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Antimicrobial Stewardship: A Call to Action for Surgeons

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Abstract

Despite current antimicrobial stewardship programs (ASPs) being advocated by infectious disease specialists and discussed by national and international policy makers, ASPs coverage remains limited to only certain hospitals as well as specific service lines within hospitals. The ASPs incorporate a variety of strategies to optimize antimicrobial agent use in the hospital, yet the exact set of interventions essential to ASP success remains unknown. Promotion of ASPs across clinical practice is crucial to their success to ensure standardization of antimicrobial agent use within an institution. To effectively accomplish this standardization, providers who actively engage in antimicrobial agent prescribing should participate in the establishment and support of these programs. Hence, surgeons need to play a major role in these collaborations. Surgeons must be aware that judicious antibiotic utilization is an integral part of any stewardship program and necessary to maximize clinical cure and minimize emergence of antimicrobial resistance. The battle against antibiotic resistance should be fought by all healthcare professionals. If surgeons around the world participate in this global fight and demonstrate awareness of the major problem of antimicrobial resistance, they will be pivotal leaders. If surgeons fail to actively engage and use antibiotics judiciously, they will find themselves deprived of the autonomy to treat their patients.

Keywords: antibiotic prophylaxis; intra-abdominal infection; necrotizing soft tissue infection; surgical site infection; trauma

Although most surgeons are aware of the problem of antimicrobial resistance, most underestimate this problem in their own hospital. Surgeons should always optimize antimicrobial management to maximize clinical outcome and minimize emergence of antimicrobial resistance. The necessity of formalized systematic approaches to the optimization of antibiotic therapy in the setting of surgical units worldwide, both for elective and emergency admissions, has become increasingly urgent.

In 2013, a Cochrane review was published to estimate the effectiveness of professional interventions in antibiotic stewardship for hospital inpatients and to evaluate the impact of these interventions on reducing the incidence of antimicrobial resistance or *Clostridium difficile* infection [1]. The results showed that interventions to reduce excessive antibiotic prescribing to hospital inpatients were able to reduce antimicrobial resistance and hospital-acquired infections (HAIs), improving clinical outcome. The meta-analysis supported the use of restrictive interventions when the need is urgent, but suggested that persuasive and restrictive interventions are equally effective after six months.

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Because physicians are primarily responsible for the decision to use antibiotics, educating them and changing the attitudes and knowledge that underlie their prescribing behavior are crucial for improving antimicrobial agent prescription. We propose that the best means of improving antimicrobial stewardship in general and emergency surgical units worldwide should involve collaboration among various specialties within a healthcare institution including prescribing clinicians.

A panel of experts from the Surgical Infection Society (SIS) and World Society of Emergency Surgery (WSES) has shared this document with the aim of defining the role of surgeons within the antimicrobial stewardship programs.

Antibiotic Prophylaxis

Pre-operative antibiotic prophylaxis (AP) has been demonstrated in multiple randomized controlled trials and meta-analyses to reduce the risk of surgical site infections (SSIs) across different types of surgical procedures [2]. Given the evidence, systemic AP is considered to be a key component of peri-operative infection prevention bundles [3]. Although compliance with appropriate timing and spectrum of AP have improved as a result of quality improvement initiatives, there remain significant deficiencies in compliance with other aspects of AP such as duration of post-operative antibiotics [3–5]. Given that approximately 15% of all antibiotic agents in hospitals are prescribed for surgical prophylaxis [6,7], peri-operative antibiotic prescribing patterns can be a major driver of some emerging infections (such as *C. difficile*) [8,9] and selection of antibiotic resistance, thus increasing healthcare costs.

Although appropriate AP plays a pivotal role in reducing the rate of SSIs [10], other factors that impact SSI rates should not be ignored. Antibiotic prophylaxis should never substitute for good medical practices, such as those of infection prevention and control. Peri-operative SSI prevention strategies should include attention to basic infection control strategies, surgical technique, hospital and operating room environments, instrument sterilization processes, and peri-operative optimization of patient risk factors [11].

