SPECIAL SECTION

ANTIMICROBIAL STEWARDSHIP

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On the cover: This Petri dish culture plate had contained cycloserine, cefoxitin, and fructose agar (CCFA), which had been inoculated with a *Clostridium difficile* bacterial culture, and had subsequently given rise to numerous bacterial colonies. In this particular view, the plate had been illuminated using long-wave UV irradiation, hence, the bacterial colonies emitted a yellow-green, or chartreuse fluorescent glow.
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JAMES GATHANY

Antimicrobial Stewardship

CHESTON B. CUNHA, MD, FACP
GUEST EDITOR

This issue of the *Rhode Island Medical Journal* (RIMJ) is devoted to Antimicrobial Stewardship. Traditionally, infectious disease (ID) clinicians have been the antibiotic stewards in hospitals. Recently, the basic tenets of antimicrobial stewardship programs (ASPs) have been defined and mandated by the Centers for Disease Control (CDC) and The Joint Commission (TJC).

The essential elements of ASP are based on a multidisciplinary approach led by an ID clinician leader supported by a team of ID-trained clinical PharmDs. Effective ASPs are dependent on close cooperation between infection control (IC) and the microbiology laboratory to track and limit antibiotic resistance. Optimal antibiotic therapy recommendations are based on ID/ASP experience and pharmacokinetic–pharmacodynamic (PK/PD) considerations while minimizing resistance and *C. difficile* potential. Since each hospital is different, ASPs need to be tailored to each hospital staff's prescribing habits, formulary restrictions, and local antibiotic usage patterns.

Vital to ASP success is enthusiastic and ongoing administrative financial support for ASP MDs and PharmDs as well as robust IT support (personnel and equipment).

Critical to ASP acceptance and success is antimicrobial education of the medical staff to optimize therapy, minimize resistance and control of *C. difficile*. ASP interventions in support of these principles include educating and implementing effective monotherapy instead of polypharmacy (often with 2–4 antibiotics when one is sufficient). Therapy should be as short as possible to cure the infection. Other important ASP components include a comprehensive IV-to-PO switch program, which decreases drug acquisition costs and adverse effects and which allows earlier discharge and decreases length-of-stay (LOS).

Following acceptance of IV-to-PO switch therapy, the next step is to acquaint the staff with the even greater advantages of entirely oral (PO) therapy.

Physicians need to be aware of each antibiotic's resistance potential when selecting therapy, e.g., "high resistance potential" drugs (ceftazidime) vs. "low resistance potential" drugs (ceftriaxone). Similarly, antibiotics also differ in their *C. difficile* potential. The antibiotics with a high *C. difficile* potential are clindamycin, and beta-lactams (excluding ceftriaxone). Many other antibiotics have little or no *C. difficile* potential, e.g., macrolides, tetracyclines, aztreonam, aminoglycosides, vancomycin, colistin, polymyxin B, TMP-SMX, fosfomycin. Some antibiotics are actually protective against *C. difficile*, e.g., doxycycline, tigecycline. Furthermore, often overlooked are various other drugs that may cause *C. difficile*; notably, proton-pump inhibitors (PPIs).

As ASPs are implemented, the effectiveness of various interventions is best assessed by prospective audits. As hospitals are all different, this analytical tool is needed to demonstrate what works best for each hospital.

This issue of the RIMJ is dedicated to Rhode Island practitioners. We are most fortunate in the state to have so many experts with a national reputation in clinical ID, antibiotic resistance, IC and hospital epidemiology, as well as medical microbiology. The articles contained in this issue of the RIMJ on ASP were written by leaders in their fields and should be of great interest and practical use to RI practitioners.

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Guest Editor

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Antimicrobial Stewardship Programs (ASP): Perspective on Problems and Potential

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Antibiotic Stewardship Programs (ASPs) are intended to optimize appropriate antibiotic use and decrease inappropriate or suboptimal antibiotic use. Infectious disease clinicians have traditionally held the role of antibiotic stewards.[1] Recently, the basic principles of optimal antibiotic use have been finalized in the Centers for Disease Control (CDC) ASP guidelines. The CDC guidelines consist of 7 principles that should be customized to the hospital's size, local epidemiology, resistance patterns, staff expertise and pharmacoeconomic considerations.[2] One size does not fit all, and effective ASP measures in one hospital may be ineffective or inappropriate in another.[3] Hospital differences may be evaluated using prospective audits to assess the effectiveness of ASP components in each hospital. (**Table 1)**

The CDC ASP guidelines consist of 7 practical ASP measures.[2] First, there must be administrative support to fund a dedicated infectious disease (ID) clinician team leader supported by a staff of ID-trained clinical pharmacists (PharmDs). Appropriate antibiotic use is the critical ASP tenet. Antibiotics should not be used to treat non-bacterial causes of fever, e.g., viral infections, drug fever, non-infectious febrile disorders. Furthermore, infection, not colonization, should be treated. The expertise of the ASP ID leader is critical as many non-ID physicians do not understand the importance of differentiating culture results that may represent either colonization (that should not be treated) or infection.[4]

These ASP principles of 1) not treating non-bacterial febrile disorders 2) not treating colonization are important cornerstones of effective ASPs. After selecting an antibiotic on the basis of appropriate spectrum, then tissue penetration (related to the site of infection) is an important consideration. Therapeutic serum levels have little relevance in treating non-serum site infections, e.g., meningitis, osteomyelitis, prostatitis.[4]

ASP programs should educate practitioners on optimal dosing based on pharmacokinetic (PK) and pharmacodynamic (PD) considerations. Dosing and duration of treatment are also important. Duration of therapy should be based on clinical response, and not a set number of days. Another key ASP objective is to further encourage IV-to-PO switch therapy or even better, oral (PO) therapy alone. Other ASP objectives are more challenging, especially the reduction of antimicrobial resistance (an institution-related problem). Antibiotic resistance is not necessarily volume/duration dependent and is not antibiotic class related. Resistance determinants are not well understood, but reducing "antibiotic tonnage" or "antibiotic cycling" often has little or no effect on resistance. Antibiotics are best viewed as being either "low or high resistance potential antibiotics." "Low

Table 1. Effective Antibiotic Stewardship Program (ASP): Core Elements

Leadership commitment from administration
A single ID Clinician/Leader responsible for outcomes
A single pharmacy leader who reports to the ID clinician
Tracking and reporting of antibiotic use
Reporting of antibiotic resistance
Educating providers on optimal use and resistance
Prospective antibiotic audits to measure appropriate use and specific improvement interventions

Adapted from: CDC ASP guidelines 2017

resistance potential" antibiotics cause little/no resistance independent of volume or duration of use, e.g., nitrofurantoin, doxycycline, ceftriaxone. In contrast, "high resistance potential" antibiotics predispose to resistance even with little use, but resistance further increases with high volume use, e.g., gentamicin, ceftazidime, imipenem. As can be inferred from these "high resistance potential" antibiotics examples, antibiotic resistance is not related to antibiotic class since each antibiotic class has both "low and high resistance potential" antibiotics. Acquired resistance must not to be confused with clonal resistance, which is not related to antibiotic use. The spread of clonal resistance is a function of the effectiveness of infection control (IC) efforts to contain/limit the in-hospital spread of resistant strains. The ASP ID clinician should have a close working relationship with IC to be aware of outbreaks unrelated to antibiotic use.[5]

Another ASP problem is minimizing the potential of antibiotic collateral damage, e.g., adverse effects such as *C. difficile* diarrhea (CDD). Clinical education is critical to overcome long-held misconceptions. It is thought, "only antibiotics cause *C. difficile.*" Certainly, clindamycin and most β-lactams can, e.g., piperacillin/tazobactam, but CDD is rare with many other antibiotics, e.g., macrolides, tetracyclines, azithromycin, aminoglycosides, TMP-SMX, tigecycline, daptomycin, linezolid, quniopristin/dalfopristin, colistin, polymyxin B, nitrofurantoin, fosfomycin. Quinolones and carbapenems alone may cause CDD, but CDD is much more likely if these drugs are used with proton pump inhibitors (PPIs).[6,7] Also, physicians need to be aware that non-antibiotic drugs are important causes of CDD, e.g., cancer chemotherapy, some psychiatric medications.

In summary, to be effective, an ASP needs full administrative support, and ID ASP team leadership to educate the medical staff on the most important determinants of optimal antimicrobial therapy.[8,9] (**Table 2)**

Table 2. Antimicrobial Stewardship Principles and Practice: Beyond the Guidelines

Colonization vs. Infection
• Treat infection, not colonization. • Provide empiric coverage primarily directed against the most probable pathogens causing the infection at the body site. • Avoid "covering" or "chasing" multiple organisms cultured that are not (pathogens and non-pathogens) at the body site cultured. • Colonization of respiratory secretions, wounds, or urine with "water" (*S. maltophilia, B. cepacia, P. aeruginosa*) or skin organisms (MSSA, MRSA, CoNS, VSE, VRE) is the rule.

Narrow vs. Broad Spectrum Therapy
• Narrow vs. broad spectrum doesn't prevent resistance, e.g., in treating E. coli urosepsis switching from a carbapenem (broad spectrum) to ampicillin (narrow spectrum) may actually increase resistance potential. • Narrow spectrum vs broad spectrum may not be clinically superior to well-chosen broad spectrum therapy, e.g., switching from ceftriaxone (broad spectrum) to penicillin in treating *S. pneumoniae* has no clinical rationale or clinical advantage and has no effect on controlling resistance. • Antibiotic resistance is not related to spectrum narrowness or broadness, e.g., levofloxacin (broad spectrum but "low resistance potential") vs. ampicillin (narrow spectrum but "high resistance potential").

Antibiotic Resistance
• The best way to control resistance is a selectively restricted formulary; restricting "high resistance potential' antibiotics, e.g., imipenem (not meropenem or ertapenem), ceftazidime (not other 3rd of 4th GC), gentamicin/tobramycin (not amikacin). • Some antibiotics may be restricted for other reasons e.g., excessive vancomycin (IV not PO) use predisposes to VRE emergence and vancomycin may cause cell wall thickening in *S. aureus* resulting in permeability related resistance (to vancomycin and other antibiotics, e.g., daptomycin). • Over restriction of antibiotics may impair timely effective therapy and does not, per se, decrease resistance. • Preferentially select antibiotics (all other things being equal) with a "low resistance potential." Avoid, if possible, "high resistance potential" antibiotics, e.g., macrolides (for respiratory infections), TMP-SMX (for UTIs). • Since resistance is, in part, concentration dependent, subtherapeutic or low antibiotic tissue concentrations, (all other things being equal) predisposes to resistance. • Suboptimal dosing or usual dosing with inadequate tissue penetration, e.g., into the body fluids or undrained abscesses (source control is key) predisposes to resistance.

Monotherapy vs. Combination Therapy
• Preferably use monotherapy whenever possible to cover the most likely pathogen or cultured pathogen clinically relevant to the site of infection. • Combination therapy should be avoided if possible. Always try to preferentially use monotherapy. • Monotherapy is usually less expensive than combination therapy and has less potential for adverse effects and drug-drug interactions. • Combination therapy is often used for potential synergy (rarely occurs and if used must be based on microbiology laboratory synergy studies), to increase spectrum (preferable to use monotherapy with same spectrum), or to prevent resistance (except for TB).

PO and IV-to-PO Switch Antibiotic Therapy
• Wherever possible, treat with entirely oral antibiotic therapy instead of IV therapy. • Switch from IV-to-PO antibiotic therapy after clinical defervescence (usually < 72 hours). • Early IV-to-PO switch therapy eliminates phlebitis and IV line associated infections.

Antibiotic De-escalation
• De-escalation is problematic if based on microbiology data alone without site-pathogen correlation. • De-escalation is appropriate in the setting of broad spectrum coverage of "presumed urosepsis" which can be narrowed after the uropathogen is identified in blood/urine. • In intubated/ventilated patients, microbiology data from respiratory secretion cultures are usually misleading and not representative of NP or VAP lung pathogens. • In patients with NP or VAP, it is more prudent to treat the most likely pathogen, e.g., *P. aeruginosa* (even if not cultured from respiratory secretions) than to be misguided into treating multiple colonizing organisms in respiratory secretions. • De-escalation can be harmful if microbiology data is misleading, e.g., represents colonization rather than being reflective of the pathogen (underlying bone pathogen, not ulcer organisms), e.g., diabetic foot ulcers/chronic osteomyelitis or sacral ulcers/chronic osteomyelitis.

C. difficile Diarrhea/Colitis
• Preferentially select antibiotics (all other things being equal) with low *C. difficile* potential. • Predisposing factors to *C. difficile* include relatively few antibiotics, e.g., clindamycin, β-lactams, ciprofloxacin. • Many antibiotics have little *C. difficile* potential, e.g., aminoglycosides, aztreonam, macrolides, TMP-SMX, colistin, polymyxin B, daptomycin, Q/D, doxycycline, minocycline, tigecycline, vancomycin, linezolid. • Some antibiotics are protective against *C. difficile*, e.g., doxycycline, tigecycline. • Always consider non-antibiotic factors that may predispose to *C. difficile*, e.g., cancer chemotherapy, anti-depressants, statins, PPIs. • Also consider person-to-person spread or acquisition for the environment.

Pharmacoeconomic Considerations
• The least expensive therapy is usually not the best therapy. • The least expensive antibiotic (acquisition cost) may, in fact, be expensive (re: total cost) when considering the cost implications to the institution of dosing frequency, *C. difficile* potential, resistance potential, and degree of activity against the known or likely pathogen, not to mention the cost of potential therapeutic failure vis-à-vis ↑ LOS and medicolegal costs. • Stewardship savings are best achieved by decreasing duration of antibiotic therapy, and by treating entirely with oral antibiotic therapy or early IV-to-PO switch therapy.

