ANALYTIC REVIEW

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The Role of Antibiotic Stewardship in Promoting Appropriate Antibiotic Use

Abstract: *Antibiotics are one of the most significant medical discoveries in human history. The widespread use of antibiotics has resulted in the emergence of antibiotic-resistant pathogens. This fact, coupled with the paucity of new antibiotic developments, has spurred efforts to combat antibiotic resistance. One of the most critical components of these efforts is antibiotic stewardship, a multidisciplinary endeavor, employing a collection of interventions in a variety of health care settings with the aim of promoting appropriate utilization of antibiotics. This article describes antibiotic stewardship programs and key practices used to minimize the development and spread of antibiotic-resistant pathogens including the optimization of antibiotic pharmacokinetics and pharmacodynamics, the application of rapid diagnostic tools, and the use of computerized provider order entry tools.*

Keywords: antibiotic stewardship; antibiotic resistance; infection control

The development of antibiotics is one of the most profound medical advances in human history, transforming the practice of medicine from a primarily diagnostic profession to both a diagnostic and therapeutic endeavor.[1] Increasing antibiotic resistance is considered to be one of the most serious threats to human health by both the US Centers for Disease Control and Prevention (CDC) and the World Health Organization.[2,3] Recent US estimates indicate antibiotic-resistant infections afflict more than 2 million people and kill at least 23 000 people annually.[2] These data, however, are dwarfed by modeling of the future impact of antibiotic resistance. A recent analysis by RAND Europe, an independent not-for-profit policy research organization, forecasts that antibiotic resistance will lead to 300 million premature deaths by the year 2050 if no action is taken to combat antibiotic resistance, exceeding the predicted combined mortality of cancer and diabetes.[4]

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The emergence of the 20th century as the "golden age" of antibiotics began with the discovery of a penicillin-producing fungus in 1928.[5,6] The clinical introduction of sulfonamides in the 1930s and penicillin in the 1940s revolutionized the practice of medicine. The succeeding 3 decades saw the discovery of many of the antibiotic classes used today. However, the resulting widespread use of antibiotics resulted in the selection and promotion of multiple drug-resistant pathogens, as antibiotic resistance is an inherent biological response to antibiotic exposure.[7] When a population of microorganisms is exposed to an antibiotic, antibiotic susceptible

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subpopulations are eradicated, while antibiotic resistant organisms survive. This leads to an increase in the prevalence of the resistant organisms in the population to a point where the antibiotic may no longer be effective.[2,8,9] Management of the antibiotic resistance problem through the continued development of novel antibiotics has not kept pace with expanding microbial resistance, due in large part to lack of financial incentive for antibiotic development.[10-12]

An important approach to slow the development of antibiotic resistance is to use existing antibiotics appropriately and in ways that are most effective. Appropriate and effective antibiotic use includes choosing the right antibiotic or combination of antibiotics to target a given microorganism, using the most appropriate antibiotic dose to achieve pharmacokinetic and pharmacodynamic efficacy while limiting toxicity and minimizing antibiotic treatment duration to the time necessary to achieve cure of infection.[13]

The fact that antibiotic exposure frequently results in antibiotic resistance has been recognized since the discovery of penicillin.[7,14,15] Despite this long-standing knowledge, multiple studies have documented antibiotic overuse in many clinical settings. Inappropriate outpatient antibiotic prescribing including overuse of broad-spectrum antibiotics, and utilization of antibiotics for common acute viral respiratory tract infections, which include sinus infections, sore throat, the common cold, and uncomplicated bronchitis, can promote antibiotic resistance.[16] While a number of reports have demonstrated an overall decrease in inappropriate antibiotic prescriptions, a significant degree continues to exist.[17,18] Data suggest that at least one third of outpatient antibiotic prescriptions are unnecessary.[16,19,20] An analysis of ambulatory antibiotic prescribing in the United States between 2007 and 2009 found that antibiotics were prescribed to adults in more than 100 million physician office visits per year and that the majority of prescriptions were for broad-spectrum agents.[21] Furthermore, the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey of US ambulatory visits from 2010 to 2011 found that of the estimated annual antibiotic prescription rate of 506 per 1000 population, only 353 prescriptions were considered appropriate.[22] In addition to outpatient overuse of antibiotics, an estimated 20% to 50% of all antibiotics prescribed in hospitals are either unnecessary or inappropriate[1] and can increase mortality[23] and hospital length of stay.[24]

