Global Alliance for Infections in Surgery

Antibiotic prescribing practices in surgery

Appropriate use of antibiotics is an integral part of good clinical practice

Prescribe
the right antibiotic
for the right patient
at the right time
at the right dose and
for the right duration

Antibiotic prescribing practices in surgery

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Preface

Appropriate use of antibiotics should be integral to good clinical practice and standards of care. However appropriate antibiotic prescribing practices are often inadequate and a great gap exists between the best evidence and clinical practice across the surgical pathway.
We hope this manual will draw attention to the need to change practices.

Massimo Sartelli

Global Alliance for Infections in Surgery

Be a champion to stop infections!

ACT NOW

Enhance infection prevention and control

Use antibiotics when they are truly needed

Prescribe appropriately antibiotics

Control the source of infection when it is needed


Antimicrobial resistance
Global Alliance for Infections in Surgery

Antimicrobial resistance

Antimicrobial resistance (AMR) is one of the greatest threats to public health, sustainable development and security worldwide. Its prevalence has increased alarmingly over the past decades.

Infections caused by antibiotic-resistant bacteria continue to be a challenge. Rice in 2008 coined the acronym of “ESKAPE” pathogens including Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species to emphasize that these bacteria currently cause the majority of hospital infections and effectively “escape” the effects of antibacterial drugs. These organisms are increasingly multi-drug- (MDR), extensive-drug- (XDR) and pan-drug- resistant (PDR) and this process is accelerating globally.

Combating resistance has become a top priority for global policy makers and public health authorities. New mechanisms of resistance continue to emerge and spread globally, threatening our ability to manage common infections. Antibacterial use in animal and agricultural industries aggravates selective pressure on microbes. A One Health approach is required urgently.

The burden of AMR is difficult to quantify in some regions of the world because enhanced surveillance requires personnel, equipment and financial resources that are not always available. However, the worldwide impact of AMR is significant in terms of economic and patient outcomes.

The global nature of AMR calls for a global response, both in the geographic sense and across all involved healthcare sectors. The impact of AMR worldwide is significant, both in economic terms and patient outcomes, as it may:

Lead to some infections becoming untreatable or requiring antimicrobials of last resort when the treatment is mandatory.

Increase length of hospital stay, morbidity, mortality and treatment cost.

In the past two decades, the incidence of infections, caused by MDR organisms, has risen dramatically across the surgical departments worldwide, in correlation with escalating levels of antibiotic exposure.

It is absolutely vital that every clinician understands the impact of AMR on public healthcare.

At the 68th World Health Assembly in May 2015, the World Health Organization (WHO) endorsed a global action plan to tackle antimicrobial resistance. It sets out five strategic objectives:

To improve awareness and understanding of antimicrobial resistance
To strengthen knowledge through surveillance and research
To reduce the incidence of infection
To optimize the use of antimicrobial agents
To develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

Antibiotic agents can be lifesaving when treating patients with bacterial infections but are often used inappropriately, specifically when unnecessary or when administered for excessive durations or without consideration of pharmacokinetic principles. Large variations in antibiotic consumption exist between countries, and while excessive use remains a major problem in some areas of the world, elsewhere there is lack of access to many antimicrobial agents. AMR is a natural phenomenon that occurs as microbes evolve. Human activities have accelerated the pace at which bacteria develop and disseminate resistance. Inappropriate use of antibiotic agents in humans and food producing animals, as well as poor infection prevention and control practices, contribute to the development and spread of AMR.
Although most physicians are aware of the problem of antimicrobial resistance, most underestimate this problem in their own hospital and prescribe inappropriately antibiotics. They can help tackle resistance by:

Enhancing infection prevention and control
Controlling the source of infection when it is needed
Prescribing antibiotics only when they are truly required
Prescribing appropriate antibiotic(s) with adequate dosages to treat the infections
Using the shortest duration of antibiotics based on evidence of guidelines
Educating the communities in which we work of the need to use antibiotics wisely.