BILIARY TRACT INFECTION AND ASP ANTIBIOTIC SELECTION: A PRACTICAL ANTIBIOTIC STEWARDSHIP VIGNETTE

Infectious Disease physicians have been the leaders in optimal antibiotic use.

Optimal antibiotic selection is based on an accurate presumptive clinical diagnosis. Without the correct diagnosis, antibiotic therapy is necessarily suboptimal. The first critical step in antibiotic selection is to identify the likely source of infection, which determines the pathogen at the site of infection. For example, in cholecystitis or cholangitis the usual pathogens are *E. coli*, *Klebsiella pneumoniae*, or vancomycin susceptible enterococci (VSE). In the absence of associated bacteremia that would identify the pathogen, therapy should be directed against all three of the usual pathogens. Therefore, the first consideration in antibiotic selection is spectrum (based on the usual pathogens at the site of infection). Any antibiotic that covers these pathogens is appropriate in terms of spectrum. Biliary tract bacteremias are caused by single organisms (vs. polymicrobial infections from the colon) but since any one of these are the pathogen, all three should be covered until or if the single pathogen is identified.

When using an antibiotic, it is important to equally consider what organisms to cover, as well as what not to cover. Non-biliary pathogens that do not require coverage empirically are *B. fragilis*, MSSA/MRSA. Using biliary infection as an example, the next ASP consideration is to select not only an antibiotic with the correct antibiotic spectrum, but the antibiotic must also penetrate the site of infection, e.g., bile and gallbladder wall in therapeutically effective concentrations. Antibiotics with therapeutic serum levels may be completely ineffective in biliary sepsis if not able to penetrate adequately into the bile/gallbladder wall. To further illustrate the importance of pharmacokinetic (PK) considerations in the biliary tract, it is assumed the common bile duct (CBD) is unobstructed (an obstructed CBD would further limit antibiotic penetration). Antibiotic selection solely based on penetration into an obstructed CBD with the requisite PK properties, but not the proper spectrum makes little sense, e.g., clindamycin penetrates even with an obstructed CBD, but doesn't have proper spectrum/activity against *E. coli*, *K. pneumoniae*, or VSE.

The next consideration in antibiotic selection, using the biliary tract sepsis example, is to understand the "resistance potential" of the antibiotics being considered. Antibiotics may be classified as either "high or low resistance potential" drugs. It is a popular misconception that antibiotic resistance is primarily related to volume or duration of use, which is not the case. Excluding clonal resistance spread, "low resistance potential" antibiotics, for unclear reasons, cause little or no resistance after high volume/prolonged use. Doxycycline, a "low resistance potential" antibiotic has been used extensively worldwide for decades and has few resistance problems. Similarly, in terms of volume of use, the "low resistance potential" antibiotic ceftriaxone has caused virtually no clinically relevant resistance problems after decades of use worldwide. In contrast, "high resistance potential" antibiotics, e.g., ceftazidime, causes widespread resistance even with minimal use, and major resistance problems with high volume use. Resistance is also not an antibiotic class phenomenon since within each class there are "high and low resistance" potential antibiotics, e.g., among carbapenems imipenem (high resistance potential) vs. meropenem, doripenem (low resistance potential).

Taking into account resistance potential, if empiric selection between levofloxacin monotherapy vs. cefazolin plus ampicillin therapy, from a resistance potential alone, levofloxacin would be preferable since ampicillin is a "high resistance potential" antibiotic.

Other considerations include side effects or adverse events, e.g., *C. difficile* potential. In selecting levofloxacin for biliary sepsis, it has the proper spectrum (*E. coli*, *K. pneumoniae*, VSE), penetrates into bile in an unobstructed biliary tract, and has a "low resistance potential." Furthermore, without concomitant PPI use, it has a relatively low *C. difficile* potential. In contrast, cefazolin and ampicillin are β-lactams which, after clindamycin, have a relatively high *C. difficile* potential.

Levofloxacin has the additional advantage of being one drug and has a PO formulation for oral or IV-to-PO switch therapy which shortens hospital length of stay (LOS) and permits earlier discharge.[1,2]

The above biliary sepsis example is illustrative of the practical considerations of antibiotic selection taking into account ASP principles.

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Overview of Antimicrobial Stewardship Activities in Rhode Island

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ABSTRACT

Due to the rise of antibiotic resistance, and the decrease of novel antibiotics coming to market, the Centers for Disease Control and Prevention (CDC) has formally recognized that action must take place to ensure appropriate antibiotic use, and maintain public health. The RI Department of Health (RIDOH) Director responded by initiating the RI Antimicrobial Stewardship and Environmental Cleaning Task Force (RIAMSEC), a multidisciplinary team that set in motion a set of tasks for RIDOH. As a result, a survey of antibiotic stewardship programs (ASP) at the RI acute care hospitals (ACHs) and long-term care (LTC) facilities revealed gaps in addressing HAI prevention and AMS goals for the state. RIDOH has therefore expanded statewide coordination efforts to form the RI Healthcare-Associated Infection Prevention and Antimicrobial Stewardship Coalition which is intended to effectively prevent HAI and ultimate improve the Centers for Medicare and Medicaid Services Hospital-acquired Condition (HAC) Reduction scores in Rhode Island.

KEYWORDS: antimicrobial stewardship, infection control, Rhode Island, acute care facilities, hospitals, long-term care facilities, public health

INTRODUCTION

Antibiotics are considered one of the greatest discoveries for human health in our lifetime. Preserving these important medications, through appropriate use, are critical to maintaining individual health, public health and national security. The CDC recognizes that the overuse of antibiotics has led to an increase in antibiotic-resistant organisms, *Clostridium difficile* infections (CDI), unnecessary hypersensitivity reactions, and general medication-related adverse events.[1] Consequently, efforts highlighting the importance of antimicrobial stewardship programs (ASP) emerged.

According to the CDC, antibiotic-resistant organisms cause two million illnesses and 23,000 deaths in the United States each year.[2] Development of antimicrobial resistance is directly related to the failure to use the right drug, at the right dose, for the right duration of time, and only when necessary (not for bacterial colonization or viral infections). As a result, antimicrobial stewardship has become a priority at the national level and has become a priority in Rhode Island as well.

In 2014 the Centers for Medicare and Medicaid Services (CMS) reported the rates of hospital-acquired conditions in hospitals throughout America. In this report, RI was ranked 51/51 in the United States for its rate of *Clostridium difficile* infections (CDI).[3,4] This stimulated a call to action by the Rhode Island Department of Health Director, Michael Fine, MD, to establish the Rhode Island Antimicrobial Stewardship and Environmental Cleaning Task Force (RIAMSEC TF), a coalition of stakeholders who recommend strategies and make recommendations to leverage resources to support antibiotic stewardship activities in health care settings as well as in the outpatient setting.

THE RI ANTIMICROBIAL STEWARDSHIP AND ENVIRONMENTAL CLEANING TASK FORCE

In August of 2014, the RIAMSEC TF convened with the mission to reduce antimicrobial resistance throughout the state. The membership, extending from acute care hospitals (ACHs), nursing homes, primary care practices, insurance companies, academia, and public health, is interdisciplinary, and includes infectious diseases, and infection-prevention experts in medicine, pharmacy, nursing, microbiology, and epidemiology throughout the state. From 2014 to 2016, this TF was chaired by the Consultant Medical Director for the Division of Infectious Diseases and Epidemiology at the Rhode Island Department of Health (RIDOH), Nicole Alexander-Scott, MD, MPH, an adult and pediatric and infectious disease physician, who has succeeded Michael Fine and is currently the state's Director of RIDOH.

To achieve the mission of the RIAMSEC TF, members recommended the following strategies and priorities to the RIDOH Director:

1. Assess antimicrobial stewardship and environmental cleaning practices by administering the CDC's Core Elements of Antibiotic Stewardship Programs (ASPs) survey to acute[5] and long-term care facilities.[6] This survey would allow RI to benchmark current practices against CDC guidelines.

2. Document the number of Full Time Equivalents (FTEs) allocated to infection control at hospitals and long-term

care facilities. Questions about the number of infection preventionists, infectious disease physicians and pharmacists at each facility should be added to the survey described above.

3. Establish guidelines for resources and staffing by using CDC guidelines and data from the surveys described above. Establish antimicrobial stewardship and environmental cleaning guidelines tailored to acute and long-term care settings.

4. Identify funding opportunities for implementation of recommended actions for multi-facility learning collaboratives and to support staff and resources for facilities.

5. Communicate antimicrobial stewardship and environmental infection control standards by sending a letter to facility executive leadership, explaining the rationale and importance of supporting stewardship and emphasizing expectations for action.

HOSPITAL SURVEY RESULTS

In November 2014, RIDOH surveyed all ACHs and long-term care (LTC) facilities in the state to assess current ASP practices. A 31-question electronic survey, adapted from the CDC's Checklist for Core Elements of Hospital ASPs, was sent (via online software program, SurveyMonkey[7]) to the executive hospital administrators at each ACH in RI. To maximize accuracy of responses, we asked respondents to answer questions in a multidisciplinary approach with antimicrobial stewardship (AMS) team members at their respective facilities.

Thirteen RI ACHs responded to the survey (response rate, 100%). Of these, 78% reported having an ASP at their facility which tracked antibiotic prescribing, use and resistance (unpublished data, RIDOH 2015). However, 44% of ACH reported not having a formal, written statement of support from leadership, and 50% did not receive any budgeted financial support for an ASP. Almost three-quarters of the hospitals (72%) reported having a physician leader responsible for ASP outcomes. Similarly, 89% of the ACHs reported having a pharmacist leader, though only 38% of them were trained in infectious diseases. Few hospitals (17%) reported having a process to review antibiotic orders after 48 hours to assess appropriateness. However, pharmacy-driven interventions were implemented in at least 50% of ACH (e.g. a physician or pharmacist needs to approve specified antibiotic agents prior to the pharmacy dispensing at the facility).

We concluded that, ASPs were present in most acute care facilities in RI. To maximize ASP practices, hospital-specific antimicrobial use recommendations should be made more readily available for use, hospital leadership should make an effort to increase the presence of an ASP leader in RI ACHs, and efforts should be made to increase review of antibiotics for appropriateness.

NURSING HOME SURVEY RESULTS

Also in 2014, the RIAMSEC TF developed a survey to assess the scope of AMS among RI LTC facilities.[8] Questions were based on CDC's Core Elements of Antibiotic Stewardship for Nursing Homes Programs, as well as on Advancing Excellence in America's Nursing Homes[9] campaign materials which were designed to evaluate processes to prevent and manage infections in LTC facilities.

RIDOH's public reporting contractor, Healthcentric Advisors, faxed a written notice to all RI LTC facilities (N= 88), and emailed copies of the survey to a subset of LTC staff on a statewide email distribution list. Notices recommended that each facility complete the survey within 3 weeks, using an online tool as a round-table exercise involving the director of nursing, infection control nurse, and any other staff responsible for infection prevention and/or AMS activities. No incentives were given for participation. Results suggest infection preventionists are largely responsible for ensuring appropriate antibiotic use in long-term care facilities and there is a need for increased interdisciplinary access to individuals with antimicrobial stewardship expertise.

In addition to conducting the survey, the RIAMSEC TF shared the results of the survey with healthcare facilities and developed a website[10] to share information and guidance. The Task force is actively seeking funding for statewide stewardship activities.

In December of 2015, RI was further jolted by CMS publishing the fiscal year 16 Healthcare-Acquired Condition (HAC) Reduction Program scores which revealed that seven of 11 RI ACHs were going to suffer reimbursement reductions.[11] This score is a cumulative score of quality measures, with 75% attributed to Healthcare Associated Infections. This was a further stimulus to stakeholders and RI Sen. Sheldon Whitehouse, who has long been a champion in this arena and charged the community to take action. In response to an urgent call to action, RIDOH expanded the RIAMSEC TF to include the already existing Healthcare-acquired Infections (HAI) subcommittee (which is the operational arm of a legislatively required RI Healthcare Quality Reporting Program Steering Committee) and formed a statewide Coalition with the goal of consolidating and coordinating resources and expertise. (**Figures 1 and 2**.)

HAI PREVENTION AND ANTIMICROBIAL STEWARDSHIP COALITION

The HAI Prevention and Antimicrobial Stewardship Coalition was developed under the leadership of the current RIDOH Director, Nicole Alexander-Scott, MD, MPH, appointed in April 2015. Consisting of partners from RIDOH, hospitals, nursing homes, physicians, pharmacists, infection preventionists, academia, community partners, and trade and professional organizations, the objectives of the Coalition are to increase collaboration and communication among
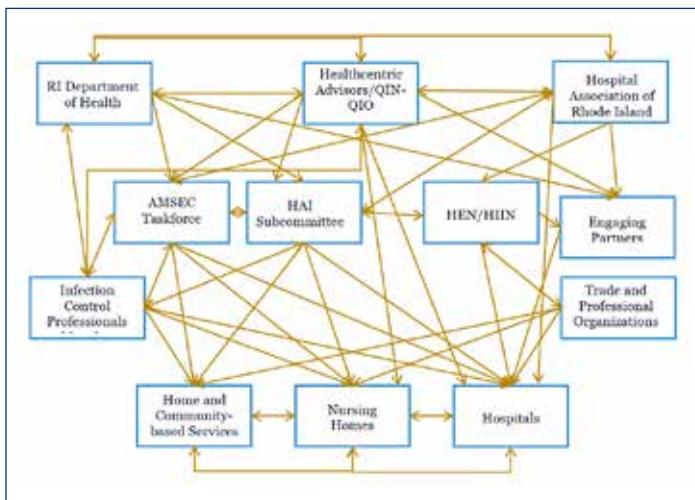
partners, and thereby reduce the duplication of effort while strengthening the effectiveness of statewide strategies. To achieve the goal of protecting the health of Rhode Islanders and reducing costs to the healthcare system, the Coalition established two groups: the "Leadership and Policy Committee" and the "Education and Best Practices Workgroup."

