolates)
All isolates	49
Patient-based algorithm (using the first isolate for each patient)	55
Episode based algorithm (using first isolate for each episode with an interval of up to 30 days between consecutive isolates)	53
Resistance phenotype-based algorithm (using the first isolate per phenotype, or bacterial strain defined by certain phenotypic characteristics, such as antimicrobial susceptibility pattern)	54

*Estimates are based on data from the same dataset

New Microbiology Laboratory Developments

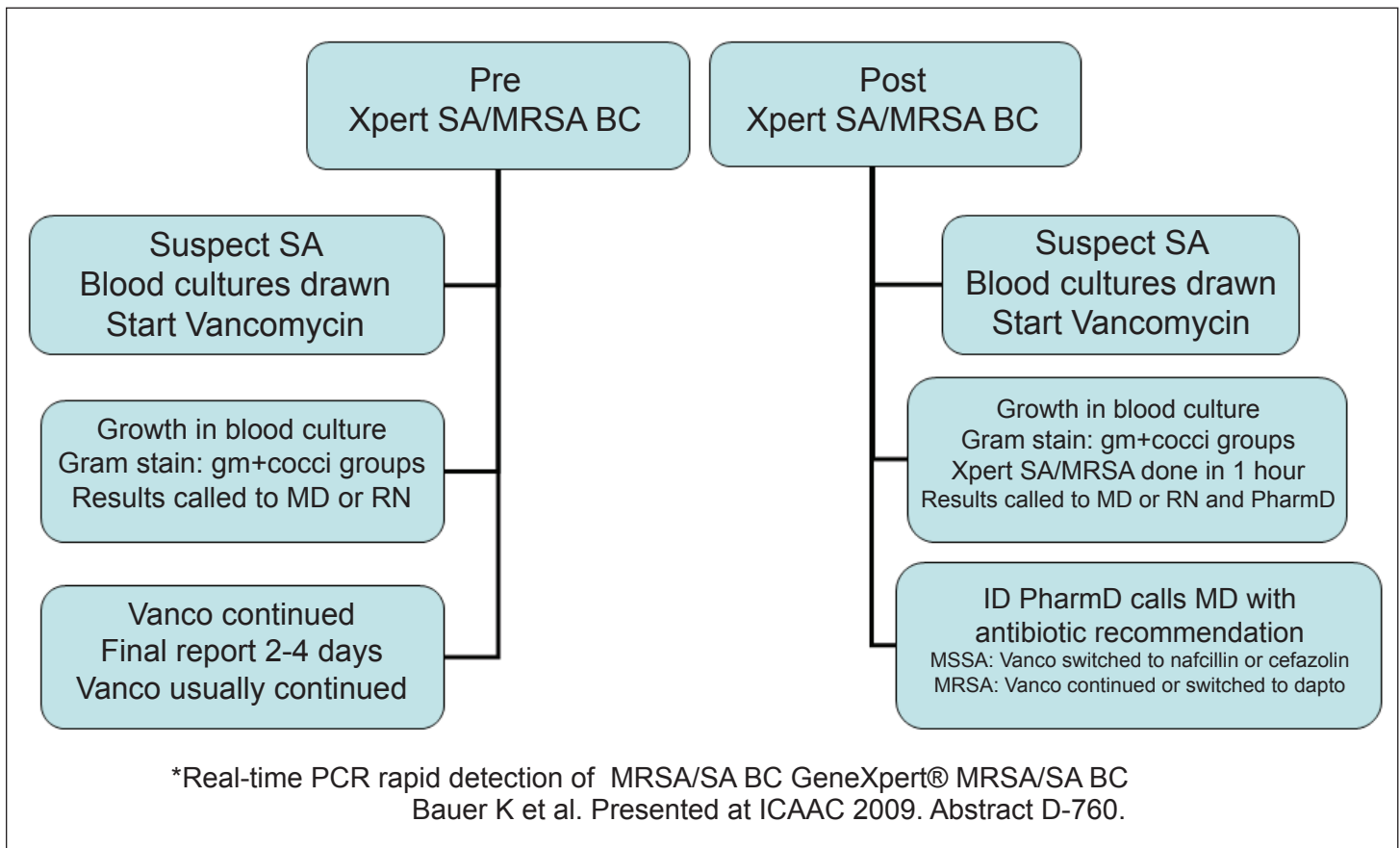
The minimum inhibitory concentration (MIC) breakpoints for susceptibility of pathogens to antibiotics are established by CLSI in its Performance Standards for Antimicrobial Susceptibility Testing, and these breakpoints are subject to change. For example, in the near future, CLSI will adjust the MIC breakpoint for susceptibility of *P. aeruginosa* to piperacillin-tazobactam based on published pharmacokinetic and pharmacodynamic data.⁵ Currently *P. aeruginosa* is reported as susceptible to piperacillin-tazobactam if the MIC is ≤ 64 mg/L, but this organism will be considered resistant when the MIC is equal to 64 mg/L in the future.

