The Importance of an Antimicrobial Stewardship Program

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Developing a program to properly use antimicrobials is essential for inpatient facilities to decrease the incidence of resistance, reduce the development of multidrug-resistant organisms, and improve patient care.

An antimicrobial stewardship program (ASP) is designed to provide guidance for the safe andcost-effective use of antimicrobial agents. This evidence-based approach addresses the correct selection of antimicrobial agents, dosages, routes of administration, and duration of therapy. In other words, the ASP necessitates the right drug, the right time, the right amount, and the right duration.[1] The ASP reduces the development of multidrug-resistant organisms (MDROs), adverse drug events (such as antibiotic-associated diarrhea and renal toxicity), hospital length of stay, collateral damage (development of *Clostridium difficile* colitis), and health care costs. Review of the literature has shown the ASP reduces hospital stays among patients with acute bacterial-skin and skin-structure infections along with other costly infections.[2]

The ASP is not a new concept, but it is a hot topic. A successful ASP cannot be achieved without the support of the hospital leadership to determine and provide the needed resources. Its success stems from being a joint collaborative effort between pharmacy, medicine, infection control (IC), microbiology, and information technology. The purpose of the ASP is to ensure proper use of antimicrobials within the health care system through the development of a formal, interdisciplinary team. The primary goal of the ASP is to optimize clinical outcomes while minimizing unintended consequences related to antimicrobial usage, such as toxicities or the emergence of resistance.

In today's world, health care clinicians are dealing with a global challenge of MDROs such as *Enterococcus faecium, Staphylococcus aureus* (*S aureus*), *Klebsiella pneumonia*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, *and Enterobacter* species (ESKAPE), better known as "bugs without borders."[3] According to the CDC, antibiotic-resistant infections affect at least 2 million people in the U.S. annually and result in > 23,000 deaths.[2] According to Thomas Frieden, director of the CDC, the pipeline of new antibiotics is nearly empty for the short term, and new drugs could be a decade away from discovery and approval by the FDA.[2]

LITERATURE REVIEW

Pasquale and colleagues conducted a retrospective, observational chart review on 62 patients who were admitted for bacterial-skin and skin-structure infections (*S aureus*, MRSA, MSSA, and *Pseudomonas aeruginosa*).[4] The data examined patient demographic characteristics, comorbidities, specific type of skin infection (the most common being cellulitis, major or deep abscesses, and surgical site infections), microbiology, surgical interventions, and recommendations obtained from the ASP committee.

The ASP recommendations were divided into 5 categories, including dosage changes, de-escalation, antibiotic regimen changes, infectious disease (ID) consults, and other (not described). The ASP offered 85 recommendations, and acceptance of the ASP recommendations by physicians was 95%. The intervention group had a significantly lower length of stay (4.4 days vs 6.2 days, $P < .001$); and the 30-day all-cause readmission rate was also significantly lower (6.5% vs 16.71%, $P = .05$). However, the skin

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and skin-related structures readmission rate did not differ significantly (3.33% vs 6.27%). It was impossible for the investigators to determine exact differences in the amount of antimicrobials used in the intervention group vs the historical controls, because the historical data were based on ICD-9 codes, which may explain the nonsignificant finding.[4]

D'Agata reviewed the antimicrobial usage and ASP programs in dialysis centers.[5] Chronic hemodialysis patients with central lines were noted to have the greatest rate of infections and antibiotic usage (6.4 per 100 patient months). The next highest group was dialysis patients with grafts (2.4 per 100 patient months), followed by patients with fistulas (1.8 per 100 patient months). Vancomycin was most commonly chosen for all antibiotic starts (73%). Interestingly, vancomycin was followed by cefazolin and third- and/or fourth-generation cephalosporin, which are risk factors for the emergence of multidrug-resistant, Gram-negative bacteria that are highly linked to increased morbidity and mortality rates. The U.S. Renal Data System stated in its 2009 report that the use of antibiotic therapy has increased from 31% in 1994 to 41% in 2007.[5]

In reviewing inappropriate choices of antimicrobial prescribing, D'Agata compared prescriptions given to the Healthcare Infection Control Practices Advisory Committee to determine whether the correct antibiotic was chosen. In 164 vancomycin prescriptions, 20% were categorized as inappropriate.[5] In another study done by Zvonar and colleagues, 163 prescriptions of vancomycin were reviewed, and 12% were considered inappropriate.[6]

Snyder and colleagues examined 278 patients on hemodialysis, and over a 1-year period, 32% of these patients received ≥ 1 antimicrobial with 29.8% of the doses classified as inappropriate.[7] The most common category for inappropriate prescribing of antimicrobials was not meeting the criteria for diagnosing infections (52.9% of cases). The second leading cause of inappropriate prescription for infections was not meeting criteria for diagnosing specific skin and skin-structure infections (51.6% of cases). Another common category was failure to choose a narrower spectrum antimicrobial prescription (26.8%).[7] Attention to the indications and duration of antimicrobial treatment accounted for 20.3% of all inappropriate doses. Correction of these problems with use of an ASP could reduce the patient's exposure to unneeded or inappropriate antibiotics by 22% to 36% and decrease hospital costs between $200,000 to $900,000.[5]