THE LEADERSHIP AND POLICY COMMITTEE

The Leadership and Policy Committee is comprised of hospital and nursing home executives who control funding and make administrative decisions at their respective facilities. It is essential to engage and educate this population about the importance of antimicrobial stewardship and the cost of antimicrobial resistance, in order to target the necessary resources to establish and support antimicrobial stewardship programs. This Committee is also tasked with developing and supporting state and national policies that align with Coalition goals.

EDUCATION AND BEST PRACTICE WORKGROUP

The Education and Best Practices Workgroup consists of HAI prevention and antimicrobial stewardship leaders, practitioners, and subject matter experts who identify gaps in state or facility programs and develop consistent best practices. The Workgroup will then share its expert information with the Leadership and Policy Committee.

The Coalition hosted a kick-off event on August 25, 2016, with approximately 300 attendees that included hospital and nursing home leadership, infection prevention specialists, quality improvement specialists, pharmacists, infectious disease physicians, laboratorians, insurers, and public health practitioners. This meeting brought all partners together to discuss how Rhode Island's healthcare community can work together
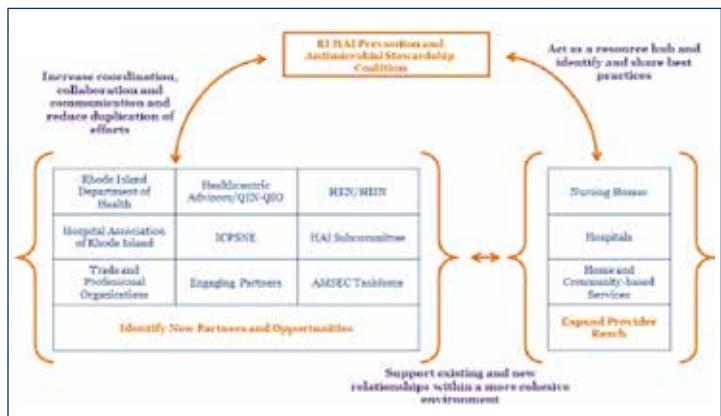
to improve antimicrobial stewardship and prevent HAIs.

The keynote speaker at the event was Captain Lauri Hicks, DO, Director of CDC's Office of Antibiotic Stewardship. Dr. Hicks, who has been an advocate for appropriate antibiotic use for nearly a decade, shared effective and practical ideas for improving and expanding antimicrobial stewardship programs at healthcare facilities. The various speakers discussed the health impact of HAIs; the financial burden of HAIs; the public health consequences of antibiotic resistance; and the need for antimicrobial stewardship.

Charged with coordinating statewide efforts to effectively prevent HAI and ultimately improve the CMS HAC Reduction scores among healthcare facilities in RI, the kick-off shared how the Coalition will be sustained going forward. With both groups of the RI HAI Prevention and AMS Coalition attending the kick-off in the summer of 2016, the Education and Best Practice Workgroup and the Leadership and Policy Committee would continue to meet at alternating dates every 3 to 6 months, targeting the respective audience for each group. Existing meetings and groups throughout the state with a focus on HAI prevention and AMS would also be leveraged to reduce duplication and to advance coordination of strengthened efforts.

On December 7, 2016 the Coalition hosted the first meeting of the "Education and Best Practice Workgroup". This meeting provided an opportunity for providers and stakeholders from across healthcare settings and disciplines to come together to coordinate efforts, share best practices, and drive improvement in Rhode Island. During the meeting, attendees reviewed the recommended guidelines for infection prevention and antimicrobial stewardship; discussed barriers to implementing these guidelines; learned about current research, quality improvement, and technical assistance projects; and listened to what colleagues in other facilities were doing to address the problem.

The next meeting organized by the Coalition was the "Leadership and Policy Meeting", held on May 8, 2017. The meeting brought together executive healthcare administration and board members from various healthcare facilities, state policy leaders, and clinical academic program leaders to discuss strategies to overcome the negative impact that HAIs have on the health of Rhode Islanders and on the financial sustainability of healthcare organizations.

Overall, Rhode Island has made a tremendous effort to increase antimicrobial stewardship and reduce the negative health impact and financial burden that HAIs have on the healthcare system. This multi-disciplinary approach of the Coalition, with the strong communication and outreach efforts, has set the stage for RI to be very successful in promoting antimicrobial stewardship and combating HAIs. Preliminary results of the fiscal year '17 HAC Reduction Program scores reveal that the previous results of seven out of 11, has now decreased to four out of 11 acute care hospitals in RI which will be penalized with reimbursement reductions.[11] There is still much more work to be done, but RI has laid the groundwork to strategically reduce HAI and improve the metrics associated with AMS statewide.

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Role of the Pharmacist in Antimicrobial Stewardship

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It is well documented in the primary Antimicrobial Stewardship literature that a multidisciplinary team is an essential element to having a successful program. The Centers for Disease Control (CDC) and the Infectious Diseases Society of America (IDSA) offer excellent guidelines for implementation and recommendations for key members of an Antimicrobial Stewardship Team (AST). The guidelines highlight the interdisciplinary nature of Antimicrobial Stewardship teams, noting that each member has a unique area of expertise and background knowledge base that strengthens the team beyond individual members.[1,2] These guidelines have existed for more than a decade. Time has passed and technology has advanced since the guidelines were first developed, and the roles of the members of the AST have changed from their initially described roles of years ago.

The role of pharmacists in particular has been expanded in the past several years. Early versions of the stewardship guidance documents had pharmacists playing a narrow role as the medication expert, with the recommendation that clinical questions or therapy guidance be handled by physicians.[3]

Numerous specialized pharmacy post-graduate residency programs, stewardship training certificate programs and additional certification exams are now available for pharmacists seeking to gain a greater knowledgebase in infectious diseases and antimicrobial stewardship.[4] Additional post-graduate certifications and training are recommended by the IDSA guidelines as a best practice for a lead stewardship pharmacist.[2]

Each of the individual elements of stewardship can be enhanced with a pharmacist's assistance. The American Society of Health-Systems Pharmacists (ASHP) highlights areas where pharmacists are uniquely positioned to provide contributions to ASP programs.[4] Each of the elements of stewardship are explored in greater detail below.

PROSPECTIVE AUDIT AND FEEDBACK

Prospective audit with direct intervention and feedback is one of the two main core strategies employed by AST programs.[1,2] It allows for providers to make their own treatment decisions, but supplemented with input from the AST. It is thought that the education provided in these encounters may not only reduce inappropriate use for an individual patient, but the increase in knowledge can be applied to similar future encounters, thus decreasing the burden of inappropriate antimicrobial use.[3] The pharmacists are uniquely situated to intervene using prospective audits, as their workflow includes chart review for appropriateness and indication when approving inpatient orders, filling outpatient prescriptions, or doing medication reconciliation as part of their daily activities in their practice site. Pharmacists can promote optimal use of antimicrobials through individualized patient dosing when intervening on medication issues.[4]

FORMULARY RESTRICTION AND PREAUTHORIZATION REQUIREMENTS

The second core strategy of many AST programs includes formulary restriction and preauthorization of selected antimicrobials.[1,2] These interventions may lead to immediate reductions in use and the costs associated with these selected antimicrobials. Restrictions, additions, deletions to Formulary in the inpatient setting, development of drug therapy and disease state guidelines or pathways for appropriate use of antimicrobials are generally handled as part of the duties of the Pharmacy and Therapeutics (P&T) Committee.[3] All of these interventions are important components to promote optimal antimicrobial use. Pharmacist involvement for shepherding stewardship initiatives is vital to achieve the needed buy-in from members of the P&T Committee who may not have a level of comfort or understanding of the elements of stewardship.

The literature cites as supporting evidence of Formulary restriction, a study published by Gross, et al, focused on the clinical and economical outcomes of their stewardship program.[5] They highlighted that their stewardship team consisting of a clinical pharmacist and an infectious diseases attending physician who reviewed requests for restricted antimicrobials was "more effective than an off-hours approval by infectious diseases fellows in recommendation appropriateness (87% vs 47%; P < .001), cure rate (64% vs 42%; P = .007), and treatment failures (15% vs 28%; P = .03)."[5]

EDUCATION

Education targeting patients and the general public about antimicrobial stewardship is an important piece in the stewardship armamentarium to combat inappropriate use.[4] In

a recent Gallup poll, pharmacists were noted to be ranked among the most honest and ethical professionals.[6] They were ranked second, with a 67% rating of "high" or "very high" ethical standards, second only to nurses in a survey of which 1028 US residents responded.[6] In an era where misinformation is rampant, and dissemination of factual information is imperative, pharmacists fulfill an important role in the community to provide unbiased and scientifically accurate information to their patients. Noting the importance of community education, the CDC has created educational literature as part of the Get Smart about Antibiotics campaign that is specifically designed for use in community pharmacy practice.[7] The CDC's recently released Core Elements of Outpatient Antimicrobial Stewardship again highlights the importance and impact of pharmacist involvement for a successful stewardship program.[4]

PHARMACY-DRIVEN INTERVENTIONS

Automatic IV to oral substitution for selected antimicrobials with excellent oral bioavailability is an intervention that is commonly cited in the stewardship literature as having a positive impact on not only use of antimicrobials, but also a reduction in harm and costs associated with intravenous administration of antimicrobials.[1,2] For many disease states, an oral option is not only safe and effective, but it is highly appropriate. Antimicrobials such as fluoroquinolones, linezolid, and fluconazole are excellent targets for and automatic substitution protocol completed by a pharmacist.[1] Protocols containing these drugs and others are well described in the literature and are associated with decreased length of stay, reduced treatment complications and increase cost savings. Additional pharmacist-driven initiatives include; individualized dose adjustments for patients with organ dysfunction (e.g. renal or hepatic adjustment), dose optimization based on therapeutic drug monitoring, and detection and prevention of antibiotic-related drug-drug interactions.[4] Pharmacists may also help with drug selection to avoid unnecessarily duplicative therapy in patients simultaneously receiving multiple agents, or suggesting alternatives when a desired medication may be unavailable due to drug shortage.[3] Use of automated alerts to highlight situations such as duplicate therapies with overlapping spectra can be reviewed and actioned on by a trained pharmacist, thus allowing higher acuity interventions to be assessed by the infectious diseases physician.[4] Time-sensitive indications, especially antibiotics administered for surgical prophylaxis can be monitored for discontinuation by pharmacists.[4]

REGULATORY COMPLIANCE

The elements of performance for the Joint Commission (TJC) Medication Management Standard for Antimicrobial Stewardship prescribe that a pharmacist be included on an AST.[8] Pharmacy involvement helps to ensure compliance with the standards set by various regulatory agencies, not limited to TJC and Centers for Medicare and Medicaid Services (CMS).[4] In addition to compliance, collection and evaluation of antimicrobial utilization data is vitally important for assessing the impact of your stewardship interventions.[1-4] The data associated with length of therapy and tonnage of antimicrobials used resides with the Pharmacy department. Working closely with pharmacists to review use patterns and report metrics on use will be at the forefront as mandatory reporting of antimicrobial use to the National Health-Safety Network (NHSN) by inpatient stewardship programs is anticipated by the end of 2018.

The role of the pharmacist in an individual AST will vary based upon the structure and needs of the individual organization.[2,3] However, the guidance on stewardship from IDSA, CDC, SHEA, ASHP and other key stakeholders makes it abundantly clear that a pharmacist is a resource that is vital to the success of any antimicrobial stewardship team.[1-4] As antimicrobials become an increasingly scarce resource, it will be imperative to have the input from our pharmacy professionals to guide us in these increasingly challenging times.

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Antimicrobial Stewardship Metrics:
Prospective Audit with Intervention and Feedback

MONICA J. DOROBISZ, PharmD; DIANE M. PARENTE, PharmD

INTRODUCTION

Prospective audit with intervention and feedback (PAIF) is one of two core antimicrobial stewardship program (ASP) strategies recommended by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America.[1] The PAIF strategy consists of a case-by-case review of patients prescribed antibiotics, typically by an infectious diseases (ID) physician or clinical pharmacist. Cases are reviewed for antibiotic appropriateness and feedback is delivered directly to the provider caring for the patient, with the goal of improving antibiotic use while minimizing unintended consequences such as bacterial resistance and adverse effects. A PAIF can be employed in a variety of ways depending on the healthcare setting (inpatient vs. outpatient), available resources, and can target a variety of interventions (e.g. duplicate antibiotic coverage, unnecessary antibiotic use, dose adjustments, route changes, indication/infection-specific, treatment duration). While PAIF can be costly and labor intensive, providers are able to maintain their prescribing autonomy. In addition, PAIF allows the antimicrobial stewardship team to provide education to prescribers at the time of intervention.[1] In this article, we review PAIF in various healthcare settings including inpatient acute care hospitals, long-term care facilities, and outpatient settings.

INPATIENT ACUTE CARE HOSPITALS

The first ASP guidelines were primarily focused on the establishment of antimicrobial stewardship (AMS) strategies in inpatient acute care settings.[2] In comparison to outpatient settings, the implementation of AMS strategies in acute care settings is easier since members of the AMS team, provider, and patient are usually in the same location. Published literature on the implementation of PAIF has shown this strategy to improve antibiotic utilization and reduce antibiotic resistance, without negatively affecting patient outcomes.[3-5] A 7-year prospective study evaluated the impact of a limited PAIF on patients receiving parenteral third-generation cephalosporins, aztreonam, parenteral fluoroquinolones, or imipenem. It noted a 22% decrease in the use of parenteral broad-spectrum antibiotics nosocomial *C. difficile* infections, and nosocomial resistant Enterobacteriaceae.

