Elements of an Antimicrobial Stewardship Program

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Target Audience
This continuing education activity was designed specifically for pharmacists.

Disclosure Statement
The author has indicated that he does not have any conflicts of interest, nor does he have financial relationships with a commercial interest, related to this activity.

Learning Objectives
At the end of this activity, participants should be able to:

- describe the elements of an antimicrobial stewardship program.
- explain the importance of an antimicrobial stewardship program within a hospital.
- discuss examples of antimicrobial stewardship activities.

Introduction
Antimicrobial agents are important to the practice of medicine because of their ability to cure infections, but it is estimated that as much as 50 percent of antibiotic prescriptions may be unnecessary. A normal risk for antimicrobial use is adverse effects such as diarrhea and nephritis, but a serious adverse event, *Clostridium difficile* infection, can develop from overuse of antibiotics. This can lead to increased health care costs. In a systematic review by Nanwa and colleagues, total health care costs to treat a *C. difficile* infection can be as high as $30,000. Antimicrobial resistance can also develop over time when broad-spectrum antibiotics are used instead of more targeted therapies. Superinfections or organisms resistant to multiple anti-infectives can lead to treatment failure and even death. A recent incident of carbapenem-resistant *enterobacteriacea* at Ronald Reagan UCLA Medical Center highlights the real danger in allowing organisms to develop resistance to antimicrobial agents. Seven patients were infected, while two patients died from the resistant infection. An antimicrobial stewardship program (ASP) is a way to help prevent these negative consequences.

The main goal of antimicrobial stewardship is to optimize positive clinical outcomes such as curing the infectious disease while minimizing negative consequences of antimicrobial use. The majority of hospitals in the United States have some strategies to promote antimicrobial stewardship but, in particular, smaller community hospitals may not have a well-developed program. It will be important for all health care facilities to develop antimicrobial stewardship programs because the government has set future goals to require certain antimicrobial stewardship activities.

On Sept. 18, 2014, President Barack Obama gave an executive order on combating antibiotic resistance. It outlined a Task Force to identify future national goals and strategies to decrease antibiotic resistance and to improve antimicrobial use through ASPs. By the end of 2016, new regulations will be implemented to require health care facilities to have robust ASPs. The Centers for Medicare and Medicaid Services (CMS) has also indicated future requirements for antimicrobial stewardship activities. These activities will likely be tied to CMS reimbursement payments to health care facilities. Health care facilities will likely have to designated leaders responsible for ASP, develop policies and procedures, require documentation of indication for all antimicrobials, and monitor antimicrobial use. Implementing or improving elements of an ASP will be vital to a hospital’s growth and success.
Elements of Antimicrobial Stewardship Program

The Infectious Diseases Society of America (IDSA) recommends certain elements or tools when developing an antimicrobial stewardship program. There are two core elements and several supplemental elements for a health care facility to perform when creating an enhanced ASP. The first core function of an ASP is prospective audit with intervention and feedback. A patient’s chart is reviewed during the hospital admission then discussed with the patient’s prescriber for potential recommendations to optimize the patient’s antimicrobial therapy. This can occur during daily rounds or through consultation with the prescriber, as needed, either verbally or in writing. It is recommended that an infectious disease physician or an infectious disease pharmacy specialist reviews the patient’s chart. The objective of the prospective review is to reduce unnecessary antimicrobial agents based on organism coverage or duration of therapy. An example of this is a patient with pneumonia who lives in a nursing home and is empirically treated with moxifloxacin. The admitting physician will likely change the patient’s therapy to include broader spectrum agents such as vancomycin and cefepime due to the patient’s risk for health care-associated pneumonia (HCAP). Later in the hospital stay, the microbiology data shows only Gram-positive organisms growing in the lungs. The antimicrobial stewardship pharmacy specialist can recommend to the attending physician to discontinue cefepime and continue with vancomycin alone. The antimicrobial stewardship pharmacy specialist is decreasing antimicrobial exposure since cefepime covers Gram-negative organisms and is no longer needed. This antibiotic review not only decreases unnecessary antimicrobial exposure but saves cost on unnecessary medications.