Rosa and colleagues discussed adherence to an ASP and the effects on mortality in hospitalized cancer patients with febrile neutropenia (FN).[8] A prospective cohort study was performed in a single facility over a 2-year period. Patients admitted with cancer and FN were followed for 28 days. The mortality rates of those treated with ASP protocol antibiotics were compared with those treated with other antibiotic regimens. One hundred sixty-nine patients with 307 episodes of FN were included. The rate of adherence to ASP recommendations was 53% with the mortality of this cohort 9.4% (29 patients).[8]

Older patients were more likely to be treated according to ASP recommendations, whereas patients with comorbidities were not treated with ASP guidelines, Rosa and colleagues noted.[8] No explanation was given, but statistical testing did uphold these findings, ensuring that the results were correctly interpreted. The 28-day mortality during FN was related to several factors, including nonadherence with ASP recommendations (P = .001) relapsing diseases stages (P = .001), and time to antibiotic start therapy > 1 hour (P = .001). Adherence to the ASP was independently associated with a higher survival rate (P = .03), whereas mortality was attributable to infection in all 29 patients who died.

The primary goal of the antimicrobial stewardship program is to optimize clinical outcomes while minimizing unintended consequences related to antimicrobial usage, such as toxicities or the emergence of resistance.

Nowak and colleagues reviewed the clinical and economic benefits of an ASP using a pre- and postanalysis of potential patients who might benefit from recommendations of the ASP.[9] Subjects included adult inpatients with pneumonia or abdominal sepsis. Recommendations from ASP that were followed decreased expenditures by 9.75% during the first year and remained stable in the following years. The cumulative cost savings was about $1.7 million. Rates of nosocomial infections decreased, and pre- and postcomparison of survival and lengths of stay for patients with pneumonia (n = 2,186) or abdominal sepsis (n = 225) revealed no significant differences. Investigators argued that this finding may have been due to the hospital's initiation of other concurrent IC programs.

Doron and colleagues conducted a survey identifying characteristics of ASP practices and factors associated with the presence of an ASP.[10] Surveys were received from 48 states (North and South Dakota were not included) and Puerto Rico. Surveys were received from 406 providers, and 96.4% identified some form of ASP. Barriers to implementation included staffing constraints (69.4%) and insufficient funding (0.6%).[10]

About 38% of the responses stated ASP was being used for adults and pediatric patients, whereas 58.8% were used for adults only.[10] The ASP teams were composed of a variety of providers, including infectious disease (ID) physicians (70.7%), IC professionals (51.1%), and clinical microbiologists (38.6%). Additional barriers to implementing an ASP were found as insufficient medical staff buy-in (32.8%), not high on the priority list (22.2%), and too many other things to consider or deal with at the time (42.8%). Interestingly, 41.1% of the subjects in facilities without an ASP responded that providers agree with limiting the use of antimicrobials compared with 66.9% of subjects in hospitals with an ASP. Factors linked to having an ASP included having an ID consultation service, an ID fellowship program, an ID pharmacist, larger hospitals, annual admissions > 10,000, having a published antibiogram, and being a teaching hospital.

ESTABLISHMENT OF AN ASP

The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) issued guidelines in 2007 for developing an institutional ASP to enhance antimicrobial stewardship and help prevent antimicrobial resistance in hospitals.[11] The ASP may vary among facilities based on available resources.

When developing an ASP, 2 core strategies are necessary. The core measures are proactive and are usually conducted by an ID clinical pharmacist assigned to the ASP in collaboration with the ID physician. These strategies are not mutually exclusive and include a prospective audit with interventions provided to the clinicians, resulting in decreased inappropriate use of antimicrobials or a formulary restriction and preauthorization to help reduce antimicrobial usage and related cost.

Using the appropriate antimicrobial dose based on the specific pathogen, patient characteristic, source of infection, along with the pharmacokinetic and pharmacodynamics should be reviewed to prevent antimicrobial overuse.

Supplemental elements may be considered and prioritized as to the core antimicrobial stewardship strategies based on local practice pattern and resources.[11] Factors to consider include education, which is considered to be an essential element of the ASP. Although education is important, it alone is only somewhat effective in changing clinicians' prescribing practices. Guidelines and clinical pathways are elements set forth in institutional management protocols for common and potentially serious infections such as intravascular catheter-related infections, hospital- and community-acquired pneumonia, bloodstream infections, and complicated urinary tract infections among other types.

Another consideration is antimicrobial cycling. This process refers to the specific schedule of alternating specific antimicrobials or antimicrobial classes to prevent or reverse the development of antimicrobial resistance. Insufficient data on antimicrobial cycling currently exist to affect major changes in practice. This element, however, could be implemented in certain institutions if needed based on the reported bacterial resistance pattern.