The structure of PAIF can vary depending on the resources of the practice setting. One study prospectively evaluated the impact of two different PAIF methods compared to no PAIF in adult intensive care units (ICU).[4] The first PAIF method involved an ID specialist physician who communicated with the ICU team via the ICU pharmacist. The second PAIF included the ID physician participating in interdisciplinary ICU rounds three times a week with the ICU pharmacist participating daily. Both PAIF methods resulted in improved rates of appropriate antimicrobial selection and lower frequencies of resistance emergence compared to no PAIF. This study demonstrated that different PAIF methods improve antibiotic use without any deleterious effects. Another study conducted in a 253-bed community hospital using limited resources demonstrated a 64% reduction in antibiotic days of therapy per 1000 patient-days and a 37% decrease in antibiotic expenditures.

In the inpatient setting, clinical decision support software (CDSS) systems are also utilized to assist in PAIF. These systems are able to target specific patient populations, antibiotics, or culture results based on the needs of the ASP. A study[7], utilizing CDSS to target patients who were on redundant antibiotic combinations, found that CDSS decreased the number of patients requiring review by 84% and of the patients reviewed, an intervention was made in 71%. Recommendations to discontinue redundant therapy were accepted in 98% of cases. This study involving 137 patients concluded an annualized cost savings of approximately $48,000. While PAIF can be labor intensive, adopting a computerized support system can increase efficiency and maximize intervention opportunities.

PAIF allows for a multidisciplinary approach to optimize patient care and enhance appropriate antibiotic use in the inpatient setting. The implementation of PAIF is one of the most valuable strategies in a comprehensive ASP.

LONG-TERM CARE FACILITIES (LTCFS)

Antimicrobials represent almost half of all prescriptions in LTCFs, and approximately 50%-70% of residents receive at least one antibiotic course annually.[8] Many of these prescriptions, unfortunately, represent overuse or inappropriate use of antibiotics.[8] The implementation of PAIF can likely improve antibiotic use in LTCFs.

Limited published evidence is available for determining

the most effective AMS strategies in LTCFs, and even fewer studies specifically evaluate PAIF. A prospective quasi-experimental study implementing an ASP team consisting of an ID-trained pharmacist and physician targeted urinary tract infections (UTIs) at three community LTCFs.[9] Two seven-month phases included baseline data collection on facility-level antimicrobial utilization and susceptibility patterns, followed by an intervention phase with weekly site visits by the ID pharmacist who conveyed recommendations to the primary treating provider via telephone or fax. Only 8% of residents started on antibiotics for UTI met Loeb criteria[10] for antibiotic initiation. There were 292 antibiotic prescriptions pre-intervention and 183 during the intervention, of which only 104 could be reviewed by the ID pharmacist. The remaining 79 prescriptions were either initiated in the acute care setting or the entire antibiotic course was completed in between the weekly visits. A therapy change recommendation was made in 38% of those reviewed, but only 10 (25%) were accepted. The most common recommendations included discontinuing antibiotics (24%), shortening the course (11%) and streamlining therapy (2%). Despite the low acceptance rate, an immediate 26% decrease in UTI antibiotic prescriptions was seen during the intervention phase with a 6% reduction continuing through the rest of the period (95% CI -8 to -3%), and an immediate 25% reduction in all antibiotic prescriptions with a continued 5% reduction throughout the phase. The authors concluded that this approach has the potential to be effective but also identified many barriers which need to be overcome in order for the PAIF strategy to be successful in LTCFs.

One barrier identified in this study was the difficulty in establishing relationships with prescribers in this setting.[10] Lack of a prior provider-to-provider relationship and the absence of face-to-face interaction are limitations in LTCFs since much of the medical care occurs remotely. Provider buy-in and recommendation acceptance can prove challenging if this relationship deficiency exists. The addition of educational seminars, face-to-face meetings and collaboration in design of the program with an identified ASP champion from within the LTCF may help strengthen the benefits of a PAIF strategy.

Secondly, there were many missed opportunities for intervention with an antibiotic review completed once weekly. Since duration of therapy for UTI is often 7 days or less, many treatment courses were completed in between the weekly review or close to completion, and feedback to providers was not provided in these cases (81% of opportunities).[10] If a once weekly frequency is all that is feasible, feedback to providers on completed antibiotic courses should be attempted in an effort to broadly change prescribing habits for future cases. An ASP with more frequent review might prove to be more useful, though this is unlikely to be feasible with limited resources and general unavailability of ID physicians and pharmacists in LTCFs. Although utilization of ID specialists

for PAIF would be ideal, involving any physicians, mid-level practitioners, pharmacists or nurses trained in antimicrobial stewardship to act as peer champions may be a more practical approach. Fortunately, there are AMS certification or informal training programs which provide learning opportunities for interested practitioners.[11,12] Additional ways to improve access to ID specialists include sharing consultants amongst facilities, utilizing telemedicine, and partnering with local hospitals or academic medical centers which may be able to incorporate LTCF activities into medical and pharmacy residency and student training.

While once weekly PAIF is already less than ideal, even this frequency may not be feasible in many LTCFs. In most cases, a comprehensive medication review is completed by a consultant pharmacist once per month on each resident. While this method could be used to provide a retrospective review with feedback to providers for future case improvement, prospective audit at this frequency would likely be a futile effort. Many LTCFs use central pharmacies which fill prescriptions for several institutions. With additional AMS training, central-fill pharmacists are in a unique position to ensure the antibiotic has an appropriate indication, dose, duration and is the best choice for the resident based on the facility's antibiogram and treatment pathways; however, these pharmacists likely lack protected time for these activities and often do not have access to resident medical records which would be necessary requirements for them to play a role in PAIF.[8]

Aside from limited personnel resources, the availability of antibiotic use data could be a challenge in some LTCFs. An electronic record with the ability to generate reports (e.g. active antibiotic orders, antibiotics completed within the last 48 hours, etc.) could serve as an ideal system for identifying opportunities; however, some LTCFs still utilize paper records or electronic systems without robust reporting capabilities. In such cases, the ASP clinician would need to rely on manual tracking mechanisms often filled out by nursing personnel which may be incomplete and add an additional task to nursing's daily workload.

Lastly, family expectations are an important barrier to primary provider acceptance of PAIF recommendations. Providers report feeling pressured by nursing staff, residents and families to send urinalyses and cultures for indications such as cloudy urine or temporary behavioral changes, and to prescribe antibiotics.[8] A recent study of 35 Boston-area nursing homes reported increased antibiotic use (adjusted OR 3.43, 95% CI 1.94-6.05) and hospital transfer (adjusted OR 3.00, 95% CI 1.19-7.53) when health care proxies were involved in decisions on residents with advanced dementia.[13] It is therefore extremely important to involve families, residents and nurses in educational opportunities discussing the risks associated with antibiotic misuse in order to increase the acceptance of PAIF recommendations in LTCFs.

OUTPATIENT

The Centers for Disease Control recently reported that approximately half of outpatient antibiotic prescribing may be suboptimal, due to antibiotic selection, dosing and duration, and at least 30% of prescriptions are unnecessary.[14] With this much room for improvement, there may be opportunity for a PAIF strategy, although data regarding how best to implement this on the outpatient side is even more lacking than in LTCFs. Audit and feedback strategies in outpatient clinics have been described with success in decreasing antibiotic misuse; however, these mechanisms utilize retrospective data and peer prescriber comparisons as feedback mechanisms.[15] A truly prospective mechanism in which a member of an ASP provides patient-specific recommendations to outpatient providers in real time is not well described.

Pharmacists in community dispensing pharmacies could play a role in PAIF; however, pharmacy business models would need to change before this type of activity could occur. These pharmacists are not allotted time for clinical activities, lack access to clinic medical records, and usually do not have an established relationship with prescribers unless a collaborative practice agreement is in place. While these pharmacists can play a vital role in counseling patients regarding their prescribed antibiotic, large drugstore companies need to invest in AMS nationwide efforts before community pharmacists could truly participate in PAIF.

Opportunities for PAIF in the outpatient setting may exist with ambulatory care pharmacists. Many clinic settings now have pharmacists on site to provide medication therapy management services. With additional training in AMS, these pharmacists could serve as clinic ASP champions along with a physician or mid-level practitioner and may be able to develop mechanisms to evaluate antibiotic prescriptions prior to patients leaving the office visit. Similar barriers as discussed above in LTCFs could be identified, including reporting abilities in electronic records, lack of ID training and expertise, protected time to perform these services, and patient and family pressure to prescribe antibiotics.

As AMS efforts expand beyond acute care hospitals, is it critical that LTCFs and outpatient practices start thinking outside the box to implement important strategies such as PAIF.

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Disclaimer

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Antimicrobial Stewardship Program Perspective: IV-to-PO Switch Therapy

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INTRODUCTION

In the past, initial antibiotic therapy was via the intravenous (IV) route. Over the years, there has been increased confidence and experience with oral (PO) antibiotic therapy. The preferred antibiotics used for PO therapy are those with excellent GI absorption, i.e., high bioavailability (> 90% absorption).[1,2] Given the pharmacokinetic (PK) and pharmacodynamic (PD) properties of selected oral antibiotics, there has been widespread acceptance of "transitional antibiotic therapy," now known as IV-to-PO switch therapy. Early experience with this therapy demonstrated that some or most antibiotic therapy in hospital could be transitioned to PO following initial IV therapy.[3,4] It became clear that patients treated with IV-to-PO therapy for common infectious diseases, e.g., community acquired pneumonia (CAP) had comparable outcomes/cure rates to patients treated with entirely IV courses of antibiotics. Therefore, it became evident that a key element of antibiotic stewardship programs (ASP) is to support IV-to-PO switch therapy.[4-6] Currently, IV-to-PO switch therapy is a key component of ASP hospital IV-to-PO switch initiatives. (**Table 1**)

The basis of the interchangeability of IV and equivalent PO antibiotics is obvious, i.e., if, at any given dose, serum/tissue levels are the same PO as IV, outcomes are the same. This most easily applies to IV and PO formulations of the same antibiotics, e.g., 100 mg of doxycycline IV/PO, 500 mg levofloxacin IV/PO or 400 mg of moxifloxacin IV/PO. Since serum/tissue time curves are the same, why not use PO antibiotic therapy whenever possible if outcomes are the same?[7,8] There are only two clinical scenarios where IV therapy may be preferred to PO therapy. Obviously, even when using antibiotics with high bioavailability (> 90%) effectiveness may be less if GI absorption is decreased. The other clinical situation is that of the "septic patient" who may succumb within an hour of initiating treatment. In this setting, initial IV therapy is preferred.[9-11] After clinical response to the initial IV antibiotic, its PO equivalent may then be used to complete/therapy.

IV-TO-PO SWITCH THERAPY USING THE SAME ANTIBIOTIC CLASS

The easiest IV-to-PO antibiotic switch therapy for various infections is using antibiotics with both IV and PO formulation.[12-16] Highly bioavailable PO antibiotics are clinically equivalent to their IV formulations. Commonly used antibiotics with dose equivalent PO and IV formulations are presented with their respective bioavailabilities in tabular form. (**Table 2**) Since PO = IV, antibiotic regimens that begin

Table 1. Clinical and Pharmacoeconomic Advantages of Oral Antibiotic Therapy

	Advantages	Comments
Oral Antibiotic therapy	Lower *antibiotic acquisition* cost (at same dose)	Avoid if markedly impaired gastrointestinal absorption
	No *IV antibiotic administration* costs ($10/dose)	*If therapeutic effect is needed in < 1 h (patient in shock), begin therapy intravenously (IV) and later switch to oral (PO) to complete therapy*
	Rapid gastrointestinal absorption (~ 1 h even in critical ill patients)	
	Eliminates phlebitis and IV line related infections	
	Decreases length of stay (LOS)	
	Patients pleased with earlier discharge	

Table 2. Bioavailability of Oral Antimicrobials

Bioavailability	Antimicrobials		
Excellent (> 90%)	Amoxicillin Cephalexin Cefprozil Cefadroxil Clindamycin Quinolones Chloramphenicol	TMP TMP-SMX Doxycycline Minocycline Fluconazole Metronidazole Cycloserine	Linezolid Tedizolid Isavuconazole Voriconazole Rifampin Isoniazid Pyrazinamide
Good (60 – 90%)	Cefixime Cefpodoxime Ceftibuten Cefuroxime	Valacyclovir Famciclovir Valganciclovir Macrolides Cefaclor Nitrofurantoin	Ethambutol 5-Flucytosine Posaconazole Itraconazole *(solution)* Nitazoxanide *(with food)*
Poor (< 60%)	Vancomycin Acyclovir	Cefdinir Cefditoren	Nitazoxanide *(without food)* Fosfomycin

with an IV antibiotic may be switched to its PO equivalent at any time during therapy, i.e., usually after clinical response/defervesce or after 72 hours.[17-20]

GIVEN ANY DOSE, IV-TO-PO SWITCH USING ANTIBIOTICS FROM DIFFERENT ANTIBIOTIC CLASSES

IV-to-PO switch therapy using the same antibiotic, e.g., IV-to-PO levofloxacin is straightforward. However, if there is no oral formulation of a particular antibiotic, the ASP infectious disease (ID) clinician can advise which PO antibiotic will provide equivalent therapy. Often, a different class of antibiotic is used at a different dose. For example, if initial IV therapy for an uncomplicated methicillin sensitive *S. aureus* (MSSA) skin abscess is with cefazolin, then IV to PO switch is best accomplished with cephalexin. Spectrum and activity of both are comparable, but differ in PK/PD aspects. Comparing the peak serum levels after cefazolin IV dose of 1 gram peak serum levels are ~185 mcg/ml. This is clearly far in excess above the minimal inhibiting concentration (MIC) for MSSA, i.e., usually ≤ 1 mcg/ml. Therefore, as long as serum levels exceed the MIC of MSSA, with an equally active drug against MSSA, e.g., cephalexin (serum levels of 18 mcg/ml), PO therapy should be more than adequate (if the skin abscess is not yet encapsulated requiring incision and drainage in addition to antibiotic therapy). Other oral (2nd and 3rd generation) cephalosporins are less active than cephalexin against MSSA, and for this reason (not PK/PD related), it is preferable to use cephalexin.[2,21,22]

The same principle pertains in treating cellulitis due to group A streptococci (GAS) with initial ceftriaxone IV therapy. Since there is no PO formulation of ceftriaxone, an antibiotic with a comparable anti-GAS spectrum and activity may be used. The MIC for GAS is lower than with MSSA, i.e., ~0.1 mcg/ml. Once again, cephalexin is preferred since a 1-gram (PO) dose results in peak serum levels of 18 mcg/ml, more than sufficient to effectively treat GAS cellulitis.