Inappropriate antibiotic prescribing also exposes patients to medication side effects, which has, in some cases, prompted warnings to prescribers from major regulatory agencies including the US Food and Drug Administration.[25] Another consequence of antibiotic use are opportunistic infections that take advantage of the alteration of microbial flora that occurs after antibiotic administration. Among the most clinically relevant is *Clostridium difficile* infection (CDI), an acute diarrheal illness strongly associated with antibiotic use, which can be both severe and persistent.[1] In 2011, *Clostridium difficile* caused nearly half a million infections and 29 000 deaths in the United States.[1,26]

To combat these issues, programs designed to improve antibiotic use, known as Antibiotic Stewardship Programs (ASPs), are increasingly common. ASPs are multidisciplinary quality improvement initiatives with proven effectiveness to optimize treatment of infections through increased infection cure rates and reduced treatment failures while limiting undesirable adverse drug reactions,[27] CDI,[27-30] and antibiotic resistance.[31,32] In so doing ASPs create improvement in patient care quality and overall healthcare cost savings.[33,34]

The documented successes of ASPs have led various governmental and regulatory agencies to promote and even require ASPs across multiple health care settings. In September 2014 the Obama Administration released an executive order to combat antibiotic-resistant bacteria.[35] This order included specific provisions for the Department of Health and Human Services (including Centers for Medicare and Medicaid Services) as well as the Department of Defense and Department of Veterans Affairs to propose regulations requiring health care institutions to implement ASPs.[35] Major independent regulatory and quality assurance organizations, including the Joint Commission[36] and The Leapfrog Group,[37] have subsequently announced that they would evaluate institutional ASPs pursuant to standards set by the CDC.[1]

Antibiotic Stewardship Programs: Who and Why?

An ASP is generally composed of a multidisciplinary team of health professionals and usually led by an individual with expertise in antibiotic use, typically a physician and/or pharmacist.[1] Formal training in infectious diseases and/or antibiotic stewardship is demonstrated to be a major advantage for ASP leaders.[38] ASP leadership is responsible for program outcomes but an effective ASP requires a team of key support groups. Team members vary by institution and resources available and may include clinicians, infection prevention specialists, nurses, epidemiologists, pharmacists, laboratory staff, information technology staff, and management.

Clinicians, including physicians and other prescribers of antibiotics, are critically important champions of appropriate antibiotic use and peer influence. In addition, clinical department leaders can advocate for the practice of appropriate antibiotic prescribing within their departments.[1,39,40] Infection preventionists and hospital epidemiologists are responsible for the control of hospital-acquired infections. Institutional infection prevention programs frequently pursue common outcomes with ASPs, including CDI,[27-29] which is directly related to antibiotic use, as well as other key infection prevention interventions such as hand hygiene and contact isolation.[41,42] Laboratory staff,

particularly those in microbiology departments, are instrumental in facilitating appropriate tests necessary for effective diagnosis and management of infections. Antibiotic resistance can vary significantly between different institutions and patient populations. For this reason, knowledge of local antibiotic resistance rates is important to guide empiric prescribing of antibiotics. Laboratory staff are essential to regularly compile institutional antibiotic resistance data into a format shareable with clinicians known as the antibiogram. The regular development of an antibiogram can be used to facilitate continual assessment of local resistance rates and adjustment of empiric antibiotic therapy accordingly.[1] Information technology staff are vital for the establishment of infection treatment protocols and decision support as well as collection of institutional outcomes data such as antibiotic utilization.[43,44] Nurses frequently perform key infection management duties such as the collection of cultures and administration of antibiotics, and are thus well positioned to promote dialogue regarding appropriate antibiotic use and infection prevention practices.[45] Quality improvement staff can be valuable in sharing ASP data with institutional administrators and leveraging their support as ASP outcomes concern both patient safety and patient care quality.[1]