Antibiotics in surgery
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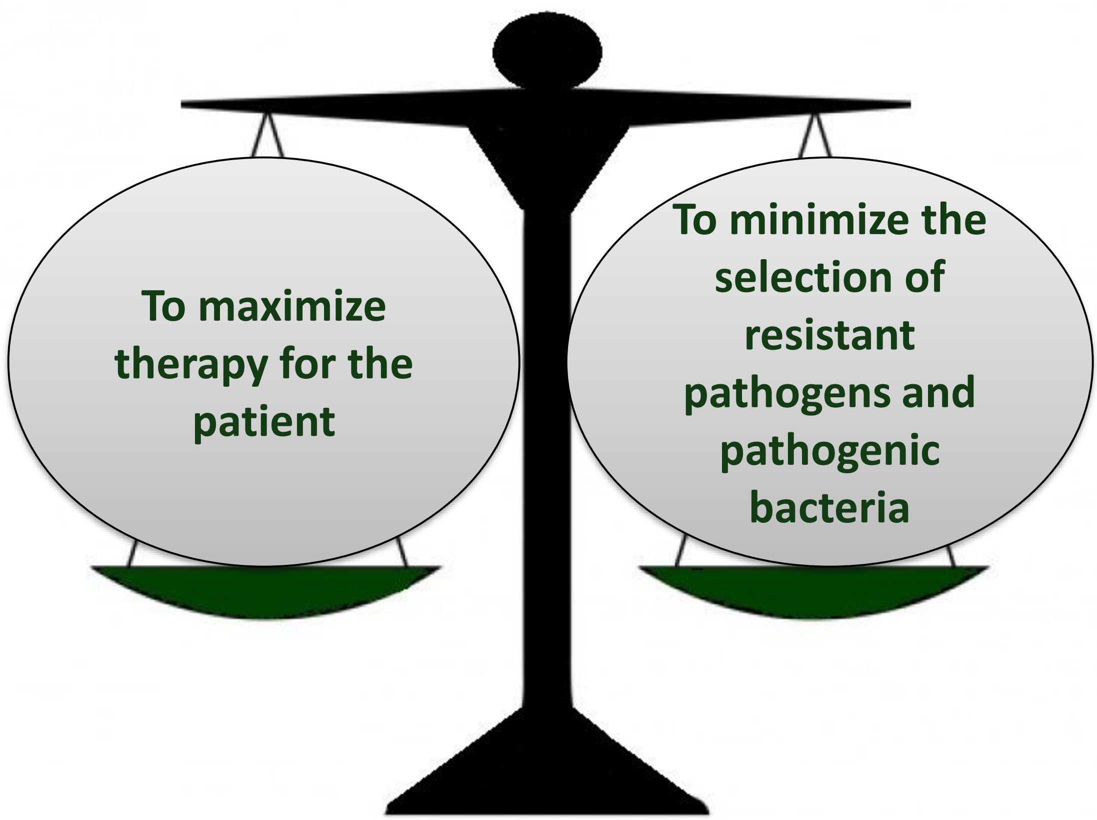
Antibiotics use: finding the right balance

Clinicians should always optimize antibiotic management to maximise clinical outcome and minimize emergence of the development of resistance and the selection of resistant pathogens. The necessity of formalized systematic approaches to the optimization of antibiotic therapy in the setting of surgical general surgery units worldwide, both for elective and emergency admissions, has become increasingly urgent.



On one hand clinicians should offer optimal therapy for the individual patient under their care; on the other hand they should limit the impact of the antibiotic in order to prevent the selection of resistant pathogens and pathogenic bacteria such as *C. difficile*.

Important considerations when prescribing antibiotic therapy include obtaining an accurate diagnosis of infection; understanding the difference between prophylaxis, empiric and targeted therapy; prescribing antibiotics for the shortest duration; understanding antibiotics characteristics (such as pharmacodynamics and pharmacokinetics); accounting for host characteristics that influence antimicrobial activity; and in turn, recognizing the adverse effects of antibiotic agents on the host.

Appropriate use of antibiotics is an integral part of good clinical practice

Antibiotics in surgery

Prophylaxis

Antibiotics to prevent infections

Empiric therapy

Antibiotics to treat clinically susptected infections

Targeted therapy

Antibiotics to treat bacteriologically confirmed infections

Antibiotic prophylaxis

Systemic antibiotic prophylaxis (AP) is one of the most important component of a perioperative infection prevention strategy. The use of AP contributes considerably to the total amount of antibiotics used in hospitals and may be associated with increases in antibiotic resistance and healthcare costs.