ANTIBIOTIC SPECTRUM AND ACTIVITY CONSIDERATIONS

Before initiating PO therapy, practitioners must be sure that different class antibiotics (IV ~ PO) have the same spectrum and a high degree of activity against the target pathogen. The PO drug equivalent need not achieve the serum level of the IV antibiotic, but serum levels should exceed the MIC of the pathogen.[2,4]

The most difficult concept for non-infectious disease practitioners to comprehend is that antibiotic susceptibility is not the same as activity. Comparing the relative activity of two different antibiotics, that are susceptible against the same organism, it is often believed in error, that the antibiotic with the lower MIC is more active and therefore

preferable. Instead, the ratio of the MIC to achievable serum levels (drug serum levels can be found in chapter 11 of reference 2) of different antibiotics must be compared. All other things being equal, the drug with a serum level of 20 mcg/ml and an MIC of 1 (20:1) is more active than one with an MIC of 0.5 mcg/ml and a peak serum level of 1.5 mcg/ml (3:1).

Another key concept to be aware of is the difference between *in vitro* susceptibility and *in vivo* effectiveness. For example, TMP-SMX is *in vitro* susceptible to GAS and MSSA/MRSA. Clinical experience has shown that TMP-SMX is suboptimal against GAS and MRSA, but is excellent clinically against MSSA. Doxycycline is commonly reported as MRSA susceptible. However, with MRSA soft tissue abscesses, doxycycline frequently fails clinically. In spite of susceptibility, its use creates its own inactivation/resistance. For these reasons, minocycline is preferable to doxycycline for MRSA.[23-25] (**Table 3**)

Table 3. Antibiotic-Organism Combinations for Which *In Vitro* Susceptibility Testing Does Not Predict *In Vivo* Effectiveness

Antibiotic	"Susceptible" Organism
Penicillin	H. influenzae, Yersinia pestis, VSE*
TMP-SMX	Klebsiella, VSE, Bartonella
Polymyxin B	Proteus, Salmonella
Imipenem	Stenotrophomonas maltophilia
Vancomycin	Erysipelothrix rhusiopathiae
Gentamicin	Mycobacterium tuberculosis
Aminoglycosides	Streptococci, Salmonella, Shigella
Clindamycin	Fusobacteria, Clostridia, Listeria
Macrolides	P. multocida
1st, 2nd generation cephalosporins	Salmonella, Shigella, Bartonella
3rd, 4th generation cephalosporins	Listeria, Bartonella, MRSA+
Quinolones	MRSA+

+In spite of apparent *in vitro* susceptibility of antibiotics against MRSA, only vancomycin, minocycline, quinupristin/dalfopristin, linezolid, tedizolid, daptomycin, ceftaroline fosamil, telavancin, dalbavancin, oritavancin, and tigecycline are effective *in vivo*.

*Effective penicillin therapy for systemic enterococcal infections due to VSE requires an amino-glycoside, e.g., gentamicin.

Adapted from: Cunha CB. Overview if Antimicrobial Therapy. In: Cunha CB, Cunha BA (Eds). Antibiotic Essentials (15th Ed). Jay Pee Medical Publishers, New Delhi, 2017. pp 6 Effective in vivo antimicrobials for these organisms can be found on pp 218-255 of this reference.

ADVANTAGES OF ANTIBIOTIC PO THERAPY: BEYOND IV-TO-PO SWITCH

Practitioners are slow to change practice habits.[2,4] Clinical logic and reasoning should be considered while gaining the confidence that comes from successful experience. Such is

Table 4. Oral Antibiotic Therapy of Selected Infectious Diseases

Acute infections	Subacute/chronic infections
Anthrax	Q fever
Plague	Brucellosis
Tularemia	Leptospirosis
Rocky Mountain spotted fever (RMSF)	Nocardia
Typhoid fever	Actinomycosis
Legionnaire's disease	Meliodosis
Diphtheria	Bartonellosis
Vibrio vulnifcus	Lung abscesses†
Cholera	Liver abscesses†
Clostridium difficile	Intraabdominal abscesses†
Pneumocystitis (jiroveci) carinii pneumonia (PCP)	Pelvis abscesses†
Malaria	Renal abscesses†
Lyme disease (neuroborreliosis, myocarditis)	Sinusitis
Febrile neutropenia	Pyelonephritis
Nosocomial pneumonia	Prostatitis
Acute bacterial endocarditis in IVDAs (MRSA)	Complicated skin/soft tissue infections (cSSSI)
	Osteomyelitis
	Pulmonary and extrapulmonary TB

† may also require abscess drainage

the case with entirely PO antibiotic therapy, i.e., if IV-to-PO switch is good (and it is), PO only is even better![5,6] (**Table 4**)

Antibiotic PO only therapy is the next step beyond IV-to-PO switch therapy. If with CAP, after initial 3 days of IV therapy and the next 11 days (total therapy IV/PO = 14 days) PO only therapy is not inferior to 14 days of IV therapy. Excluding immediate life threatening infection, it is not a great leap of faith to treat for the full course entirely with a PO antibiotic. Antibiotic PO therapy, using antibiotics with high bioavailability > 90%, e.g., levofloxacin, moxifloxacin, doxycycline for PO therapy should be used as often as possible for CAP. Entirely PO therapy results in shorter LOS and earlier discharge. The patient goes home earlier and is not burdened by home IV therapy and eliminates IV associated phlebitis or IV line infections. Furthermore, as with IV-to-PO therapy, the cost of PO antibiotic therapy is markedly less than for equivalent IV therapy. Antibiotic cost is always much lower PO (except with linezolid) than IV (at the same dose). There are no IV administration costs (which may exceed the cost of the IV antibiotic) with PO therapy. While certain PO medications may result in GI upset, this is usually manageable and should not dissuade providers from

using PO therapy whenever possible. Risk of *C. difficile* is antibiotic specific and there is no difference in risk whether the IV or PO route is selected. However, many PO options, e.g. doxycycline, are C. *difficile* protective. In short, entirely PO antibiotic therapy for nearly all outpatient and inpatient infections (non-septic) is clinically equivalent and preferred for the above reasons to IV therapy.[2-6]

As experience increases, confidence in entirely PO antibiotic therapy will become as established and accepted as the PO component of IV-to-PO switch therapy. In ASPs, oral therapy is to the natural extension of antibiotic IV-to-PO switch therapy.

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Infection Control and Antimicrobial Stewardship

JOHN R. LONKS, MD

ABSTRACT

Infection Control measures can reduce the transmission of bacteria in the hospital. Reduction in the use of antibiotics via Antimicrobial Stewardship programs can reduce antibiotic resistance. The combination of Infection Control measures and Antimicrobial Stewardship can lead to a greater reduction in antibiotic resistant bacteria.

KEYWORDS: infection control, antimicrobial stewardship, antibiotic resistance, *Clostridium difficile*

Infection control involves preventing the transmission of infectious agents from patient-to-patient, patient-to-staff, staff-to-patient, visitor-to-patient, visitor-to-staff, etc. Commonly encountered infectious agents include viruses and bacteria. Among the bacteria some are antibiotic susceptible and others resistant. During the 1980s with concern for transmission of the HIV in healthcare settings, universal precautions was developed. The concept of universal precautions is such that any patient should be considered potentially infectious without having direct evidence of infection because patients may be asymptomatic yet seropositive.[1] Over time the concept of considering all patients as potentially infectious has evolved into the practice of Standard Precautions.[2]

During the 1970s and 1980s methicillin-resistant *Staphylococcus aureus* (MRSA) started to emerge in the hospital setting. *S. aureus* is a gram-positive bacterium. About 30% of adults at any given time are colonized with *S. aureus*. Some people are transiently colonized, others are colonized for a prolonged period. *S. aureus* may be methicillin susceptible or methicillin resistant. One of the strategies to reduce the transmission of MRSA in hospitals is the use of Contact Precautions. Contact Precautions involves the use of gowns and gloves upon entry into the patient's room. Gowns and gloves protects healthcare workers from contaminating their hands or clothing. Gowns and gloves are removed when exiting a patient's room, hands are then cleaned; thus, preventing the transmission of bacteria from one patient to another.

During the late 1980s and early 1990s vancomycin resistant enterococcus (VRE) emerged. The use of Contact Precautions was recommended for the prevention of transmission of VRE. Additionally, the prudent use of vancomycin was recommended including situations in which vancomycin use should be discouraged.[3] This recommendation was probably based upon the concept that the use of antibiotics may drive antibiotic resistance.

Community-acquired MRSA emerged during the late 1990s. This was initially noticed among pediatric patients who had no predisposing risk factor for MRSA.[4] Treatment failure and deaths occurred among children empirically treated with a beta-lactam antibiotic.[5] Soon thereafter there was an emergence of community-acquired MRSA among children and adults in the United States. With the emergence of community-acquired MRSA there was an increase in the empiric use of vancomycin.

Hospital-acquired *Clostridium difficile* is a serious problem. A recent study using data from 10 geographically distinct areas in the United States showed that *C. difficile* is the most common hospital-acquired pathogen, more common than *S. aureus*.[6] Pseudomembranous colitis associated with antibiotic use was recognized during the 1950s and 1960s. *C. difficile* was identified as the causative agent of antibiotic-associated pseudomembranous colitis in 1978.[7] *C. difficile* is a gram-positive rod that produces two different toxins, toxin A and toxin B. It is the toxin that causes pseudomembranous colitis and the clinical symptom of diarrhea. Antibiotic treatment disrupts the normal flora of the intestinal tract allowing *C. difficile* to grow and produce toxins. Early on it was noted that pseudomembranous colitis due to *C. difficile* was associated with the use of clindamycin.[7] Since that time other antibiotics, including the third- generation cephalosporins and fluoroquinolones, were identified as a risk for the development of *C. difficile* infection. Third-generation cephalosporins, fluoroquinolones and clindamycin are associated with a higher risk while penicillin, tetracyclines, trimethoprim/sulfamethoxazole are associated with a lower risk of developing *C. difficile* infection (**See Figure 1**).[8] From an Antimicrobial Stewardship point of view, antibiotics with a lower risk of developing *C. difficile* are preferable to other antibiotics provided they have the same clinical efficacy. Hence, strategies to reduce *C. difficile* infection include reduction of the total use of antibiotics and when an antibiotic is necessary then choose an antibiotic that has a lower risk for the development of *C. difficile*. Infection Control practices used to reduce the transmission of *C. difficile* include Contact Precautions, daily room cleaning and using cleaning agents that are sporicidal, for example, sodium hypochlorite.

Figure 1. Pooled Odds Ratio with 95% CI for each antibiotic in relation to the main outcome of interest (*C. difficile* diarrhoea).[8]
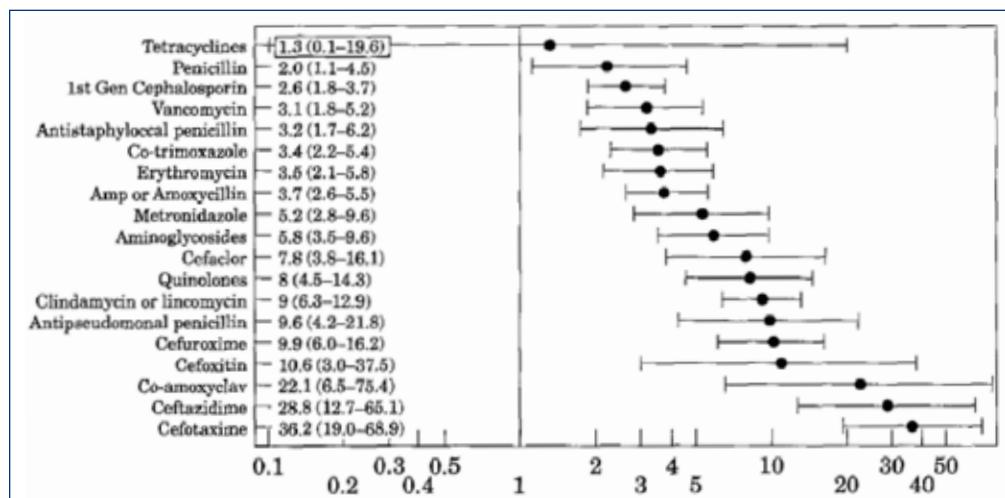
MRSA and VRE are classic examples and continue to be a concern for transmission of antibiotic-resistant bacteria in the hospital. Over the past two decades, gram-negative rods resistant to extended spectrum beta-lactams, such as third- and fourth-generation cephalosporins, have increased. More recently common gram-negative bacteria such as *E. coli* and *Klebsiella pneumoniae* have become resistant to carbapenems (imipenem and meropenem). Common gram negative bacteria are resistant to beta-lactam antibiotics because they produce a beta-lactamase. Beta-lactamases are enzymes produced by resistant bacteria that break the beta-lactam ring, hence inactivating the beta-lactam antibiotic. There are more than 1000 beta-lactamases. When an *Enterobacteriaceae* is resistant to carbapenems they are referred to as CRE (carbapenem- resistant *Enterobacteriaceae*). There are different beta-lactamases that confer resistance to carbapenems. KPC is a carbapenemase that inactivates carbapenems; it is the most commonly found mechanism for carbapenem resistance in the United States. NDM (New Delhi metallo-beta-lactamase) is another carbapenemase that inactivates carbapenems and is less common in the United States.