Prospective audit has shown cost savings in both large teaching hospitals and small community hospitals. A study by Frazer and colleagues done in a 600-bed tertiary teaching hospital randomized patients to either be reviewed by an infectious disease fellow or pharmacist or not reviewed. The study showed an average cost savings of $400 per patient compared to the patients who were not reviewed. In another study by Yu and colleagues, pharmacists on an antimicrobial stewardship team providing recommendations to physicians on antimicrobial therapy showed a cost savings of more than $127,000 when compared to hospitals without antimicrobial stewardship. In hospitals where daily review of antimicrobial therapy is not realistic due to limited resources, less frequent reviews can still be beneficial. In a study done at a 120-bed community hospital, an infectious disease physician or clinical pharmacist focused on reviewing patients with multiple antimicrobials. They would review the patients’ antimicrobial regimens three times weekly. The study found a 19 percent reduction in antimicrobial cost and estimated annual cost savings of more than $175,000. As health care costs rise over time, there will be more pressure to audit antimicrobial therapies and restrict antimicrobial prescribing.

Formulary restriction and preauthorization is another core element to an ASP. A hospital should have a Pharmacy and Therapeutics Committee or equivalent group to review medications that should be included in the hospital formulary. The formulary is the first line of defense to control antimicrobial usage and cost. The Committee should evaluate the efficacy, safety and placement on the formulary. A new antimicrobial agent may be added to the formulary even though it is expensive but useful in treatment in a specific type of infection. If the medication is expensive but does not have better efficacy than other cheaper options, it may not be added to the formulary.

Preauthorization requirements such as requiring a consult to an infectious disease physician or allowing only certain physicians to prescribe certain antimicrobial agents allows the hospital to control usage and cost. A study by Seligman demonstrated a 29 percent decrease in antibiotic cost when requiring an infectious disease consult for an oral cephalosporin agent, which accounted for 31 percent of total antibiotic expenditure. The cost savings from antimicrobial medications can be used in another aspect of the patient’s care or help the hospital overall with care to its patients. More
importantly, antimicrobial resistance with overuse of broad-spectrum antimicrobial medications is a concern. Agents such as vancomycin and carbapenems have developed resistance to Enterococcus and Enterobacteriaceae strains. A study by Quale and colleagues showed a significant decrease in vancomycin-resistant Enterococci after restricting cefotaxime and vancomycin use. Preventing resistance is vital because the pharmaceutical market has only produced a few new antimicrobial agents over the past decade. There is a real threat of superinfections to become more common because current agents are losing efficacy to new resistant infections.

STOP AND REFLECT
What government organization will be requiring antimicrobial stewardship activities for health care facilities to participate with them and receive reimbursement payments? What is the goal behind these activities?

Education is a supplemental element to a successful ASP. The education is designed to influence prescribing behavior. Passive activities such as lectures, informational booklets, signs and e-mail alerts remind and reinforce proper antimicrobial use and stewardship. An example is a hospital antibiogram given out to physicians to educate them on the hospital’s formulary antibiotic agents and sensitivity against different pathogens seen within the hospital. However, passive activities have a limit to their effectiveness. Passive activities have a more direct effect on health care providers when combined with active interventions. In one study by Bantar and colleagues, passive education was followed by active prospective reviews, which showed more than $900,000 in savings and more than 45 percent of interventions resulted in changing to narrower spectrum of activity.

Guidelines and clinical pathways are supplemental strategies in antimicrobial stewardship. Guidelines such as those from the IDSA can help direct a prescriber on the proper treatment for a certain infectious disease. It is important to note that guidelines are recommendations given for a certain disease or condition, but the prescriber can vary on the final treatment choice based on the patient’s specific characteristics. Guidelines also can help create policies within a hospital or health system on how to use antimicrobial agents. A study by Dranitsaris and colleagues evaluated an institutional guideline concerning cefotaxime usage. Pharmacists promoting the institutional guidelines showed more appropriate use of the antibiotic agent better than without the intervention.