Although AP plays a pivotal role in reducing the rate of surgical site infections, other factors such as attention to basic infection-control strategies may have a strong impact on surgical site infections rates.

Perioperative surgical AP should be recommended for operative procedures that have a high rate of postoperative wound infection or when foreign material is implanted.

Prophylactic antibiotic agents should be nontoxic and inexpensive and have in vitro activity against the common organisms that cause postoperative wound infection after a specific surgical procedure.

Therapeutic concentrations of antibiotics should be present in the tissue throughout the all period that the wound is open.

Principles of appropriate antibiotic prophylaxis

Antibiotic agents alone are unable to prevent surgical site infections. Strategies to prevent surgical site infections should always include attention to:

- **IPC strategies including correct and compliant hand hygiene practices**
- **Meticulous surgical techniques and minimization of tissue trauma**
- **Hospital and operating room environments**
- **Instrument sterilization processes**
- **Peri-operative optimization of patient risk factors**
- **Peri-operative temperature, fluid, and oxygenation management**
- **Targeted glycemic control**
- **Appropriate management of surgical wounds**

Antibiotic prophylaxis should be administered for operative procedures that have a high rate of postoperative surgical site infection, or when foreign materials are implanted.

Antibiotic agents given as prophylaxis should be effective against the aerobic and anaerobic pathogens most likely to contaminate the surgical site—i.e., gram-positive skin commensals or normal flora colonizing the incised mucosae.

Antibiotic prophylaxis should be administered within 120 minutes before the incision. Administration of the first dose of antibiotic agents beginning within 30 to 60 minutes before surgical incision, however, is recommended for most antibiotic agents (e.g., cefazolin), to ensure adequate serum and tissue concentrations during the period of potential contamination. Obese patients ‡120 kg require higher doses of antibiotic agents.

A single dose generally is sufficient. Additional antibiotic doses should be administered intra-operatively for procedures >2–4 hours (typically where duration exceeds two half-lives of the antibiotic) or with associated significant blood loss (>1.5 L).

There is no evidence to support the use of postoperative antibiotic prophylaxis.

Each institution is encouraged to develop guidelines for proper surgical prophylaxis.

Antibiotic selection for empirical therapy

The treatment of patients with surgical infections involves both source control and antibiotic therapy.

Source control encompasses all measures undertaken to eliminate the source of infection, reduce the bacterial inoculum and correct or control anatomic derangements to restore normal physiologic function.

The process of infection is a complex state that involves both microorganism and host mechanisms. A local initial inflammatory respond attracts neutrophils, macrophages, and other phagocytes promoting the release of cytokines. In some cases this is accompanied by liquefaction necrosis and the release of pus with replicating microorganisms in the site. Defensive host responses include the formation of fibrin deposits to shield healthy tissues from the dissemination, establishing an abscess. The abscess protects both host and bacteria, where no antibiotics can penetrate well enough to control the infection.

Antibiotics should be used after a treatable infection has been recognized or when there is a high degree of suspicion for infection. Initial antimicrobial therapy is typically empirical in nature because they need immediate treatment (especially in critically-ill patients), and microbiological data (culture and susceptibility results) usually requires ≥24 h for the identification of pathogens and antibiotic susceptibility patterns.

Isolation and identification of bacterial strains take more time, and results of antibiotic susceptibility are usually only available after 48 h and later.

The decision tree for the empiric antibiotic regimen should depend mainly on three factors: presumed pathogens involved and risk factors for major resistance patterns, clinical patient's severity and presumed/identified source of infection.

Generally, the most important factors in predicting the presence of resistant pathogens in surgical infections is acquisition in a healthcare setting (particularly if the patient becomes infected in the ICU or has been hospitalized for more than 1 week), corticosteroid use, organ transplantation, baseline pulmonary or hepatic disease, and previous antimicrobial therapy.

Previous antimicrobial therapy is one of the most important risk factors for resistant pathogens.

Knowledge of local rates of resistance and the risk factors that suggest resistant bacteria should be involved as essential components of the clinical decision-making process when deciding on which antibiotic regimen to use for empiric treatment of infection. Every clinician starting empiric therapy should know the local epidemiology. Surveillance initiatives are important, both in a local and in a global context. If local epidemiology suggests that a patient may be infected with a strain already known to be resistant to antibiotics, then inappropriate antibiotic therapy, which fails to cover known resistance patterns risks further disruption of the natural flora and selecting for resistant variants without providing effective treatment.