The emergence of antibiotic-resistant bacteria is associated with the use of antibiotics. When antibiotics were introduced into clinical medicine during the 1940s, common bacteria such as *S. aureus*, *E. coli* and *Streptococcus pneumoniae* were not antibiotic resistant. Once an antibiotic-resistance mechanism (mutation or gene) entered these organisms there was spread of these antibiotic-resistant strains of bacteria due to the selective pressure exerted by the use of antibiotics. If there was no use of antibiotics (no selective pressure of antibiotics) then there would not be spread of the antibiotic-resistant bacteria. Thus, when asked "does use of antibiotics lead to antibiotic resistance?" the answer is "yes." However, it has not been fully elucidated whether there is a quantitative association between antibiotic use and antibiotic resistance. From a conceptual point of view, it seems plausible that a very low use of an antibiotic would not drive antibiotic resistance and a very high use of an antibiotic could lead to high rates of resistance.

Reducing the use of an antibiotic can reduce the rate of resistance to that antibiotic. In one hospital, an 80% reduction of third-generation cephalosporin use was associated with a 44% reduction of the rate of ceftazidime resistance among *K. pneumoniae*.[9] In Finland, the outpatient reduction in the use of macrolide antibiotics (erythromycin, azithromycin, clarithromycin, roxithromycin) was associated with a reduction in the rate of macrolide resistance among Group A streptococci.[10] Hence, reduction in use of a specific antibiotic or class of antibiotic can lead to a reduction in the rate of resistance. However, in the ceftazidime-resistant *K. pneumoniae* study, there was an increase in the use of imipenem, a carbapenem, that was associated with an increase in the rate of imipenem resistance among *Pseudomonas aeruginosa*, and in the macrolide- resistant group A streptococcus study the reduction in the use of macrolide antibiotics was compensated for by using other antibiotics.[9,10] Hence, reducing antibiotic use may lead to a decrease in resistance; however, this reduction should not be compensated for by using another antibiotic.

The exact magnitude of the impact of the use of infection control practices such as contact precautions involving the use of gowns and gloves on the transmission of certain bacteria including MRSA, VRE and ESBL has not been fully elucidated. Additionally, it seems as if transmission, albeit at a lower rate, still occurs despite these efforts. Another or an additional approach would be to decrease the amount of antibiotic use that occurs in healthcare settings. By decreasing and possibly eliminating the use of antibiotics may help decrease the transmission of resistant bacteria in the hospital.

The rate of prescription of antibiotics for acute respiratory tract infections in the outpatient setting decreased from 1995 to 2006.[11] There was a 36% reduction in antibiotic prescription for acute respiratory tract infections in those less than 5 years and an 18% reduction among those 5 years of age and older. Although among adults there was an overall decrease in antibiotic prescription, the prescription of quinolones increased 5-fold. A Blue Cross Blue Shield report showed an overall 9% reduction in outpatient antibiotic prescription fill rate during the period 2010 to 2016.[12] There was a 22% reduction among infants, 16% reduction among

children and a 6% reduction among adults. Hence, there is some data showing a reduction in the use of antibiotics in the outpatient setting. A report from the CDC showed that 55.7% of hospitalized patients in that study received an antibiotic during their hospitalization. It was also shown that there could be a 37% improvement in the use of antibiotics in two specific areas, one area was selected urinary tract infections and other was the use of intravenous vancomycin.[13] They also showed, using mathematical modeling, that a 30% reduction in the use of broad-spectrum antibiotics would lead to a 26% reduction in *C. difficile* infection.

A recent systemic review and meta-analysis showed that antimicrobial stewardship programs reduced the incidence of multidrug resistant gram-negative bacteria, ESBL producing gram-negative bacteria, MRSA and *C. difficile*. The combination of antimicrobial stewardship and infection control was more effective than antimicrobial stewardship alone.[14]

SUMMARY

Infection control measures can reduce the transmission of infectious agents such as multidrug-resistant bacteria and *C. difficile* in the hospital. Antimicrobial stewardship can reduce the unnecessary or inappropriate use of antibiotics leading to a reduction in the prevalence of antibiotic resistance. Together, infection control measures and antibiotic stewardship can lead to a further decline in *C. difficile* and multidrug-resistant bacteria.

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Antimicrobial Stewardship in Community Hospitals

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ABSTRACT

Antimicrobial Stewardship Programs (ASP) help hospitals optimize antibiotic utilization, minimize the risk of developing antibiotic resistance and improve patients' health outcomes. Community hospitals can successfully implement an ASP that incorporates CDC-defined core elements of hospital ASP. The antimicrobial stewardship model should be customized to leadership, available resources and targeted interventions.

KEYWORDS: Antimicrobial, stewardship, community hospital

INTRODUCTION

Antibiotic misuse is associated with antibiotic-related adverse events, toxicity, antibiotic resistance, *C. difficile* infection, and overall worse outcomes and mortality for patients. Antimicrobial Stewardship has been defined as "coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal drug regimen including dosing, duration of therapy, and route of administration".[1] Optimization of antibiotic prescribing will improve patients' safety and outcomes and secondarily deliver cost-effective therapy.

The implementation of Antimicrobial Stewardship Programs (ASP) across all health-care settings as an effort to promote appropriate antibiotic use and combat antibiotic resistance in the community has become a public health

and national security priority in recent years.[2] Effective January 2017, The Joint Commission required that all hospitals (including community hospitals) and nursing-care centers have ASP implemented.[3] Expansion of antimicrobial stewardship interventions for all inpatient and eventually outpatient practices will ultimately result in better antibiotic use and reduce antibiotic resistance at a population level.

BENEFIT OF ASP IN COMMUNITY HOSPITALS

About half of patients admitted to the hospital receive an antibiotic during their hospital stay.[4] The most common infections treated with antibiotics in hospitalized patients include respiratory infections, followed by urinary tract infections, and presumed gram-positive resistant infections. However, up to 50% of those antibiotics prescribed in hospitals are unnecessary.[4] Longer use than recommended, noninfectious or nonbacterial syndromes and treatment of colonizing or contaminating microorganisms are among the most common reasons of inappropriate inpatient antibiotic use.[5] This data supports the crucial need of ASP in the inpatient setting.

Most of the evidence on the impact of antimicrobial stewardship derives from large tertiary academic centers. Multiple studies have demonstrated that antimicrobial stewardship interventions reduce unnecessary antibiotic use, shorten hospital stay, decrease the rates of *C. difficile* and nosocomial infections, decrease the prevalence of drug-resistant infection and reduce costs.[1] Data from smaller community hospitals have shown similar outcomes (**Table 1**).

Table 1. Impact of Antimicrobial Stewardship in Community Hospitals

Setting	Location	ASP Team	Intervention	Impact
174-bed community teaching hospital [6]	Boston, MA	ID physician, clinical pharmacist	Prospective audit and feedback, IV to PO conversion, use of practice guidelines, pharmacy restrictions and education	22% reduction in parenteral antibiotic use, significant decrease in *C. difficile* incidence (2.2 to 1.4 cases per 1000 patient-days), significant decrease in nosocomial infections by resistant Enterobacteriaceae.
120-bed community hospital [7]	West Monroe, LA	ID physician, clinical pharmacist, Infection control	Prospective audit and feedback	Reduction in total antimicrobial cost of 19% and total estimated savings of $177,000 over 1 year.
344-bed urban community hospital [8]	Philadelphia, PA	Pharmacy team and database	Restriction of ceftriaxone and ceftazidime use	95% reduction of ceftriaxone use and 97% reduction in ceftazidime use, and a 22% (non significant) reduction in ESBL-EK* prevalence.

ASP STRUCTURE FOR COMMUNITY HOSPITALS

Community hospitals are responsible for a large portion of US health care. In 2015, over 70% of hospitals in the United States had less than 200 beds.[9] These hospitals have similar rates of antibiotic use compared to large tertiary hospitals (median, 436 Days of Therapy/1000 patients-days).[10] However, less than half of community hospitals have implemented a structured ASP.[1, 11, 12]

ASP can be successfully implemented in community hospitals. The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America have published evidence-based guidelines for implementation of inpatient ASP.[13] These guidelines are complemented by the Centers for Disease Control and Prevention (CDC) Core Elements required for a successful hospital ASP released in 2016 (**Table 2**).[14] Both documents emphasize the success of an ASP is defined by its leadership and a coordinated multidisciplinary approach. Ideally the team should be lead by an infectious disease-trained physician and co-leaded by a pharmacist with experience in antimicrobial stewardship. Collaboration with the microbiology department, hospital infection control and epidemiology, clinical providers and information technology staff as well as support from the hospital administration and medical staff leadership are essential.

Most community hospitals have an assigned infection-control preventionist, on-site pharmacist and microbiology capabilities. But a singular ASP structure will not fit all medical facilities. Different ASP models have been proposed for specific community hospital settings (rural vs. urban vs. affiliated teaching facility).[15] Targeted interventions should be customized to local needs, prescriber behaviors, hospital size, resources and barriers. A wide variety of antimicrobial stewardship interventions have been recommended, most of which have been implemented successfully in community hospitals (**Table 3**).[13]

Successful incorporation of all CDC Core elements in community hospitals ASP can be challenging, particularly if there is no designated salary support for a physician leader or pharmacist. An initial crucial initial step in implementing an ASP team is engagement of the hospital administration to recognize antimicrobial stewardship as a quality and safety issue and a commitment to support the program. Then, based on the available resources, create the team. If the hospital does not have a dedicated infectious disease specialist to lead, it will be important to assign a local physician champion that can work with the local pharmacist to establish a formulary and review antimicrobial use and outsource infectious diseases expertise. Additional actions will include assessment of resources, determine priority areas and decide which of the above-mentioned interventions will be feasible and most helpful. One of the initial activities should be to create a hospital antibiogram if it is not already available to identify current institutional-resistance patterns and individualize antibiotic choices. Tracking and

Table 2. CDC's Core Elements for Hospital ASP.

Leadership Commitment
Dedicated human, financial and information technology resources.
Accountability
Appointing a single leader responsible for program outcomes. A physician with formal training in Infectious Diseases and/or antimicrobial stewardship will benefit the program.
Drug Expertise
Appointing a single pharmacist leader responsible for working to improve antibiotic use.
Action
Implementing specific interventions for ongoing evaluation of antibiotic treatment after initiation.
Tracking
Monitoring antibiotic prescribing and resistance patterns.
Reporting
Periodic measurement of antibiotic use by use of specific metrics and track clinical outcomes to report NHSN*, inpatient quality committees and feedback to providers and relevant staff.
Education
Educating clinicians about resistance and optimal prescribing.

*NHSN: National Healthcare Safety Network

reporting antibiotic use can be a difficult step to implement in community hospitals as the preferred metric to measure antibiotics (Days of Therapy or DOT) can be difficult to calculate and may limit successful reporting to the National Healthcare Safety Network (NHSN).

ASP AND COMMUNITY HOSPITALS IN RI

In Rhode Island, there are 16 acute-care hospitals licensed by the Department of Health. The majority are non-federal short-term hospitals that serve a particular community. Nonetheless, 55–77% of Rhode Island's hospitals have implemented ASP following the CDC's Core Elements.[1]

Newport Hospital is a 129-bed non-teaching community hospital that offers acute care and community health services to Newport County, greater Rhode Island, and nearby Massachusetts. Newport Hospital has successfully established an antimicrobial stewardship program since 2014. The infectious disease specialist, an infection control RN and a clinical pharmacist form the antimicrobial stewardship team. Prospective audit and feedback is performed on a daily basis by the lead physician using Theradoc, a commercially-licensed software that allows active clinical surveillance. Alerts are preselected but not limited to detect drug-bug mismatches, indications for antimicrobial use, targeted drugs, targeted organisms, and renal dysfunction. Feedback focusing in antibiotic de-escalation, discontinuation of antibiotics if inappropriate or no longer necessary, and parenteral to oral conversion is provided, written in the patient's chart or by direct verbal communication when

Table 3. Evidence-based Antimicrobial Stewardship Interventions

Intervention	Description	Recommendation Grade*
Formulary restriction and pre-authorization	Physicians are required to request an approval before using certain antibiotics	Strong
Prospective audit and feedback	Daily review of antimicrobial use followed by direct feedback to prescribers.	Strong
Education	Didactic lectures and materials directed to medical, nursing, pharmacy staff and trainees focusing on appropriate use of antibiotics and antimicrobial stewardship interventions.	Weak
Facility-Specific Clinical Practice Guidelines	Guidelines that provide guidance on initial choice of antibiotics and duration of therapy for specific syndromes.	Weak
Syndrome specific interventions	Targeted toward specific infection syndromes and may include electronic order sets, recruitment of physician champions, and quarterly feedback to providers of compliance with the guidelines.	Weak
Interventions designed to reduce the use of antibiotics associated with a high risk of *Clostridium difficile* infection	Restriction of high-risk and broad spectrum antibiotics	Weak
Prescriber-led review strategies	Antibiotic time-outs, automatic stop orders, review of indications for antibiotic use when ordering are some of the strategies to encourage prescribers to perform routine review of antibiotic regimen.	Weak
Computerized Clinical Decision Support Systems	Implementation of computerized decision support systems for prescribers to facilitate interventions	Weak
Dedicated pharmacokinetic monitoring and adjustment program	For dose optimization of aminoglycosides. For dose optimization of vancomycin and cost effective dosing of B- lactam drugs.	Strong Weak
Parenteral to oral conversion strategies	Prompt transition to oral therapies	Strong
Promote allergy assessments	Penicillin skin testing for patients with listed B-lactam allergies and desensitization strategies to enhance use of first-line agents.	Weak
Interventions to reduce the length of antibiotic therapy	Written guidelines specifying duration of therapy, as part of patient specific prospective audit interventions or electronic order sets with pre-set duration.	Strong
Development of stratified antibiograms	Hospital based antibiograms stratified by specific populations such as patient location and age.	Weak
Selective and cascade antibiotic susceptibility reporting by microbiology laboratory	Release of a limited number of antibiotics followed by a report of secondary antibiotics only if an organism is resistant to the primary antibiotic class.	Weak
Rapid viral testing	Use of rapid viral testing for respiratory pathogens to reduce the use of inappropriate antibiotics	Weak
Rapid diagnostic blood testing	Use rapid diagnostic testing such as rapid molecular assays and mass spectrometry in addition to conventional culture.	Weak
Serial procalcitonin measurements in Intensive Care	In patients admitted to intensive care units to guide early discontinuation of antibiotics.	Weak
Non culture-Based Fungal Markers in patients with haematologic malignancies	Such as galactomannan , 1,3-β-D-glucan or single- or multi-pathogen fungal PCR for patient with hematologic malignancies at risk of invasive fungal infections to optimize antifungal use.	Weak
Use of Days of Therapy (DOT) to measure antibiotic use	DOTs are preferred, but Defined Daily Dose s remains an alternative for sites that cannot obtain patient-level antibiotic use data.	Weak

*Strength of recommendation was based on rating the quality of evidence and using the GRADE methodology.

necessary. Pharmacy staff also reviews antibiotic dosing and helps streamline parenteral to oral conversions. In addition, physicians have access to our annually updated antibiogram and utilize facility-based evidence-based guidelines available for Lifespan-affiliated hospitals. In 2016, we reviewed 1364 charts that yielded 173 recommendations; 94% of recommendations were followed (50% were related to discontinuation or de-escalation of antibiotics and 36% were related to IV to PO conversion). Measurement of specific antimicrobial stewardship metrics has been challenging but future efforts are dedicated to upgrade our electronic medical records with a specific infection control and antimicrobial stewardship module that will allow us to calculate standardized metrics and report to NHSN.

