CE IN THE MORNINGS
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Ask the Expert: Antimicrobial Stewardship in Health Systems

Initiative Faculty

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A continuing pharmacy education (CE) activity entitled *Antimicrobial Stewardship in Health Systems: Opportunities for the Multidisciplinary Team to Improve Patient Care* was presented as one of four CE in the Mornings topics at the 46th ASHP Midyear Clinical Meeting and Exhibition in New Orleans, Louisiana, in December 2011. The program was presented by Craig Martin, Pharm.D., BCPS-ID. Attendees submitted questions about unresolved issues and controversies that were later addressed by Dr. Martin in a live webinar conducted on March 15, 2012. The highlights of the webinar pertaining to the role of antimicrobial stewardship in health systems and the use of extended (i.e., prolonged) infusions of β-lactam antibiotics are described in this e-newsletter. Highlights pertaining to empiric therapy for suspected invasive candidiasis, the use of rapid diagnostic tests, ways to maximize the success of an antimicrobial stewardship program, and the role of the staff pharmacist in antimicrobial stewardship will be discussed in an e-newsletter to be released in May 2012.

Expand Your Knowledge

On-demand CPE Activities

If you were unable to attend the live symposium, *Antimicrobial Stewardship in Health Systems: Opportunities for the Multidisciplinary Team to Improve Patient Care*, conducted at the 2011 ASHP Midyear Clinical Meeting, a **1-hour CPE activity is available on demand.**

Faculty Podcast Interviews

Visit the CE in the Mornings **web portal** to listen to podcast interviews with the faculty. Four interviews, each lasting approximately 5 to 14 minutes, are available.

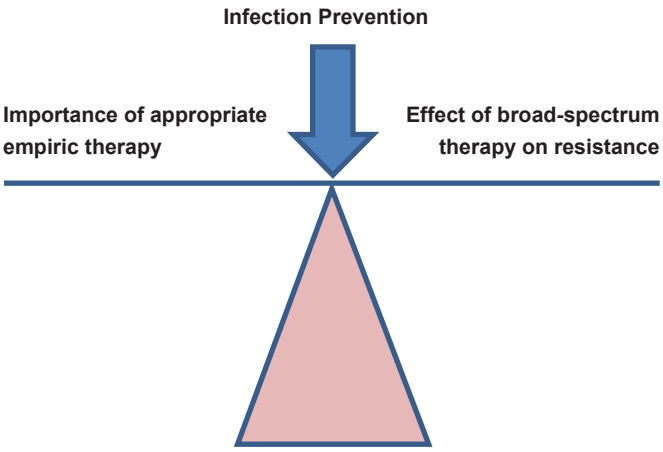
Question: What is antimicrobial stewardship, and what role does it play in health systems?

Antimicrobial stewardship is a coordinated effort to ensure the judicious and effective use of antimicrobial therapy that includes but is not limited to the appropriate selection, dosing, route of administration, and duration of antimicrobial therapy.[1]

Antimicrobial stewardship in conjunction with infection prevention and control is an important tool used to achieve a balance between (1) the need for appropriate empiric antimicrobial therapy (i.e., a drug to which the pathogen is

susceptible and results in clinical success) and (2) the risk of collateral damage through the selection of resistant pathogens from the unnecessary use of broad-spectrum antibiotics (Figure 1).

Figure 1.
The Antimicrobial Stewardship Balance



This balance is needed to prevent and control infection, and achieving a balance can be difficult. The needs of future patients must be weighed in addressing the needs of current patients because of the risk of emergence of resistance. Mismanagement of current patients by using broad-spectrum antibiotics when the agents are not needed can result in multidrug-resistant infections in future patients.

The goal of antimicrobial stewardship in its most narrow definition is to reduce the overuse of antimicrobial agents. This is an important component of antimicrobial stewardship but it does not suffice alone. A more broad definition of antimicrobial stewardship is needed, with the goal of improving all aspects of antimicrobial use, including:

- Diagnostics (when to use drugs)
- Education (which drugs to use)
- Dosing (which dosage is safest and most effective)
- Duration of therapy
    - stopping therapy when appropriate
    - de-escalating therapy when appropriate
- Timeliness of initial therapy

Improving the antimicrobial-use process requires consideration of a variety of patient-specific characteristics (e.g., prior antibiotic use, drug allergies) and institution-specific factors. The institution-specific factors include policies and procedures for medication ordering, preparation, delivery, and administration and the prevalence and antimicrobial susceptibility and resistance patterns of pathogens in various areas within the health system (Figure 2).