Examples of ASP Intervention

There is great potential to slow the development of resistance through the appropriate use of antibiotics. Appropriate antibiotic use includes (1) accurate diagnosis of infection, (2) the correct drug or combination of drugs to target specific pathogen(s), (3) the proper drug dosage to achieve efficacy while limiting toxicity, and (4) the appropriate treatment duration,[13] as Joseph and Rodvold called the "4 Ds" of optimal antibiotic therapy: drug, dose, deescalation, and duration.[46] Influencing antibiotic prescribing practices is a primary goal of ASPs, but can be challenging given the quantity, distribution, and diversity of antibiotic prescribers. A number of interventions are proven to be highly effective in accomplishing this goal.[47]

Prospective audit and feedback is one of the most studied interventions in antibiotic stewardship and is considered a core component of ASPs.[1,30] It involves review of prescribed antibiotic therapy by an individual or group with expertise in antibiotic use, frequently a pharmacist and/or physician, with recommendations regarding antibiotic therapy communicated directly to the prescriber.[31,48] Other effective ASP interventions include antibiotic prior authorization, in which antibiotic therapy is reviewed by an expert prior to dispensing, or antibiotic "time outs," where the clinician re-assesses the need for antibiotic therapy 48 hours or more after antibiotic initiation.[30]

Some ASP interventions can be built into ASP and pharmacy staff daily workflow, including institution-approved protocols for transitions from intravenous to oral antibiotic therapy,[49] dose adjustments for renal dysfunction, antibiotic dose optimization,[50] development of institution-specific order sets,[51] and time-sensitive automatic stop orders.[1,30] The ASP team at each facility must deploy interventions based on consideration of the specific requirements of the institution and available resources, including support from clinicians, hospital staff, and administration.

Improved Dosing: Optimizing Pharmacokinetics and Pharmacodynamics

While sometimes overlooked by prescribers, dosing of antibiotics is a major focus of ASPs. A suboptimal antibiotic dose may lead to reduced efficacy and development of antibiotic resistance while an excessive dose may lead to drug toxicity.[30] The relationship between the dosage of an antibiotic and its resultant clinical efficacy and/or toxicity exists through pharmacokinetics and pharmacodynamics. Pharmacokinetics describes the absorption, distribution, and elimination of drugs,[52] which determines the ability of the drug to reach the site of infection and to maintain adequate concentration at that site for sufficient time to result in antimicrobial activity. Pharmacodynamics is the association between drug concentration and antibiotic activity and toxicity.[52] The optimization of antibiotic pharmacokinetic and pharmacodynamic parameters is essential to improving antibiotic stewardship. An implicit pharmacodynamic parameter is the minimum inhibitory concentration (MIC), a surrogate marker for antibiotic activity at an infection site, which is defined as the lowest concentration of antibiotic which inhibits bacterial growth in vitro.[52,53] This parameter, specific to in vitro, or laboratory analysis, is important in determining *whether* a particular antibiotic is active and *how* active it is against a given bacteria. The lower the MIC, the more potent an antibiotic is against a given bacteria.[53] The breakpoint MIC, the point at which an antibiotic is no longer considered effective against an organism, is decided by national and/or international experts and varies for each drug-organism combination.[54,55] However, this information does not fully characterize the interaction of antibiotic with an organism. The MIC fails to describe the rate of bacteria killing or whether higher concentrations of antibiotics can increase the rate of bacterial killing. In an individual infection, pharmacokinetic and pharmacodynamic parameters are dependent on the combination of antibiotic drug, infecting organism, infection site, and patient characteristics, highlighting the importance of an individualized approach to antibiotic dosing.