Successful implementation of ASP in all community hospitals in Rhode Island is the ultimate goal. The Antimicrobial Stewardship and Environmental Cleaning Task Force was created by the Department of Health to provide resources to healthcare facilities and help them implement ASP and improve infection control practices throughout the state of Rhode Island. Acute-care hospitals and skilled nursing facilities have committed with the Sate's Department of Health to expand and implement antimicrobial stewardship programs in their facilities. The ASP at Newport Hospital can serve as a model for other community hospitals with similar resources.

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Antimicrobial Stewardship in Long-Term Care Facilities

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ABSTRACT

Antimicrobial stewardship (AMS) has become a major component of patient safety across all healthcare settings. The risk of *Clostridium difficile,* increasing antibiotic-resistant organisms, and potential adverse events from antibiotic misuse have led to the demand for AMS programs in long-term care facilities (LTCFs). LTCFs face several unique barriers in implementing antibiotic stewardship; however, with a change in culture through leadership, education, and accountability to the whole team these barriers can be overcome.

KEYWORDS: Antimicrobial stewardship, long-term care, nursing homes, asymptomatic bacteriuria

INTRODUCTION

A substantial proportion of our older population reside in long-term care facilities (LTCF) with around ~1.5 million residents in the US; when adding in those who are admitted to LTCF for post-acute care and short term rehabilitation, it is closer to 4 million (Centers for Disease Control and Prevention (CDC)).[1] This is a population with more comorbidities and risk for infections than the general population. Antibiotics are one of the most commonly prescribed medication classes, and up to 70% of residents receive at least one course of antibiotics each year.[2] Studies estimate that 40-75% of the time these antibiotics are inappropriate or unnecessary.[3] Furthermore, the long-term care (LTC) population is at an increased risk for harm from antibiotics including: *clostridium difficile* infection, adverse drug events, and increased risk of antibiotic resistance. For these reasons, LTCFs are one of the most important health-care settings for antimicrobial stewardship programs. The Centers for Medicare and Medicaid Services (CMS) recently released the "mega-rule" requiring antimicrobial stewardship programs and an infection control officer be in place for all LTCFs by November 28, 2017.[4]

Though the need for antimicrobial stewardship in a LTCF is well understood, this setting faces barriers that are unique, making it more difficult to develop and implement. In this article, we will review some of these unique barriers, as well as highlight some solutions.

BARRIERS IN LTCF

The barriers faced in LTCFs for antimicrobial stewardship include patient characteristics, resource limitations, structure of on-site vs. off-site care, family engagement and the home aspect of the facility (**Table 1**). As mentioned above, residents may have multiple comorbidities that increase the risk of infection (ie: diabetes, vascular disease, COPD, chronic wounds, indwelling devices), as well as immunosenescence.[5] It can be difficult to recognize infections due to the lack of typical signs (fever, leukocytosis) and the high prevalence of cognitive deficits that make it difficult to confirm symptoms.[6] Furthermore, they are at increased risk of resistant bacteria (both colonization and infection) given prior antibiotic exposure and increased healthcare exposure, particularly hospitalizations. Given the "home" aspect of LTCFs, residents travel back and forth from common areas to their private or semi-private rooms. This makes it difficult to fully isolate those who are colonized with or have a history of resistant organisms, leading to an unintentional spread of antibiotic resistance among residents.[7,8] Further complicating this situation is the concern for missing an infection, leading to the initiation of unnecessary antibiotics.

Most facilities, both acute and long-term care, report

Table 1. Barriers to Antimicrobial Stewardship in Long Term Care Facilities

Medically complex patients with multiple comorbidities
Many residents colonized with resistant organisms
Inability of LTCF to completely isolate patients
Delay in return of diagnostic information needed for decision making
Medial provider attitude and limited on-site coverage
Limited infectious disease consultation or pharmacy availability
Cost factor with Medicare Part A and the use of expensive broad spectrum antibiotics
Back and forth hospital transfers
Heavily engaged families with their own misconceptions about antibiotic use
Many residents are end of life and goals of care not consistent with aggressive testing/treatment

limited funding for dedicated antimicrobial stewardship programs. Salary support for pharmacists, physicians, nursing champions or IT remains a challenge for many institutions. In a 2014 survey of RI LTCFs, only 23 of 87 (26%) reported one dedicated AMS-specific FTE for the infection preventionist and even less support for physician or pharmacy FTE. These findings were similar to other state surveys in Nebraska and Michigan.[9]

LTCFs face additional resource limitations as most diagnostics are off-site, including routine labs, microbiology, and imaging. This leads to a delay in results that could help guide the clinician in diagnosis and treatment. Couple these challenges with the limited on-site provider coverage in the LTC setting. In a 2009 report, less than 20% of LTCFs employed full-time staff physicians. Most LTCFs have physicians that are covering at multiple facilities, splitting time between office-based practices and LTCFs.[10] Though in some areas on-site coverage is provided by mid-level providers, many facilities are relying on off-site phone coverage by the physician with nursing assessment of the patient.[11] The communication by nursing of the patient's status has significant influence on treatment decision by the provider. This can be difficult for nursing to provide detailed status change in residents as they face high nurse-resident ratios and at times family pressure for an antibiotic order.

Family (or patient) pressure is a barrier to antimicrobial stewardship across healthcare facilities, but in LTCFs it can be more significant. With geriatric patients who may not have the cognitive faculties to speak for themselves, as in severe dementia, the family may feel obligated to advocate for antibiotics based on their own assessment of their loved one.[6,12] Their demand for action/treatment in the absence of face-to-face discussion with a physician (as in an office visit) can lead to unnecessary antibiotic use that can cause more harm than good.[13] Along with this is the notion that the facility is, in fact, their home. To keep them at home, and not transfer to a hospital, providers are more likely to start antibiotics before confirmation of bacterial infection, continue for longer than recommended guidelines, and to not de-escalate even if indicated.[14,15]

These are some of the barriers that are unique to LTCFs in antimicrobial stewardship development and implementation. Additional barriers include limited access to infectious disease consultation or an infectious disease-trained pharmacist, medical cost limitations with expensive broad-spectrum antibiotics, as well as the goals of care for patients at the end of life.[6,7]

SOLUTIONS FOR LTCF ANTIMICROBIAL STEWARDSHIP

Though LTCFs face multiple barriers to antimicrobial stewardship (AMS) implementation, success has been shown with several different approaches that involves changing the culture and expectations of providers, nurses, and families. The CDCs 7 *Core Elements for Nursing Homes* include: 1. Leadership commitment; 2. Accountability; 3. Drug expertise; 4. Action; 5. Tracking; 6. Reporting, and 7. Education.[3] In LTCFs, the importance of leadership commitment and accountability cannot be overstated given the staffing and resource limitations described above. Without an on-site pharmacist or on-site physician available, the task for AMS (as well as infection control) is usually given to senior nursing leads who already juggle multiple roles. Instead, a team approach including representation from the medical director, director of nursing, infection preventionist, and pharmacist leads to better outcomes with increased support and accountability.[5]

In addition to identifying champions and leadership commitment, putting into place routine protocols that address the decision to start, continue, or stop an antibiotic has been successful in different studies.[5,12] This is most useful in the decision to treat for suspected urinary tract infections, the most common reason antibiotics are prescribed in LTCFs. However, a significant proportion of the time (~33%), it is asymptomatic bacteriuria rather than a true infection.[16,17,18] Some LTCFs have developed a urinary tract protocol where a resident is placed on a 24–48 hour symptom watch when concern of UTI is raised rather than ordering urine analysis and culture at the start. In the older population, pyuria and bacteriuria are common even in absence of infection, and it is the result of a positive culture that often triggers initiation of antibiotics.[16] By having a protocol to assess for objective signs of UTI (using recommended guideline criteria in the literature), staff can assure the resident/family that action is being taken without misuse of antibiotics and unnecessary harm. Several facilities in RI have urinary tract protocols in place with success in decreasing treatment of asymptomatic bacteriuria.

Another protocol that is used more frequently in acute care hospitals, but being encouraged as well in long-term care, is the antibiotic "time-out." In hospitals with electronic medical records (EMR), ordering of antibiotics can be structured to allow only for a certain number of days before the clinician must renew the order, and thus decide if it is still warranted. This can work well given the daily rounds by providers in the hospital. In LTCFs, this can be more difficult with many orders provided off-site and not reassessed daily by the provider.

One solution is a protocol where, at the initiation of treatment, the clinician must provide the diagnosis, dose, and duration of the antibiotic for the nurse to document. Then at 24-48 hrs., a "time-out" is held to determine if antibiotics should be continued, de-escalated based on sensitivities, or discontinued if there are no findings of infection.[19] The antibiotic "time-out" is a protocol that could be initiated by either nursing or pharmacy with the support of the clinicians in the facility.

Finally, a vital part of the solution to implementing antimicrobial stewardship programs is the education and engagement of residents and their families.[12,20] In LTCFs, the families of many residents are interested in not only the care of their loved one, but also in the activities and programs of the facility. If they are educated on the commitment to antimicrobial stewardship and how the facility plans to reduce misuse of antibiotics, they will likely become partners in it. For example, as part of a UTI protocol, a family member could help monitor for subtle symptom changes. By engaging family in the process, it can help to reduce the pressure for starting antibiotics that are unnecessary and potentially harmful.

These are examples of ways to overcome some of the barriers to antimicrobial stewardship in LTCFs. This does not address how to access drug expertise, i.e., ID-trained pharmacist, or the difficulties in tracking and reporting that facilities experience with fewer staff, limited IT capability, and lack of training. However, as the landscape changes with increased focus on antimicrobial stewardship and infection prevention across all healthcare settings, LTCFs will need to ensure that they have AMS champions who are supported, educated, and trained in implementing a full antimicrobial stewardship program.[20]

CONCLUSION

Long-term care facilities are a key player in the fight against increasing antibiotic resistance and adverse events such as *Clostridium difficile.* The culture of antibiotic use must change, not only because of increasing pressure from federal guidance and potential penalties, but more importantly for the safety and health of our current and future residents in LTCFs.

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Communicating with Facility Leadership; Metrics for Successful Antimicrobial Stewardship Programs (ASP) in Acute Care and Long-Term Care Facilities

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ABSTRACT

Up to 50% of hospital-administered and 70% of nursing home-administered antimicrobials are inappropriately prescribed. There is a great need to focus local, national and global efforts on appropriate antibiotic use. Formal programs dedicated to appropriate antibiotic use have been established in most US hospitals. These antimicrobial stewardship programs (ASP) exist to ensure that the correct drug, dose and duration of an antimicrobial is given, and only when there is a true bacterial infection (as opposed to bacterial colonization or a viral infection). These programs increase patient safety and reduce unintended consequences including *Clostridium difficile* infections, medication-related adverse effects, and antimicrobial resistance. Most of these programs are co-lead by an interdisciplinary team consisting of an infectious diseases (ID) pharmacist and an ID physician. However, consistent and meaningful metrics to study the impact of ASPs have not been elucidated. With the Joint Commission Standards for Acute Care facilities, and Centers for Medicare and Medicare (CMS) for long-term care facilities making antimicrobial stewardship (AMS) a condition of participation, both facilities will be scrambling to create appropriate quality care indicators to measure program success. One major theme across all healthcare settings is that ASPs must collaborate with facility leadership and key stakeholders at each institution in order to have an impactful benefit on patient quality of care, and safety. It is the purpose of this review to offer several economic, process, and patient-outcome measurements for ASP to optimally communicate with facility leadership.