Joint guidelines for AP in surgical procedures were revised and updated in 2013 by the American Society of Health-System Pharmacists, Infectious Diseases Society of America, SIS, and Society for Healthcare Epidemiology of America [11]. These guidelines focus on the effective and safe use of AP. To be effective, prophylactic antimicrobial agents should be bactericidal and have in vitro activity against the common organisms that cause post-operative SSIs after a specific surgical procedure. Further, therapeutic serum and tissue concentrations of antimicrobial agents should be present during the period of potential contamination. Additional antibiotic doses may need to be administered intra-operatively for prolonged procedures or for agents with short half-lives. To be safe, AP should have no or few adverse effects and should have the narrowest spectrum of activity necessary to prevent post-operative infections.

The need for AP for procedures with a low risk of SSIs should be re-assessed, however. For example, the joint guidelines do not support AP for patients at low risk who are undergoing elective laparoscopic cholecystectomy, which has a SSI rate of 1%–4% [11,12]. Given that the relative risk reduction in SSIs from AP appears to be constant across procedures [2], the lower the rate of SSIs, the smaller the absolute risk reduction that can be expected with AP. On the other hand, although the incidence of SSI is low for clean procedures where there is implanted foreign material (such as joint replacements), the guidelines suggest that the devastating consequences of a prosthetic-related SSI justify the use of AP in these procedures. Therefore, the magnitude of both benefits and risks in addition to the adverse effects of AP need to be carefully considered in individual patients, depending on their risk factors and the planned procedure.

The joint guidelines recommend limiting the duration of AP to minimize cost, toxicity, and antimicrobial agent resistance. The duration of AP for most procedures should not exceed 24 hours [11]. Despite these guidelines, high rates of inappropriate continuation of prophylactic antibiotic agents in surgical procedures continue to be reported in the literature [4]. Moreover, whereas quality improvement efforts have resulted in higher compliance with timing and spectrum of AP, minimization of post-operative prophylaxis continues to be problematic. Several institutions have reported varying degrees of success with local interventions (e.g., educational programs) [4]. Further research needs to focus on identifying and implementing effective strategies for promoting antimicrobial agent stewardship in AP prescribing.

Antibiotic Therapy

Antibiotic therapy is integral to the daily work of surgeons, but this therapy comes with competing responsibilities. Antimicrobial therapy must be optimized for individual patients, but this prime directive often directly contradicts the public interests to preserve the efficacy of antimicrobial agents, prevent the emergence of antimicrobial-resistant strains, and minimize the collateral damage of antibiotics (e.g., *C. difficile* infection). Many factors underlie inappropriate prescription of antimicrobial agents, including unjustified use, improper dosing intervals, incorrect duration, as well as prescription of antimicrobial agents when more effective alternatives are available. For reasons beyond the scope of this review, surgeons commonly have to make a decision to initiate antimicrobial therapy when evidence for a definite infection is lacking, circumstantial, or overlaps with non-infectious syndromes that may better explain the patient's clinical picture.

Once antimicrobial agents have been chosen as a potential therapy, the decision tree for an antimicrobial agent regimen should depend mainly on six elements: (1) The presumed pathogens involved, (2) the likelihood of pre-treatment antimicrobial agent resistance, (3) the clinical severity of illness, (4) the presumed site of infection [13], (5) the ability to deliver the agents to the site of infection, and (6) the risks associated with the agents themselves. The likelihood of antimicrobial agent resistance depends on local resistance profiles and previous antimicrobial agent exposure.

Initial antibiotic therapy is typically empiric in nature, because the patient needs immediate attention, and microbiologic data (culture and susceptibility results) can require up to 48–72 hours before they are available for a more detailed analysis. Especially in critically ill patients, empiric therapy should be started immediately [14]. Antimicrobial therapy should be tailored to the individual patient, with narrower spectrum agents used to manage community-acquired infections, and broader spectrum agents used for HAIs [15]. Subsequent modification (de-escalation) of the initial regimen should be reviewed as soon as possible when susceptibility results are available [14]. The timing, regimen, dose, route of administration, and duration of antimicrobial therapy should be optimized. In the context of a multidisciplinary approach, active communication with the infectious disease specialist and the microbiologist can improve appropriate antimicrobial use and patient outcomes.