Clinical pathways can also narrow the selection of antimicrobial agents. A clinical pathway is a stepwise guide to certain treatments depending on the patient’s signs and symptoms. This allows clinicians to make quicker and more educated decisions about treatment. It can lead to decreased hospital length of stay and days on antibiotics, as found in the study by Marrie and colleagues. A clinical pathway was randomly implemented among 20 hospitals and it showed a 1.7-day decrease in hospital length of stay and a decrease mean of 1.7 days of intravenous therapy without increasing readmissions or mortality. Clinical pathways can also lead to cost savings. Singh and colleagues implemented an algorithm in an intensive care unit to direct antibiotic therapy with pulmonary infection scores. The score would direct how long the patient should be on antimicrobial agents. The study showed a decrease in antimicrobial-resistant infections and duration of therapy but no difference in mortality.

Dose optimization is another supplemental element to antimicrobial stewardship. It is the use of a patient’s characteristics along with a drug’s pharmacodynamic and pharmacokinetic
properties to optimize therapy. A common example of this is β-lactam agents being dose adjusted for renal function. β-lactam agents such as amoxicillin and cefepime have bactericidal activity that correlates with time above the minimum inhibitory concentration. The antibiotic agents can be given over longer intervals if the patient has poor renal function. This would have a pharmacokinetic effect to maintain antibiotic concentrations but given in fewer doses. A pharmacodynamic effect would be using single-dose fosfomycin instead of four times daily dose cephalexin for an uncomplicated urinary tract infection due to fosfomycin’s high concentration in the urine with a single dose.

Antimicrobial de-escalation or streamlining is another tool to be used along with the core elements of antimicrobial stewardship. The action can be described as switching empiric antimicrobial therapy to targeted therapy. Microbiology data such as culture results and susceptibility data can streamline empiric antimicrobial therapy to the causative pathogen and eliminate unnecessary or redundant medications. Broad-spectrum antimicrobial agents are often changed to narrow-spectrum agents, though this is not always the case. An example is a patient who is treated with ceftriaxone when the susceptibility data indicates *Klebsiella pneumoniae* sensitive to only cefepime. The key to antimicrobial de-escalation is to use the most effective agent for the infecting organism while limiting exposure to other antimicrobial agents to prevent the development of resistance. Continuous broad-spectrum empiric therapy has shown to contribute to antimicrobial-resistant organisms. When microbiology data becomes available, this is the time to choose a more selective antimicrobial agent. This can lead to overall cost savings, as multiple agents are removed and more expensive agents are switched with cheaper generic agents. A study by Briceland and colleagues concerning streamlining by an infectious disease physician and pharmacist showed a projected annual savings of more than $100,000.

Conversion from parenteral to oral dosage form is another supplemental element to antimicrobial stewardship. Patients with serious infections or when oral bioavailability is uncertain are often started on parenteral therapy. Intravenous antibiotics may initially be more beneficial because they have a 100 percent bioavailability in the blood stream and may quicken the onset of the medication. However, intravenous medications can be burdensome if the patient has poor intravenous access or if a medication has to be infused over several hours. Conversion to oral therapy may be preferred since it is easier to administer, causes less frequent adverse effects and saves cost. Routine monitoring for conversion has shown to decrease length of hospital stay and health care costs while not compromising patient care. One ideal time to have the conversion from parenteral to oral therapy is when the patient is being transferred out of an intensive care unit onto a general practice unit. The patient’s condition is less serious and more likely to tolerate oral medications.
Antimicrobial order sets are another tool to be used for ASP. Pre-specified order sets can be developed by the antimicrobial stewardship team. An order set can limit the overuse of antimicrobials through automatic stop times and physician requirements to justify the continued use of the antimicrobial agent. Order sets were found to be particularly useful on perioperative antibiotic orders in a study by Durbin and colleagues. The study showed a decrease in mean duration of antimicrobial use from 4.9 days to 2.9 days when automatic two-day discontinuation order sets were used.\textsuperscript{23}