KEYWORDS: antimicrobial stewardship, outcome assessment, process assessment, hospitals, long-term care facilities

INTRODUCTION

Antimicrobial stewardship programs (ASP) consistently demonstrate a reduction in antimicrobial utilization, favorable patient outcomes, and cost savings in both large academic medical centers and smaller community hospitals.[1,2] The demand for ASPs follows studies which indicate that up to 50% of hospital-administered antimicrobials, and up to 70% of long-term care facility-administered antimicrobials are prescribed inappropriately.[2,3] Misuse of antimicrobial agents (i.e. incorrect selection of drug, dose, frequency, duration or indication) has led to a rapid rise in antimicrobial-resistant bacteria that are estimated to cause at least 2 million illnesses and 23,000 deaths, annually.[4] The most common antimicrobial-related adverse events are *Clostridium difficile* infection (CDI), hypersensitivity reactions, and general medication-related adverse events.[5]

In acute care facilities, ASPs are ideally comprised of multidisciplinary teams consisting of an infectious diseases physician, an infectious diseases clinical pharmacy specialist, a clinical microbiologist, an infection control professional, an information system specialist, and a hospital epidemiologist.[2] These programs have repeatedly demonstrated a positive influence on patient outcomes (e.g. reduction in adverse drug events, CDI, morbidity and mortality, length of stay, antimicrobial resistance, and inappropriate prescribing), as well as healthcare expenditures.[5] In long-term care facilities, the responsibilities of AMS typically fall on the infection control and prevention nurse, ideally with assistance from consultant pharmacists, the directors of nursing and medical center directors.

Appropriate antimicrobial utilization aims to improve patient outcomes and minimize multi-drug resistance (MDR). Appropriate antibiotic use is a national priority (National Action Plan for Combating Antibiotic-Resistant Bacteria) that calls for establishment of ASPs in accordance with the Centers for Disease Control and Prevention (CDC) "Core Elements of Hospital Antibiotic Stewardship Programs" (**Table 1**).[3,6] The 2017 Joint Commission and Centers for Medicare and Medicaid Services will require hospitals and long-term care facilities to develop ASPs following these elements. Two of these CDC core elements relate to tracking and reporting measures of ASP success. However, selecting metrics to evaluate ASPs, their impact on patient outcomes, and development of resistance is challenging for a variety of reasons, including patient complexity, confounding factors, and metric selection that accurately depicts the program's impact.[7] The purpose of this review is to discuss available metrics and provide guidance for selecting metrics within institutions.

Table 1. Centers for Disease Control and Prevention (CDC) Core Elements of Hospital Antibiotic Stewardship Programs

Element	Description
Leadership commitment	Dedicating personnel, as well as financial and information technology resources
Accountability	Appointing single leader to be responsible for program outcomes
Drug Expertise	Appointing single pharmacist leader to support optimal antimicrobial utilization
Action	Implementing at least one actionable recommendation (e.g. antimicrobial time-out 48 hours post-empiric therapy)
Tracking	Monitoring antimicrobial prescribing and resistance patterns
Reporting	Regular reporting of tracked data to relevant staff
Education	Educating clinicians on optimal prescribing and resistance

Table 2. Metrics and Target Interventions

Measure (Level of Ease)	Conceivable Metrics*	Application of conceivable metrics to sample syndrome-specific targets
Process (Least difficult)	• Days of therapy (DOT) • Unnecessary days of therapy avoided • Provider adherence to syndrome-specific guideline/clinical pathway • Time to effective antimicrobial therapy • Time to optimal antimicrobial therapy after organism identification and sensitivity report • Proportion of patients converted from intravenous to oral medication • Number of urinalyses ordered in the ED	• Optimize therapy for bloodstream infections after implementation of molecular rapid diagnostic testing (e.g. MALDI-TOF MS, Film Array [BioFire], Verigene [Nanosphere], Accelerate Pheno and Accelerate PhenoTest [Accelarate Diagnostics], etc.) • Reduce inappropriate antimicrobial prescribing for respiratory viral infections ruled in via PCR-respiratory panel without signs of bacterial infection • Reduce or eliminate inappropriate antimicrobial prescribing for asymptomatic bacteriuria
Outcomes (Moderately difficult)	• Hospital length of stay • Intensive care unit (ICU) length of stay • 30-day mortality • Infection-related mortality • Unplanned 30-day hospital readmission • Proportion of patients with hospital-acquired CDI • Proportion of patients with clinical failure	• Optimize antimicrobial use for infections in immunocompromised hosts • Reduce or eliminate inappropriate antimicrobial prescribing for skin and soft tissue infections • Reduce vancomycin use in low-MRSA risk patient population with pneumonia • Optimize empiric antimicrobial use toward common resistance patterns in nursing home and/or long-term facilities
Resistance (Most difficult)	• Resistance patterns via annual antibiogram • Pathogen-specific resistance • Patient population-specific resistance	

*Does not represent a complete list;
MALDI-TOF MS= matrix-assisted laser/desorption ionization time of flight mass spectrometry

METRICS

Process and Antimicrobial Use Measures

Tracking and reporting antimicrobial use and outcomes data is critical to not only evaluating the success of the ASP, but also in identifying areas for improvement.[3,8,9] Generally, interventions are implemented to evaluate process and/or outcome measures (**Table 2**).[3,8,10] Process measures are easiest to evaluate as they utilize surrogate indicators to demonstrate whether an ASP successfully changed processes (e.g. guidelines/clinical pathway adherence), prescriber behavior (e.g. accurate diagnosis; appropriate drug-indication pairing, correct antimicrobial dose, frequency, and duration; appropriate and timely therapeutic modifications), resource utilization, or expenditure.[10,11] From the administrative standpoint, process measures, particularly resource utilization and expenditures, are critical to track as they highlight the need for continued support of ASPs. ASPs are associated with substantial cost savings that often stabilize after an initial period.[2,3] However, continued support is warranted as costs increase after program termination.[12]

Antimicrobial consumption can be evaluated using metrics such as days of therapy (DOT) or defined daily doses (DDD). These metrics reflect an aggregate amount of antimicrobial consumption, and are often standardized with patient-days in the denominator to allow for comparison between hospitals, regions, and/or countries.[3] Despite multiple available metrics, the CDC recommends utilizing DOT as the primary antimicrobial consumption metric because it provides more clinically relevant data than other metrics, including DDD.[3] However, calculating DOTs requires patient-level antimicrobial use data, which may not be feasible for all facilities. Under such circumstances, DDD may be utilized as an alternative despite several key disadvantages.[3,8] DDD reflects the amount of drug a typical, adult patient would receive for any given day utilizing World Health Organization (WHO)-approved DDD values, and therefore cannot be used for pediatric patients requiring weight-based dosing, as DDD interpretation is not translatable into meaningful data for that population.[13] This measure was not originally designed as an antimicrobial stewardship (AMS)

Table 3. Days of Therapy (DOT) versus Defined Daily Doses (DDD)

Description	DOT	DDD
	• Summation of days patient receives at least one dose of antimicrobial agent without regard to dose	• Average maintenance dose for main indication in 70kg-adults • Total grams used*/ World Health Organization (WHO)-approved DDD value**
Example	• Patient receives ceftriaxone 2gm Q12h plus ampicillin 2gm Q4h for 42 days • 2 antimicrobials X 42 days = 84 DOT	• Patient receiving ceftriaxone (CRO) 2gm Q12h plus ampicillin (AMP) 2gm Q4h for 42 days • DDD-values for ceftriaxone and ampicillin =2gm • DDD_{CRO}= (4gm dose/ 2gm DDD) x 42 days= 84 DDD; DDD_{AMP}= (12gm dose/ 2gm DDD) x 42 days= 252 DDD; total= 336 DDD
Standardization	• DOT/ patient-days • DOT/ patient-admission	• DDD/ patient-days • DDD/ patient-admission
Advantages	• Clinically relevant data • Expanded utilization in both adult and pediatric patients • Standardizing DOT can be used as benchmark to compare antimicrobial consumption between facilities, and regions	• Easy to obtain and does not require patient-level data • Standardizing DDDs can be used as benchmark to compare antimicrobial consumption between facilities, and regions
Limitations	• Requires patient-level antimicrobial use data • Optimal DOT unknown • Combination therapy yields higher DOT regardless of spectrum of activity	• Assumes all dosing is routine and may overestimate DDD in patients who require appropriately higher dosing (e.g. central nervous system infections, obesity, high-MIC pathogen infections, etc.) • May underestimate DDD in patients that appropriately require lower doses (e.g. renal impairment) • Combination therapy yields higher DDD regardless of spectrum of activity • Institutions must have similar antimicrobial composition/formulary to allow for comparison • Cannot be utilized for pediatric patients

*Obtained from purchased, dispensed, or administered data
** Available at: https://www.whocc.no/atc_ddd_index/

metric, and should not be used as such, when possible, as it has numerous flaws and biases.[3,8] DOT is not without flaws either. Although it provides useful overall antimicrobial consumption data, the optimal DOT number to target remains unknown. Reduction in DOT may not be beneficial for hospitals with already lean numbers. Indication-specific DOT data may be more optimal; however, data is currently unavailable. Comparison between DOT and DDD is further detailed in **Table 3**.

Other metrics, including length of therapy (i.e. sum of day's patient received antimicrobials regardless of drug or dose), grams used (obtained from purchased, dispensed, or administered data) and expenditures (i.e. monetary value spent obtained from purchased, dispensed, or administered data) are available. However, they are not recommended as a consumption measure as these metrics cannot be used to compare specific antimicrobial usage, are inaccurate, and may be affected by changes in cost, respectively.[14]

Outcome measures

Although process measures are substantially easier to collect and provide useful data, particularly during early program design, it is not enough to meet goals of ASPs.[11] The primary goals of ASPs include: 1) minimizing the progression of resistance; 2) optimizing antimicrobial selection (i.e. drug, dose and duration); and 3) reducing adverse drug events (i.e. CDIs, morbidity and mortality, length of stay and healthcare expenditures).[10] These goals cannot be evaluated through process measures alone.[11,15] For example, while improvement in antimicrobial utilization has demonstrated reduction in CDI[16], it cannot be completely explained by this process measure as additional unmeasured factors, including the role of infection control measures, can influence CDI rates.[5] Regardless, data on CDI rates are often collected and may be useful when interventions targeting reduction of highly CDI-associated antimicrobials (e.g. fluoroquinolones) are implemented.

Other helpful metrics evaluating outcomes related to ASPs in acute care facilities include: length of stay, 30-day mortality, unplanned hospital readmission, proportion of patients with clinical failure, days of avoided hospitalization (readmission, emergency room visits), as well as days of avoided central venous access and parenteral therapy administration.[5] Measuring such outcomes is challenging, particularly

for new programs and may become more feasible in the future as clear definitions and guidance is provided.[7] Interventions focused on syndrome-specific outcomes may be more practical.[5] With development and implementation of molecular rapid diagnostic testing (mRDT), measuring patient outcomes in bloodstream infections has demonstrated a reduction in mortality, particularly in institutions with ASPs.[17] Likewise, directing AMS efforts to antimicrobial discontinuation in institutions with high rates of inappropriate prescribing for respiratory tract infections[18], particularly in setting of polymerase chain reaction (PCR)-positive respiratory panels and low procalcitonin levels, is reasonable.[19]

Resistance

Antimicrobial resistance is perhaps the most challenging outcome to measure due to its multi-factorial development and dispersal.[3,5] Implementation of ASPs has been associated with a reduction in both Gram-positive and Gram-negative resistance[20], but similar to CDI rates, these findings may be confounded by other factors that impact antimicrobial resistance, including infection control measures, changes in prevalent organisms within an institution, patient demographics, and other care practices.[5] Tracking resistance of select pathogens, or patient populations that benefit most from AMS intervention may provide additional benefit to solely tracking and reporting overall resistance patterns.[5]

SELECTING AND APPLYING METRICS AT YOUR INSTITUTION

Expert consensus studies focusing on metric selection have been conducted.[7-9] These groups propose six patient-level metrics ready for immediate use in acute care settings and we offer personnel expertise that may best assist in data collection. These six areas include; hospital-onset CDI (infection control and prevention); healthcare-associated CDI (infection control and prevention); incidence of drug resistant infections (microbiology and infection control and prevention); antimicrobial DOT per patient-admission (pharmacy); DOT per patient-days (pharmacy); and redundant therapy events (pharmacy).[7] Clinical outcome measures were not selected due to concerns with accurately associating outcomes to AMS intervention in setting of unmeasured confounding factors (e.g. severity of illness, infection-control activities).[7] Similarly, unmeasured confounding factors including improved infection control measures, may influence CDI rates. Another structured panel used to identify quality-improvement metrics had several similarities to the patient-level expert consensus.[8] However, these panel members chose to include clinical outcome measures (i.e. antimicrobial-related organism mortality, 30-day mortality, conservable days of therapy, and unplanned 30-day hospital readmission).[8] Ideal metrics have yet to be elucidated as no single metric demonstrated superiority to others. Metrics should be individualized for each facility and aimed to satisfy short-term (e.g. reduction in antimicrobial consumption, patient outcomes) and long-term (e.g. resistance) goals.[3]

CONCLUSION

Tracking and reporting measures that ensure ASP success and highlight areas for improvement is challenging as ideal metrics remain unknown. Regardless of metric selection, ensuring accurate and consistent data collection is critical. The CDC assists providers through various resources. Particularly helpful is the National Healthcare Safety Network (NHSN), a widely used tracking system designed to measure antimicrobial utilization with risk adjustment that allows for inter- and intra-facility comparison. NHSN website provides several useful resources including various slide-sets and YouTube videos that assist providers with several components of ASP development. Other helpful resources are outlined in **Table 4**.

Table 4. Helpful Resources

Description	Link
CDC NHSN hospital-acquired infections tracker	https://www.cdc.gov/nhsn/acute-care-hospital/
Joint Commission new antimicrobial stewardship standard	https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf
CDC Long-term Care Facility infections prevention guidance	https://www.cdc.gov/longtermcare/index.html
CMS guidance for long-term care facilities	https://www.cms.gov
University of Rhode Island antimicrobial stewardship treatment pathways	http://web.uri.edu/antimicrobial-stewardship/treatment-pathways/
Rhode Island Department of Health antimicrobial stewardship	http://www.health.ri.gov/healthcare/about/antimicrobialstewardship/

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