The duration of antimicrobial therapy should be shortened in patients with no signs of on-going infections. The recent prospective trial by Sawyer et al. [16] demonstrated that, in patients with complicated intra-abdominal infections who are undergoing an adequate source-control procedure, the outcomes after approximately 4-day fixed-duration antibiotic therapy were similar to those after a longer course of antibiotic agents that extended until after the resolution of physiologic abnormalities. Patients who have signs of on-going infection or systemic illness beyond 5–7 days of antibiotic treatment benefit from further diagnostic investigations to determine whether an uncontrolled source of infection exists or the antimicrobial agent regimen requires modification [14]. Recommendations for antibiotics management are illustrated in Table 1.

In treating patients with HAIs, the threat of antimicrobial resistance is one of the major challenges associated with antimicrobial management. In the past few decades, an increased prevalence of surgical infections caused by antibiotic-resistant pathogens, including extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, *Pseudomonas aeruginosa,* methicillin-resistant *Staphylococcus aureus* (MRSA), and carbapenemase-resistant Enterobacteriaceae (CRE) have been observed [14]. ESBL-producing Enterobacteriaceae are now also present in community-acquired infections, and CRE are now endemic in many regions of the world and represent one of the most serious public health threats [17]. Many gram-negative bacteria are fully resistant to many commonly used antibiotic agents [18], and some infections actually require older, more toxic antibiotic agents (e.g., polymyxins, aminoglycosides) to ensure adequate antimicrobial coverage.

Emergence of antimicrobial resistance, combined with the lack of new antimicrobial agents in the drug development pipeline, indicates that judicious antimicrobial management is necessary. Ethical and proper collaboration with pharmaceutical industries is necessary to preserve the antimicrobial agents currently available and to appropriately use the few new antibiotic agents that will be marketed in the next years. The problem of antimicrobial resistance is widespread worldwide. Clinicians should be always aware of their role and responsibility for maintaining the effectiveness of current and future antimicrobial agents.

Table 1. Recommendations for Antibiotics Management

Antibiotic Prophylaxis (AP)
• Perioperative SSI prevention strategies should include attention to -infection control strategies -surgical technique -hospital and operating room environments -instrument sterilization processes -perioperative optimization of patient risk factors
• AP should be administered for operative procedures that have a high rate of postoperative surgical site infection, or when foreign material is implanted.
• AP should be bactericidal, nontoxic, and inexpensive. It should have in vitro activity against the common organisms that cause postoperative surgical site infection after a specific surgical procedure. Broad-spectrum antibiotics should be avoided for surgical prophylaxis.
• AP should be administered not more than 30 to 60 minutes before surgery. Therapeutic concentrations of antimicrobial agents should be present in the tissue throughout the period that the wound is open.
• Additional antibiotic doses should be administered intraoperatively for prolonged procedures.
• Prolonged postoperative AP should be always discouraged.
Antibiotic therapy
• Antimicrobial agents should be used after a treatable IAI has been recognized or if there is a high degree of suspicion of an infection.
• Empiric antimicrobial therapy should be started in patients with surgical infection.
• Knowledge of local rates of resistance should be always an essential component in the determination of the empiric antimicrobial regimen.
• For patients with community-acquired infections, empiric agents with narrower spectra of activity are preferred.
• For patients with hospital-acquired infections, antimicrobial regimens with broader spectra of activity are preferred.
• Targeted antimicrobial therapy regimens should be adapted when culture and antimicrobial susceptibility test results are available.
• The antimicrobial therapy should be shortened in patients with no signs of on-going infection.
• Patients having signs of sepsis beyond 5 to 7 days of antibiotic treatment should undergo aggressive diagnostic investigation to determine an ongoing uncontrolled source of infection or antimicrobial treatment failure.

SSI = surgical site infection; IAI = intra-abdominal infection.