Antibiotic pharmacodynamics can be divided broadly into concentration-dependent activity or time-dependent activity.[52,53,56] Concentration-dependent antibiotic activity is mainly determined by the magnitude of the dose, as drug efficacy is associated with the maximum drug concentration post-dose (C_{max}) versus the organism MIC. Concentration-dependent antibiotic classes include aminoglycosides and fluoroquinolones.

In contrast, for time-dependent antibiotics, such as beta-lactams, vancomycin, and macrolides, antibiotic efficacy is based on either the percent time antibiotic concentration is above the MIC (T > MIC) or the area under the concentration versus time curve versus the MIC (AUC/MIC). The MIC has a significant impact on pharmacodynamics, as an increase in the MIC negatively influences all pharmacodynamic parameters. As the MIC increases, it becomes more difficult to attain pharmacodynamic targets rendering the antibiotic clinically ineffective against an infecting organism.

In addition to the MIC of the antibiotic to the infecting organism, antibiotic concentration at the site of infection is an important contributor to clinical outcome. Antibiotic concentration at the site of infection is determined by (1) whether the drug penetrates a given site; (2) the dose, infusion time, and dose interval; and (3) patient- and disease-specific factors that may influence pharmacokinetics.

The host response to infection can also significantly affect antibiotic pharmacokinetics and pharmacodynamics.[57] Sepsis is a dynamic syndrome triggered by interactions between the infecting pathogen and the host immune system, resulting in dysregulated inflammatory and coagulation cascades, and potential subsequent organ dysfunction or death.[58-61] Dramatic fluid shifts occur during sepsis, expanding extracellular fluid and thereby increasing the volume of distribution of hydrophilic drugs like beta-lactams, aminoglycosides, glycopeptides, and some antifungal and antiviral agents. Furthermore, patients with severe sepsis may demonstrate enhanced renal drug clearance, potentially accelerating the elimination of antibiotics.[62] Additional physiologic changes in the critically ill, such as the development of hypoalbuminemia, may lead to additional increases in drug clearance.[62,63]

A 2009 retrospective multicountry study from 22 medical institutions revealed inappropriate initial antibiotic treatment was correlated with a 5-fold decrease in survival in patients with septic shock.[64] Multiple reports have demonstrated that efficacy of antibiotic treatment is related not only to antibiotic susceptibility patterns but also dose optimization to enhance drug exposure at the site of infection.[57,65,66] A number of dosing techniques currently exist to optimize antibiotic dosing in the setting of sepsis. First, effective loading doses at the initiation of therapy aim to rapidly fill the volume of distribution and attain effective antibiotic concentrations.[67] Second, in the case of beta-lactam antibiotics, where time above MIC is critical for antibiotic efficacy, the dosing interval and duration of infusion can be extended to optimize drug pharmacodynamics.[39,68]

Pharmacokinetics and pharmacodynamics concepts can be applied in ways that enhance the utilization of antibiotics, better target resistant organisms, or help prevent the development of newly resistant organisms.[50] The pharmacokinetics and pharmacodynamics of a given therapy may vary between individuals based on the MIC of the infecting organism, infection site, infection severity, volume of distribution, and patient drug clearance.[13,39,52,57,66,68-72] A key function of antibiotic stewardship is to identify patient- and disease-specific factors that may influence antibiotic pharmacokinetics and to optimize the treatment approaches via augmented dosing, altered infusion time, or dosing intervals to both enhance therapeutic efficacy and lower the emergence of drug resistance.

Rapid Diagnostics: Accelerating Appropriate Antibiotic Selection

Delays in the identification of causative pathogens during an acute infection hinder the ability of clinicians to narrow and streamline therapy to the most optimal antibiotic agent, resulting in excessive utilization of broad-spectrum antibiotics, thereby potentiating the development of antibiotic resistance. Improved rapid point-of-care tools have been shown to improve diagnostic timeliness and accuracy and curtail unnecessary antibiotic use.