Practitioners involved in antimicrobial stewardship programs should evaluate the *P. aeruginosa* isolates in their institution to ascertain the percentage with a piperacillin-tazobactam MIC of 64 mg/L. If the percentage is high, the change in MIC breakpoint represents an opportunity to modify prescribing of antimicrobial therapy to overcome resistance in many patients. At OSUMC, if the piperacillin-tazobactam MIC = 64 mg/L for *P. aeruginosa* isolated from a patient, alternative therapy is recommended by the ASP pharmacist.

New Assay

The introduction of new assays and technology for use in the microbiology laboratory can have a large impact on antimicrobial clinical decision making and patient outcomes. A blood culture rapid polymerase chain reaction (PCR) assay for the detection of *S. aureus* bacteremia and differentiation between methicillin-resistant and methicillin-susceptible strains is one such development. At OSUMC, the introduction of this assay shortened the time to optimal antimicrobial therapy (OAT) after blood cultures were drawn in patients with methicillin-susceptible *S. aureus* bacteremia.⁶ In patients with suspected *S. aureus* infections, blood samples are obtained and vancomycin is started empirically while awaiting culture results. Before the rapid PCR assay became available, most patients with infections caused by methicillin-susceptible strains continued to receive empiric vancomycin unnecessarily (Figure 1). The rapid differentiation between susceptible and resistant strains permitted an early switch from empiric vancomycin therapy to more appropriate antibiotic therapy in such patients. The average time to OAT in patients with methicillin-susceptible *S. aureus* bacteremia decreased from 3.6 days before the assay was introduced to 2 days with use of the assay. Decreases in length of stay and costs were associated with the shorter time to OAT.

Figure 1. The Ohio State University ASP Management of S. aureus Bacteremia Using a Rapid PCR Test^{6*}



Extend Your Knowledge

If you missed the CPE activity “Working Together: Implementing Interdisciplinary Antimicrobial Stewardship Programs” at the 2009 ASHP Midyear Clinical Meeting and Exhibition and want to learn more about this topic, a web-based activity based on the program is now available. One hour (0.1 CEUs) of continuing pharmacy education credit is offered. Find complete information for this topic, including a newsletter released March 2010, and other learning activities in the CE in the Mornings 2010 Educational Initiative at www.ashpadvantage.com/cemornings.

Planned and coordinated by ASHP Advantage.
 Supported by an educational grant from Merck.



References

1. Dellit TH, Owens RC, McGowan JE Jr et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007; 44:159–77.
2. Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillin-tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis*. 2007; 44:357-63.
3. Moran GJ, Krishnadasan A, Gorwitz RJ et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med*. 2006; 355:666-74.
4. Hindler JF, Stelling J. Analysis and presentation of cumulative antibiograms: a new consensus guideline from the Clinical and Laboratory Standards Institute. *Clin Infect Dis*. 2007; 44:867-73.
5. Clinical and Laboratory Standards Institute. M100-S20: performance standards for antimicrobial susceptibility testing. 20th informational supplement. Wayne, Pennsylvania: Clinical and Laboratory Standards Institute; Jan 2010.
6. Bauer K, West J, Taylor J et al. Clinical impact of the Cepheid GeneXpert blood culture rapid polymerase chain reaction for detection of *Staphylococcus aureus* or methicillin-resistant *Staphylococcus aureus*. Presented at the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, CA: September 13, 2009. Abstract D-760.