Combination antimicrobial therapy is another strategy to help improve clinical outcomes. A study by Harbarth and colleagues focusing on sepsis showed inadequate initial therapy is associated with increased mortality.\textsuperscript{24} The goal of combination therapy is to use broad-spectrum empiric therapies for serious infections especially for multidrug-resistant organism infections.\textsuperscript{5} The concern with combination therapy is unnecessary and redundant coverage, which may lead to antimicrobial resistance.\textsuperscript{25} An example is the combination of a \(\beta\)-lactam and an aminoglycoside. A meta-analysis by Bliziotis and colleagues reviewed the combination versus \(\beta\)-lactam monotherapy. Monotherapy was associated with less treatment failure and superinfections compared to the combination.\textsuperscript{25}

Antimicrobial cycling is one activity that is not recommended in an ASP. Cycling is described as scheduled removing and switching of similar antimicrobial agents or classes within a facility.\textsuperscript{5} It was thought to have a benefit to antimicrobial stewardship by decreasing the occurrence of antimicrobial resistance. Though, studies have mixed support for the use of antimicrobial cycling.\textsuperscript{26,27} Mathematical modeling has suggested the only benefit is slowing the spread of resistance but not preventing it.\textsuperscript{28}

**The Pharmacist’s Impact**

Pharmacists can play an important role in antimicrobial stewardship. Staff pharmacists play a daily role in verifying anti-infective medications. They can be involved in the core elements of prospective antibiotic review and formulary restriction, along with supplemental elements such as intravenous to oral dosage form conversion. Ideally, a pharmacist with infectious disease training should be working with the hospital’s infectious disease physicians to optimize antibiotic stewardship.\textsuperscript{5} Clinical pathways can assist staff pharmacists in providing recommendations for the most suitable antibiotic for the patient and restrict overuse of certain antibiotics.\textsuperscript{16} A study by Lancaster and colleagues showed a pharmacist-driven intervention led to improved hospital-acquired pneumonia (HAP) therapy.\textsuperscript{29} Pharmacists used an approved HAP protocol to review antibiotic therapy for appropriate empiric antibiotic coverage and recommend when to de-escalate therapy. The pharmacists made 59 interventions in 29 patients with about a 50 percent physician accepted recommendation rate.\textsuperscript{29}

Pharmacists can promote optimal use of antimicrobial agents. There are several ways this can be achieved.\textsuperscript{27} First, pharmacists need to encourage multidisciplinary collaboration within the health care system. Pharmacists should assist in appropriate selection, optimal dosing, proper monitoring and de-escalation when on rounds or verifying medication orders. Pharmacists should be involved in the hospital Therapeutics Committee and Infectious Disease Subcommittees to help develop policies such as therapeutic interchange and restricted antimicrobial-use.\textsuperscript{30} Collaboration with microbiology laboratory personnel is also important to have appropriate microbiology and susceptibility data communicated in a timely fashion to the health care provider.\textsuperscript{30} The goal is to have open communication to help mitigate any delays or issues when trying to determine the infectious disease origins.

Pharmacists can collect antimicrobial data from the electronic health record (EHR) to analyze clinical and economic outcomes.\textsuperscript{30} This data can be used to create or optimize antimicrobial guidelines, policies and procedures. The data can be individualized to specific hospitals within a
health-system to help lead physicians to the most effective antimicrobial agents at their facility. Pharmacists can also use the EHR to track and monitor antimicrobial utilization. This can lead to improved antimicrobial therapy, as showed by Evans and colleagues. A monitoring system identified changes in renal function for patients on specific antibiotics. Pharmacists would review the list and adjust doses of the patients’ medications when warranted. When a guideline embedded computer-assisted system was implemented at a 520-bed hospital, it resulted in a pharmacy antimicrobial drug expenditure decrease from 24.8 to 12.9 percent, while showing a 30 percent decrease in antimicrobial-associated adverse events.