Rapid diagnostic technologies have been a focus of a number of diagnostic companies and research institutions. This has been supported by a core goal identified in the 2014 National Strategy for Combating Antibiotic-Resistant Bacteria: to advance "rapid and innovative diagnostic tests for identification and characterization of resistant bacteria."[73] Recently developed rapid diagnostic technologies such as multiplex real-time polymerase chain reaction assays,[74] peptide nucleic acid-fluorescence in situ hybridization, nucleic acid microarrays, and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF) reduce the time required to identify a causative pathogen in an infection and some systems also provide antibiotic susceptibility information and can identify parasitic, fungal, viral, or bacterial pathogens.[75-77] The net effect of these new tools is exponential, allowing clinicians to choose the most appropriate antibiotic therapy sooner and deescalate therapy in a timely fashion.[30]

Until recently, the identification of organisms from positive blood cultures was a several day process dependent on bacterial growth in the laboratory for both identification through biochemical analysis and antibiotic susceptibility testing. In one recent analysis, the integration of rapid diagnostic and susceptibility techniques within an ASP improved the time to optimal antibiotic therapy from 80.9 hours to 23.2 hours, leading to shorter hospital stays (15.3 days post-integration vs 23.3 days pre-integration) and decreased mortality (8.9% post-integration compared to 21% pre-integration).[78] Other studies have shown similar benefits of rapid diagnostic tests such as MALDI-TOF.[79-81] For example, compared to traditional testing methods, MALDI-TOF improves time to organism identification by 1.2 to 1.5 days.[80,81] A recent study reported that the implementation of a nucleic acid microarray-centered early identification and resistance marker detection system

allowed for more rapid detection and identification (10.9 hours with the microarray vs 37.9 hours via conventional testing methods) of causative pathogens in gram-negative bacteremia infections.[82]

As part of the movement to develop new rapid point-of-care diagnostics, the National Institutes of Health (NIH) has sponsored public seminars[83] and a $20 million Antimicrobial Resistance Diagnostic Challenge federal prize competition for the discovery and innovation of new rapid point-of-care diagnostic tests for infectious diseases.[84] In 2015, the National Institute of Allergy and Infectious Diseases, as part of the NIH, awarded $11 million for 9 research projects aimed at advancing the development of rapid and innovative diagnostic tests.[85,86] Further developments and innovations are expected to follow these efforts.

Computerized Provider Order Entry: A Vehicle to Support Antibiotic Stewardship

To be effective, ASPs require information and computer applications that allow for timely and logistically feasible optimization of antibiotic therapy. Reductions in time to appropriate antibiotic therapy directly correlates to reduced infection-related mortality.[64,87] Two important stewardship strategies include formulary restriction and preauthorization prior to utilization of restricted antibiotics.[38] Computerized Provider Order Entry enables (1) restricting antibiotics and requiring preapproval for use in cases deemed appropriate by an authorized infectious disease physician or pharmacist expert, (2) real-time decision support to improve antibiotic utilization via dose-checking or drug-bug mismatches,[88] (3) prospective audit and feedback to reduce inappropriate antibiotic use,[31] and (4) supplementing the aforementioned ASP activities with addition of antibiotic indications to computer order entry, dose optimization, deescalation based on antibiotic susceptibility, IV to PO antibiotic substitutions,[49] and implementation of order-sets streamlining therapy.[1] A recent publication by the Kaiser Permanente Medical Group showed the development of treatment algorithms, order sets, Best Practice Alerts, and charting tools within their electronic medical record reduced inpatient sepsis mortality by about 40%.[89] Computerized decision support systems may have a role in improving adherence to prescribing guidelines for specific infections.[30,90]

Measuring the Effectiveness of an ASP

A variety of strategies are used to measure and evaluate the effectiveness of an ASP.[91,92] Consistency in this practice enables an ASP to allocate resources to high-value intervention as well as adjust activities to account for changes in disease epidemiology, antibiotic resistance, and prescribing patterns. Measures of ASP effectiveness can be broadly classified as either process or outcome measures with regard to treatment of infections.