Antimicrobial Stewardship Programs (ASPs) in Surgical Departments

A growing body of evidence demonstrates that hospital based programs dedicated to improving antibiotic use—ASPs—can both optimize the management of infections and reduce adverse events associated with antibiotic use [19–22]. Ten years after the jointly published guidelines by the Centers for Disease Control and Prevention, Society for Healthcare Epidemiology of America, and Infectious Diseases Society of America, however, many acute care centers worldwide do not have any type of antimicrobial improvement program [23]. Hospitals everywhere should work within their resources to create an effective collaborative team.

Very few studies have been published on the role of ASPs in general surgical departments. In 2015, Çakmakçi [24] suggested that the engagement of surgeons in ASPs might be crucial to their success. In 2013, however, Duane et al. [25] showed poor compliance of surgical services with ASP recommendations; this was especially true for interventions targeting selective pressure. The authors concluded that by identifying services that are less compliant, programs could target their educational efforts to improve outcomes.

A retrospective study by Sartelli et al. [26] showed that implementation of an education-based ASP achieved a significant improvement in all antimicrobial agent prescriptions and a reduction in antimicrobial drug consumption. In a surgical unit performing mainly elective major abdominal operations and emergency surgical procedures, they introduced both a local protocol of surgical prophylaxis and a set of guidelines for management of intra-abdominal infections (IAIs) and control of antimicrobial agent use. Comparing the pre-intervention and post-intervention periods, the mean total monthly antimicrobial agent use decreased by 18.8%, from 1074.9 defined daily doses (DDD) per 1,000 patient days to 873.0 DDD per 1,000 patient days after the intervention.

To optimize surgical unit ASPs, focus should be on both surgical pre-operative prophylaxis and surgical infections. High rates of inappropriate use of prophylactic antibiotics in surgery continue to be reported in the literature, and although evidence-based guidelines exist, poor adherence to them has been reported worldwide [27–36]. Studies reporting the impact of ASPs in surgical prophylaxis are few and often contradictory.

Knox and Edye [4] demonstrated that an educational ASP was ineffective in changing surgical prophylactic antibiotic prescribing in an Australian Hospital. Overall adherence rates in the pre- and post-intervention periods demonstrated no substantial change ($p = 0.568$). There were no substantial decreases in error rates across any category, including drug choice, dosage, timing of administration, duration of administration, or re-dosing. The apparent decrease in the rate of inappropriate broad-spectrum cephalosporin usage was not statistically significant. Although that study was disappointing as far as showing improved behaviors, others have shown that ASPs may have a significant impact on optimizing antibiotic use in surgical prophylaxis practices [12,37–39].

Van Kasteren et al. [39] in a prospective multi-site study of elective procedures in 13 Dutch hospitals evaluated the quality of prophylaxis auditing before and after an intervention that consisted of performance feedback and implementation of national clinical practice guidelines. Antimicrobial use decreased from 121 to 79 DDD/100 procedures, and costs were reduced by 25% per procedure. Post-intervention, the choice of antibiotic was inappropriate in 37.5% of the cases—not in 93.5% expected cases had the intervention not occurred. Prolonged prophylaxis was observed in 31.4% (not in 46.8% expected cases) and inappropriate timing in 39.4% (not in the expected 51.8%. All improvements were statistically significant ($p < 0.01$), as shown in time series analysis. Pre- and post-intervention, overall SSI rates were 5.4% (95% confidence interval [CI]: 4.3–6.5) and 4.6% (95% CI: 3.6–5.4), respectively.

Huh et al. [38] performed an interrupted time series study of an ASP relating to surgical prophylaxis in a tertiary care hospital. The ASP consisted of monitoring of performance indicators and implementation of a computerized decision support system. The program was effective in improving multiple measures including the total use of antibiotics, use of third-generation cephalosporins and aminoglycosides, trends in proportions of resistant bacterial strains such as meropenem-resistant *P. aeruginosa,* and length of stay.

