Ask the Expert: Antimicrobial Stewardship in Health Systems

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. 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...
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).

**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. 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

<table>
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<tr>
<th>Core Strategies</th>
<th>Supplemental Strategies</th>
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<td>Prospective audit with intervention and feedback</td>
<td>Education</td>
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<td>Formulary restriction with preauthorization</td>
<td>Guidelines and clinical pathways</td>
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<td>Antimicrobial cycling</td>
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<td>Dose optimization</td>
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<td>Parenteral-to-oral conversion</td>
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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. 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%. 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 facilita-
tion instead of restriction. Immediate dispensing of a first dose
is allowed without restrictions, with evaluation of the therapeu-
tic 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). 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 supplemen-
tal strategies recommended by IDSA/SHEA in its guidelines for
developing an institutional program to enhance antimicrobial
stewardship. 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. 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.
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. 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. 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. 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 piper-
acillin-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 an intermittent regimen of 3.375 g over 30 minutes every 6 hours (the control group) in 194 patients with *P. aeruginosa* infection. 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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References