Process measures can be used to determine appropriateness of infection management as well as follow response to clinician-directed intervention. Examples of process measures include antibiotic prescribing patterns for specific infectious syndromes and acceptance of audit and feedback intervention.[1,38] Process measures shed light on aggregate prescribing practices as well as the success of certain ASP interventions, creating opportunity for education on best practices, adjustments in institutional procedures, or even, where necessary, disciplinary action. Outcome measures are used to demonstrate the impact of ASP intervention and may be dependent on process measures to a degree. Examples of outcome measures include antibiotic utilization and expenditures, as well as clinical outcome measures including CDI and antibiotic resistance rates.[1,38]

The CDC National Healthcare Safety Network has created a mechanism for facilities to submit antibiotic utilization and resistance data as well as CDI rates and benchmark themselves against other institutions.[1,93] CDI, a costly complication of antibiotic use, affects institutional financial reimbursement. Thus, institutional administrators should be involved in discussion of actionable intervention to improve CDI rates. CDI rates are also affected by infection control practices like hand hygiene and surface decontamination, underscoring the importance of inclusion of infection preventionists on the ASP team and a collaborative approach to reducing CDI.

Process measures are generally more specific to ASP activities and can be directly used to assess the success of individual types of intervention. Outcome measures are typically more relevant to clinicians and administrators though specifically tying them to ASP activities can be challenging as they can be affected by a variety of contributing factors. Process and outcomes measures are complementary, interdependent, and distinct, and can be employed at the institutional-, departmental-, and even individual provider-level to produce a comprehensive analysis of antibiotic use and infection management. Process and outcome measures should lead to actionable interventions to optimize best practices in antibiotic use.

Antibiotic Stewardship Outside the Hospital

Antibiotic stewardship has historically been championed in hospitals and health systems due in large part to organizational encouragement, availability of resources, and, in some cases, regulatory requirements. However, the majority of antibiotic prescribing occurs outside the hospital setting and over half of outpatient antibiotic prescriptions may be inappropriate.[21] Antibiotic stewardship principles and formal programs are emerging outside of hospitals and health systems, including nursing homes, outpatient ambulatory care and surgery facilities, and dentistry.[1,2,21,94,95] Regulatory bodies are following suit and seek to require ASPs in such settings.[1,36]

A major challenge to antibiotic stewardship practices in these settings is

the paucity of resources and differences in the nature of health care delivery compared with a hospital. For this reason, certain clinicians may take on nontraditional roles and practices and will access individuals with antibiotic expertise like pharmacists or physicians on a consultant basis.[95] Lessons learned from antibiotic stewardship in hospitals are generally useful and have laid a framework for the approach to developing an ASP in nonhospital settings; however, continued evaluation and refinement of best antibiotic stewardship practices in these settings is essential.

Conclusion

The development of antibiotics has been one of the most effective medical advances in human history. Misuse of antibiotics has led to the development of antibiotic resistance and other consequences, including CDI, prolonged hospital stays, and hospital readmissions with combinatorial increases in morbidity and mortality. Antibiotic stewardship has been identified as a major global strategy to combat antibiotic resistance by a number of professional, governmental, and regulatory organizations, and as a result, ASPs are becoming increasingly common across a number of health care settings. Successful ASPs utilize a multidisciplinary team of health care practitioners and administrators and employ a variety of strategies to improve the appropriateness of antibiotic use and track outcomes. Antibiotic stewardship practices continue to broaden to include outpatient practice, nursing facilities, and other health care settings.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. AJLM

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