Saied et al. [12] implemented ASPs in five tertiary, acute-care surgical hospitals. The ASPs consisted of education aimed at surgeons and anesthesiologists, audit and feedback, and selection of surgeon champions. The efficacy of the intervention on timing and duration of antibiotic prophylaxis varied across hospitals when measured pre- and post-ASP implementation. Local factors such as available resources and stakeholder engagement likely play a role in the conflicting results of ASPs addressing surgical prophylaxis across different settings, as observed in these studies.

A number of guidelines have been published evaluating antimicrobial management of IAIs [13,40–47]. Only few studies have documented the impact of ASPs in the management of IAIs, however. A retrospective study by De Simone et al. [19] showed that an inexpensive and easily applied evidence-based guideline in the use of antibiotics led to a significant reduction of hospital costs with improved outcomes.

Hoffmann et al. [20] published a review focusing on treatment modalities and antimicrobial stewardship initiatives in the management of IAIs. The authors concluded that to prevent the overuse of broad-spectrum agents, ASPs should work with their microbiology department. This collaboration would focus on institution-specific resistance patterns to develop local guidelines for the empiric management of IAIs.

In 2015, Popovski et al. [21] published a multi-faceted intervention to optimize antibiotic use for IAIs. The intervention consisted of continuing educational sessions, internal guideline pocket cards and posters, and collaboration among all key stakeholders. The intervention started in December 2010. The ASP emphasized the need of risk stratification and the use of third-generation cephalosporins for management of low-risk IAIs, and discouraged fluoroquinolone use because of the high local resistance rates. When patients with IAI in a surgical unit at a tertiary care teaching hospital were compared before the intervention (April–November 2010) with those after guideline implementation (April–November 2011), investigators found a significant reduction in the proportion of patients who received ciprofloxacin therapy. Also, a reduction in the DOT/1,000 PD for piperacillin/tazobactam was demonstrated (from 116 to 67; odds ratio [OR] 0.6, 95% CI 0.5–0.7).

Dubrovskaya et al. [22] in 2012 developed an ASP for the empiric management of IAIs because of high rates of Enterobacteriaceae resistant to ciprofloxacin and ampicillin-sulbactam in their institution. The authors found a significant decrease in intravenous ciprofloxacin use by 22.6 DDD/1,000 PD ($p = 0.003$), with no significant changes in ampicillin/sulbactam use or piperacillin/tazobactam use. The hospital-acquired *C. difficile* infection rate, 30-day re-admission rate, and mean length of stay did not differ significantly between groups. The authors concluded that the new protocol showed an improvement in antimicrobial use with no significant changes in hospital metrics.

The recent and rapid spread of carbapenem resistant *Klebsiella pneumoniae* [48–50] poses a serious challenge for clinicians, and a preserved carbapenems approach should be considered in every hospital setting. In 2011, Leone et al. [51] expressed concern regarding the overuse of anti-*Pseudomonas* carbapenems and the development of carbapenem resistance among Enterobacteriaceae in management of IAIs.

In a recent article published by Sartelli et al. [26], the most important result of an ASP was the significant reduction of the use of group 2 carbapenems including imipenem-cilastatin and meropenem, and ciprofloxacin. The reduction of carbapenems is important because CRE are rapidly emerging worldwide, and several epidemiologic studies have shown a link between carbapenem use and resistance [52]. The reduction in fluoroquinolones use, both ciprofloxacin and levofloxacin [26], is important, because these antibiotics have been associated with a low threshold for emergence of resistance including ESBL as well as an increased risk of development of *C. difficile* infection [53,54].

Discussion

Despite current ASPs being advocated by infectious disease specialists and discussed by national and international policy makers, ASPs coverage remains limited to only certain hospitals as well as specific service lines within hospitals. ASPs incorporate a variety of strategies to optimize antimicrobial use in the hospital, yet the exact set of interventions essential to ASP success remains unknown. Promotion of ASPs across clinical practice is crucial to their success to ensure standardization of antimicrobial use within an institution [55].