Figure 2.
Improving the Antimicrobial-Use Process

Question: What can be done to address the problem of inappropriate antimicrobial use in health systems?

The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) have acknowledged that inappropriate antimicrobial use in health systems is a multidisciplinary problem that cannot be solved unilaterally by members of any one department or service. Guidelines for developing an institutional program to enhance antimicrobial stewardship released by IDSA

and SHEA in 2007 call for a collaborative multidisciplinary antimicrobial stewardship team with a clinical pharmacist with infectious diseases (ID) training and an ID physician serving as core members.[1] Additional team members ideally include a clinical microbiologist, information technology specialist, infection control professional, and hospital epidemiologist.

The IDSA/SHEA guidelines call for two core and several supplemental strategies for antimicrobial stewardship (Table 1). Although the core strategies are central to antimicrobial stewardship, the supplemental strategies can play a pivotal role in the success of antimicrobial stewardship. I often think of the supplemental strategies as the infrastructure for the core strategies. Education is particularly important because all health care personnel involved in antimicrobial use in the health system need to understand the importance of prudent use of these agents to minimize the emergence of resistance and ensure the prompt administration of the first dose in seriously-ill patients. I'd even go so far as to say that education ought to be a core strategy because of its tremendous importance.

Table 1.

IDSA/SHEA Core and Supplemental Antimicrobial Stewardship Strategies[1]

Core Strategies	*Supplemental Strategies*
Prospective audit with intervention and feedback	Education
Formulary restriction with preauthorization	Guidelines and clinical pathways
	Antimicrobial cycling
	Antimicrobial order forms
	Combination therapy
	Streamlining or de-escalation of therapy
	Dose optimization
	Parenteral-to-oral conversion

IDSA = Infectious Diseases Society of America
SHEA = Society for Healthcare Epidemiology of America

Question: What are the possible disadvantages of antimicrobial stewardship?

Formulary restriction with preauthorization can be promptly and highly effective in reducing the use of problematic antimicrobial agents. However, heavy-handed restrictions can inadvertently harm patients by delaying the initiation of agents needed to ensure a favorable clinical outcome.[2] Prompt initiation of therapy in seriously-ill patients using a broad-spectrum antibiotic to which the probable pathogen will be susceptible is imperative. In patients with septic shock, every hour of delay in initiating appropriate empiric antimicrobial therapy after the onset of hypotension is associated with an increase in mortality of 7.6%.[3] Using an antibiotic with a narrow spectrum to which the pathogen is not susceptible can have dire consequences. De-escalation of therapy once the results of culture and susceptibility tests are available (i.e., discontinuing broad-spectrum therapy and initiating targeted therapy with a narrower spectrum of activity suited to the isolated pathogen) is a necessity to minimize selection pressure that leads to resistance. At UK HealthCare, we have established policies and procedures for a rapid response when sepsis is observed at the bedside, using a tool box that we keep on hand containing two sets of appropriate antibiotics for use based on whether the patient is allergic to penicillin.

The right drug is always the agent with the narrowest spectrum that produces a successful response and causes the fewest significant adverse effects and the least collateral damage at the lowest cost. Convincing prescribers to de-escalate therapy in a patient with a favorable clinical response can be difficult, even though continuation of therapy with a needlessly broad spectrum promotes resistance.

The longer a regimen has been used, the more difficult it is to discontinue it. Ideally, antimicrobial therapy should be discontinued after an appropriate length of time, but data for what constitutes an appropriate duration are not available for many diseases. Patient response should be used to make decisions about the duration of therapy.

At UK HealthCare, we focus more on promptly providing the right drug to the patient rather than merely restricting

antimicrobial use, an approach that we characterize as facilitation instead of restriction. Immediate dispensing of a first dose is allowed without restrictions, with evaluation of the therapeutic appropriateness of the antimicrobial regimen performed after the first dose or day of therapy or another appropriate interval when data to guide the therapeutic choice become available (e.g., 2-3 days).[2] This approach works well when used in conjunction with institutional guidelines. De-escalation of therapy is the key to success of this approach. I advise my students and residents that the only dose of an antimicrobial agent proven to save lives is the first dose (i.e., the timing and selection of the first dose are critical).