Antimicrobial order forms can be used to help monitor the implementation of formulated institutional clinical practice pathways. However, the authors feel that documenting this indication in the clinician notes may be adequate and save time for everyone involved; additionally, reviewing combination therapy, which if avoided, may prevent the emergence of resistance. Although combination therapy is needed in certain clinical diagnostic situations, careful consideration of its use is essential.

Streamlining or de-escalation of therapy by using a narrower spectrum agent, based on culture and sensitivity results, prevents duplicative therapy with a patient when double coverage is not indicated or intended. Another goal is the discontinuation of therapy based on negative culture results and lack of supporting clinical signs and symptoms of infection. Dose optimization and adjustment should also be reviewed. Using the appropriate antimicrobial dose based on the specific pathogen, patient characteristic, source of infection, along with the pharmacokinetic and pharmacodynamics should be reviewed to prevent antimicrobial overuse and subsequent potentially avoidable adverse effects.

Parenteral to oral conversion from IV to oral administration (IV to oral) antimicrobials must be considered

when the patient is clinically and hemodynamically stable, thus limiting the length of hospital stays and health care costs. However, it is important to keep in mind pharmacokinetic studies examining the bioavailability of antibiotics are usually conducted with healthy volunteers. Therefore, when treating patients who are elderly, on multiple medications, or severely ill, proper usage of these antibiotics is required. Also, having antibiotics with excellent bioavailability does not necessarily mean switching from IV to oral routes when treating serious infections such as bacteremia. Special consideration should be given when changing the route of administration. In addition, approval—or at least notification by the treating physician or ID specialist—should be included in the absence of an institutional policy, allowing for automatic IV to oral conversion.

THE ASP TEAM

The participation of specific clinicians has been suggested as key to having a successful ASP team.[12] Members should include an ID physician (director) who serves as the lead physician and supervises the overall function of the ASP, makes recommendations to the ASP team, and contributes to the educational activities. A clinical ID pharmacist (codirector) provides suggestions to clinicians on preferred first-line antimicrobials and reviews medication orders for antimicrobials and resistance patterns, microbiological data, patient data, and clinical information. The codirector also tracks any ASP-related data and submits monitoring reports on a regular basis.

If accessible, an IC professional should participate, implementing and monitoring prevention strategies that decrease health care-associated infections. These infections play a significant role in reducing MDROs and decreasing the use of antibiotics. Additionally, the IC professional can assist in the early identification of patients with MDROs, aid patient placement on transmission-based precautions, and flag a patient in the medical record for hightened awareness. Also, IC professionals promote hand hygiene, standard precautions, and contribute to infection prevention strategies, such as hospital bundle practices, to prevent catheter-associated bloodstream infections and ventilator-associated pneumonias, among others.

If possible, a microbiologist who can prepare culture and susceptibility data to optimize antimicrobial management and conduct timely documentation of microbial pathogens should be a member of the team. Microbiologists can report organism susceptibility, assist in the surveillance of specific organisms, and provide early identification of patients with MDROs that require transmission-based precautions. The microbiologist can perform a semiannual update of a local antibiogram while reporting antimicrobial susceptibility profiles. Based on the information gathered, microbiologists can provide new drug panels to the members of the ASP, who will decide which antibiotic panel will be used. Another possible member of the ASP team is a program analyst who provides data retrieval, performs data analysis, and delivers necessary reports to the team.

It is the responsibility of medical staff to review and implement suggestions made by the ASP when appropriate. However, these suggestions are not considered a substitute for clinical decisions, and discretion is required when treating individual patients. The VHA, in response to the IDSA/SHEA published guidelines, chartered an antimicrobial stewardship task force in May 2011 with the sole purpose "To optimize the care of Veterans by developing, deploying and monitoring a national-level strategic plan for improvements in antimicrobial therapy management."[1] In 2011, the Office of Inspector General in a combined assessment program summary report for management of MDROs in VHA facilities recommended that "the Under Secretary for Health, in conjunction with VISN and facility senior managers, ensures that facilities develop policies and programs that control and reduce antimicrobial agent use."[13]

In 2012, the VHA conducted a survey to obtain baseline data regarding ASP activities, presence of dedicated personnel, current related practice policies, available resources, and outcomes. There were 140 voluntary participating VA facilities, of which 130 had inpatient services. The survey found that 26 facilities (20%) did not have an attending ID physician, 49 facilities (38%) reported having an ASP, 19 facilities (15%) had developed policy in place addressing de-escalation of antimicrobials, 87 facilities (67%) had not developed a business plan for an ASP, and 61 facilities (47%) had completed a medication usage evaluation.[14] Feedback following the analysis of the survey data recommended integrating more ID personnel as needed, along with the development of ASP teams for all facilities with inpatient services, who would have the authority to change the antimicrobial therapy selection and have policies in place related to ASP principles.

CONCLUSIONS

Increased MDROs and decreased anti-infective development requires stricter management of antibiotics. An ASP is essential in any hospital or health care facility to decrease the

incidence of resistance and improve patient care. The ASP is a collaborative effort that involves multiple specialties and departments. A successful ASP is one that changes based on local prescribing trends and resistance patterns while focusing on a patient as an individual. ●

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