Successful ASPs should focus on collaboration between healthcare professionals to ensure consistency in approach, shared knowledge, and widespread diffusion of practice. It is essential that the antimicrobial stewardship team include an infectious diseases physician and a clinical pharmacist with infectious diseases training. Moreover, an alliance with the clinical microbiologist, the epidemiologist, and the clinical administrator is essential to a well-functioning program. Finally, the inclusion of prescribing clinicians including surgeons in ASPs is paramount to their success.

Taken together, the preferable means of improving antimicrobial stewardship is to involve a comprehensive program that incorporates collaboration among various specialties within a healthcare institution. In this context, the direct involvement of surgeons in ASPs can be highly impactful [24].

Surgeons with satisfactory knowledge in surgical infections involved in ASPs may audit antibiotic prescriptions, provide feedback to the prescribers and integrate the best practice of antimicrobial use among surgeons. Because they are at the forefront in treating patients with infections, they provide insight into source control within the operating theater. As a result, surgeons may be better able to stratify patients according to their risk for infectious complications and to guide their antimicrobial therapy more effectively. Surgeons must be aware, however, that judicious antibiotic utilization is an integral part of any stewardship program and necessary to maximize clinical cure and minimize emergence of antimicrobial resistance.

It is well known that antimicrobial restriction, including pre-prescription authorization, is not more effective than the persuasive tactic in achieving the goal of controlling antimicrobial use in the long term [1]. Moreover, in many settings, there may be inadequate personnel for a restrictive approach, and restriction strategies fail to consider the appropriateness of use of non-restricted antimicrobial agents, which makes up the vast majority of antimicrobial agents used in the hospital [56].

The impact on surgeon autonomy with antimicrobial restriction may also create barriers to collaboration with members of the ASP resulting in less communication about stewardship. Therefore, the emphasis needs to be on surgeon incorporation into the ASP and education overall.

Education must be a fundamental part of every ASP. Effective and optimal antibiotic prescribing and management is part of a decision making process that requires a fundamental understanding of the key principles of microbiology and of the evolving relation between antibiotic consumption and the emergence of resistance and prevalence of HAIs [57]. Unfortunately, because medical professionals have already established their knowledge, attitudes, and behaviors about antibiotic use, it is difficult to change their deeply established views and practice patterns [58]. Efforts to improve educational programs are required that focus on judicious use of antimicrobial agents with early de-escalation therapy and emphasis on etiologies of antimicrobial resistance patterns.

Facility-specific treatment recommendations, based on guidelines and local formulary options promoted by the APS team, can guide general surgeons in antibiotic agent selection and duration, particularly for the most common indications for antibiotic use including treatment of community-acquired infections (e.g., IAIs and skin and soft tissue infections), management of HAIs (e.g., hospital-acquired pneumonia and urinary tract infections), and surgical prophylaxis. Local guidelines and protocols using national recommendations should always incorporate local trends in antimicrobial resistance and hospital-specific targets for decreased use. The ASP team should promote audit and feedback regarding the use of antibiotics and adherence to local protocols.

Excessive antimicrobial use contributes to the emergence and spread of multi–drug-resistant organisms [59], and there is a direct correlation between the overuse of antibiotics and the development of antibiotic resistance [60]. Therefore, the battle against antibiotic resistance should be fought by all healthcare professionals in every hospital. If surgeons around the world participate in this global fight and demonstrate awareness of the major problem of antimicrobial resistance, they will be pivotal leaders. If surgeons fail to engage actively and use antibiotics judiciously, they will find themselves deprived of the autonomy to treat their patients.

Conclusions

Despite the advocacy for ASPs, these collaborations are few and far between. Many hospitals remain without formal programs, and those that do have programs continue to struggle to get acceptance across service lines. Moreover, identifying optimal efforts to impact positive change has remained challenging. Restriction strategies may be effective at controlling use but raise issues of prescriber autonomy and require a large personnel commitment. Encouraging multidisciplinary collaboration within the health system to ensure that the prophylactic, empiric, and therapeutic uses of antimicrobial agents result in optimal patient outcomes is mandatory in the era of antimicrobial resistance.

Surgeons: Hear your call. It is your time to participate and your time to lead. Now is the time to act!

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