Question: What is the role of extended infusion of antimicrobial agents in antimicrobial stewardship? Should the dose be decreased when an extended interval for infusion is used?

In the past, the dosing and administration of antimicrobial agents to treat infections caused by pathogens with low minimum inhibitory concentrations (MICs) was not critical because plasma concentrations exceeded the MIC for most of the dosing interval. Moreover, alternative agents to which the pathogen was susceptible were available in the event of therapeutic failure. However, the emergence of multidrug resistance and lack of new antimicrobial agents in the research and development pipeline make it imperative that clinicians optimize the dosing and administration of currently available agents. Dose optimization is one of the supplemental strategies recommended by IDSA/SHEA in its guidelines for developing an institutional program to enhance antimicrobial stewardship.[1] Extended or continuous infusion of β-lactam antibiotics is suggested for dose optimization because the bactericidal activity of these agents correlates with the percentage of time that the plasma drug concentration exceeds the MIC.[1]

Using continuous infusions of β-lactam antibiotics instead of intermittent infusions reduces the total dosage and may maximize the time during which the plasma drug concentration exceeds the MIC, minimize adverse effects associated with high peak plasma concentrations, reduce costs, and facilitate therapy in the home setting instead of an institutional setting. However, drug stability limitations, lack of a well-defined plasma concentration-to-MIC ratio associated with clinical success, and the need for dedicated venous access are potential problems with the use of continuous infusions.

It is not necessary for β-lactam antibiotic plasma concentrations to exceed the MIC on a continuous basis.[4] Bactericidal effects are optimized with penicillins, cephalosporins, and carbapenems when the fraction of time during the dosing interval in which the unbound drug concentration exceeds the MIC is 50%, 60% to 70%, and 40%, respectively.[5] Therefore, the use of extended infusions instead of continuous infusions represents a reasonable compromise.

> **"The only dose of an antimicrobial agent proven to save lives is the first dose."**
>
> — Craig Martin, Pharm.D., BCPS-ID

Results of pharmacokinetic and pharmacodynamic studies support the use of extended infusion dosing strategies for β-lactam antibiotics.[4,5] The probability of exceeding the 50% threshold for fraction of time during the dosing interval in which the drug concentration exceeds the MIC of piperacillin-tazobactam for 470 *Pseudomonas aeruginosa* (*P. aeruginosa*) isolates (i.e., a response) in 5000 surgical patients and patients with neutropenia was simulated for intermittent (i.e., over 30 minutes), extended (i.e., over 3 or 4 hours), and continuous infusions (i.e., over 24 hours) using several different daily dosages of piperacillin.[6] The cumulative response rates (i.e., rate of the 50% target achievement) with the extended and continuous infusions were similar and these rates were higher than with intermittent infusions when the same daily dosage of the piperacillin component was used. For example, a 16-g/day piperacillin dosage delivered by continuous infusion of piperacillin-tazobactam 18 g over 24 hours, extended infusion of piperacillin-tazobactam 4.5 g over 3 hours every 6 hours,

or intermittent infusion of piperacillin-tazobactam 4.5 g over 30 minutes every 6 hours was associated with a response rate of 89.2%, 89.6%, and 79.7%, respectively. Reducing the piperacillin dosage to 9 g/day is not advisable, even when extended dosing is used (e.g., piperacillin-tazobactam 3.375 g over 4 hours every 8 hours) because the response rate is 83.3%.

In a single-center, historic control study, an extended infusion regimen of piperacillin-tazobactam 3.375 g over 4 hours every 8 hours was compared with a intermittent regimen of 3.375 g over 30 minutes every 6 hours (the control group) in 194 patients with *P. aeruginosa* infection.[7] In a subset of the 79 sickest patients with an Acute Physiological and Chronic Health Evaluation-II (APACHE-II) score of 17 or higher, extended infusion was associated with a significantly lower 14-day mortality rate (12.2%) than intermittent infusion (31.6%) and a significantly shorter median duration of hospital stay (21 days vs. 38 days with intermittent infusion). There were no significant differences in outcomes for less sick patients with an APACHE-II score less than 17. At UK HealthCare we use a larger piperacillin-tazobactam dose for *P. aeruginosa* (4.5 g) than what was used in this study regardless of the infusion strategy because of uncertainty about the *P. aeruginosa* response rate. When we choose to use extended infusions, we merely use the same dose but extend the infusion time to 3-4 hours.

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