Pharmacists should participate in the prevention and reduction of the transmission of infections. Pharmacists play an important role, as compounding of intravenous medications start in the pharmacy. Policies and procedures can be created and put in place to ensure sterility of drug products. Pharmacist should encourage the use of single-dose vials as opposed to multiple-dose containers. Along with compounding, they can ensure proper handling and storage of sterile products. Pharmacists should ensure proper standard precautions such as hand washing and routine immunizations of health care workers. Other areas where a pharmacist can be involved are preventing surgical site infections, catheter-associated infections and ventilator-associated pneumonia by following proper procedures and policies. An example is a pharmacist making sure pre-operation antibiotics are given on time before starting a surgical procedure.

The pharmacist’s role should also include educational activities. Pharmacists should be knowledgeable in recent news and developments in antimicrobial use. The pharmacist can give presentations, create newsletters or give topic discussions to health care professionals to spread current knowledge in antimicrobial use. Education should include patients and caregivers, not only in the inpatient setting but in ambulatory and home care settings as well. Antimicrobial education can be presented at public health awareness events such as at senior centers and conferences. Prudent use of antimicrobial agents, immunization and proper hand hygiene should be emphasized at health awareness events.

Conclusion

Antimicrobial stewardship plays a vital role in health care. It can improve infectious disease outcomes while decreasing C. difficile infections and antimicrobial resistance. The presidential executive order on combating antibiotic resistance highlights the importance of ASPs, and CMS will be tying financial reimbursement to antimicrobial stewardship activities at health care facilities. Large academic centers along with smaller community hospitals will need to have an ASP in place. The core elements for stewardship are prospective review and formulary restriction. Supplemental elements are education, guidelines, dose optimization and de-escalation among others. Pharmacists can play an important role with these core elements, along with the supplemental elements. Pharmacists can be actively involved with infectious disease rounding, Therapeutic Committees and antimicrobial de-escalation. Pharmacists are directly involved with preventing hospital-acquired infections with maintaining product sterility. Lastly, antimicrobial education through presentations and patient interaction is another example of how pharmacists can be actively involved in antimicrobial stewardship. As government agencies communicate more specific information for requirements, pharmacists can play an important role in ASPs.
Continuing Education Self-assessment Questions

1. What is a positive outcome of antimicrobial stewardship?
   a. Cure disease
   b. *Clostridium difficile* infections
   c. Antimicrobial resistance
   d. Extended broad-spectrum antimicrobial therapy

2. What is a core component of an antimicrobial stewardship program?
   a. Antimicrobial de-escalation
   b. Education
   c. Formulary restriction
   d. Dose optimization

3. What government agency will be tying reimbursement payments to stewardship activities?
   a. Center for Disease Control and Prevention (CDC)
   b. Centers for Medicare and Medicaid Services (CMS)
   c. The White House
   d. Infectious Diseases Society of America (IDSA)

4. Which of the following describes antimicrobial de-escalation?
   a. Empiric therapy changed to targeted therapy
   b. Only using monotherapy
   c. Adding a medication to cover for suspected *Pseudomonas aeruginosa*
   d. Narrow therapy changed to empiric therapy

5. Who should be involved in prospective review and audit?
   a. Only the prescribing physician
   b. A pharmacist with infectious disease training
   c. Nurse’s aide
   d. Laboratory personnel

6. What activity can guide health care providers to appropriate antimicrobial choices?
   a. Intravenous to oral medication conversion
   b. Clinical pathway
   c. Antimicrobial de-escalation
   d. Antimicrobial cycling

7. Pharmacists should be involved in what Committee(s)?
   a. Physician and Therapeutics Committee
   b. Laboratory Subcommittee
   c. Infectious Disease Subcommittee
   d. A and C
8. Which of the following is an example of passive education?
   a. Presentations
   b. E-mail alerts
   c. Prospective audit
   d. A and B

9. What activity has not been shown to be beneficial to antimicrobial stewardship?
   a. Antimicrobial de-escalation
   b. Formulary restriction
   c. IV to PO conversation
   d. Antibiotic cycling

10. How can pharmacists impact antimicrobial stewardship?
    a. Promote optimal antimicrobial use
    b. Input on antimicrobial guidelines and policies
    c. Antimicrobial de-escalation
    d. All of the above
References:

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