Especially in critically ill patients inappropriate therapy may have a strong negative impact on outcome.

Clinical stability and physiological well-being is an important factor. Critically ill patients can suffer increased morbidity and mortality if initial therapy is ineffective. In contrast, less severely ill patients may have more time for the clinician to know that initial therapy was not active.

An ineffective or inadequate antimicrobial regimen is one of the variables more strongly associated with unfavorable outcomes in critically ill patients. Broad empiric antimicrobial therapy should be started as soon as possible in patients with organ dysfunction (sepsis) and septic shock. International guidelines for the management of sepsis and septic shock (the Surviving Sepsis Campaign) recommend intravenously administered antibiotics as soon as possible and in any case within the first hour of onset of sepsis and the use of broad-spectrum agents with adequate penetration of the presumed site of infection.

Dosage

The antibiotic dosing regimen should be established depending on host factors and properties of antibiotic agents. Antibiotic pharmacokinetics describes the fundamental processes of absorption, distribution, metabolism, and elimination and the resulting concentration-versus-time profile of an agent administered in vivo. The achievement of appropriate target site concentrations of antibiotics is essential to eradicate the relevant pathogen. Suboptimal target site concentrations may have important clinical implications, and may explain therapeutic failures, in particular, for bacteria for which in vitro MICs are high. Antibiotics typically need to reach a site of action outside the plasma. This requires the drug to pass through the capillary membranes. Disease and drug-related factors can contribute to differential tissue distribution.

Knowledge of the pharmacokinetic and pharmacodynamic antibiotic properties of each drug including (inhibition of growth, rate and extent of bactericidal action, and post-antibiotic effect) may provide a more rational determination of optimal dosing regimens in terms of the dose and the dosing interval. Optimal use of the pharmacokinetic/pharmacodynamic relationship of anti-infective agents is important for obtaining good clinical outcomes and reduction of resistance. Dosing frequency is related to the concept of time-dependent versus concentration-dependent killing. Beta-lactams exhibit time-dependent activity and exert optimal bactericidal activity when drug concentrations are maintained above the MIC. Therefore, it is important that the serum concentration exceeds the MIC for appropriate duration of the dosing interval for the antimicrobial and the organism. Higher frequency dosing, prolonged infusions and continuous infusions have been utilized to achieve this effect. In contrast, antibiotics such as aminoglycosides exhibit concentration-dependent activity and should be administered in a once daily manner (or with the least possible number of daily administrations) in order to achieve high peak plasma concentrations. With these agents, the peak serum concentration, and not the time the concentration remains above the MIC, is more closely associated with efficacy. In terms of toxicity, aminoglycosides nephrotoxicity is caused by a direct effect on the renal cortex and its uptake saturation. Thus, an extended interval dosing strategy reduces the renal cortex exposure to aminoglycosides and reduces the risk of nephrotoxicity.

In patients with septic shock, administering an optimal first dose is probably as equally important as to the timing of administration. This optimal first dose could be described as a loading, or front-loaded dose and is calculated from the volume of distribution (Vd) of the drug and the desired plasma concentration. The Vd of hydrophilic agents (which disperse mainly in water such as beta-lactams, aminoglycosides and glycopeptides) in patients with septic shock may be altered by changes in the permeability of the microvascular endothelium and consequent alterations in extracellular body water. This may lead to lower than expected plasma concentrations during the first day of therapy resulting in sub-optimal achievement of antibiotic levels. In the setting of alterations in the volume of distribution, loading doses and/or a higher overall total daily dose of beta-lactams, aminoglycosides, or glycopeptides are often required to maximize the pharmodynamics ensuring optimal drug exposure to the infection site in patients with sepsis or septic shock.

Once an appropriate initial loading dose is achieved, the antibiotic regimen should be reassessed, at least daily, because pathophysiological changes may significantly affect drug availability in the critically ill patients. Lower than standard dosages of renally excreted drugs must be administered in the presence of impaired renal function, while higher than standard dosages of renally excreted drugs may be needed for optimal activity in patients with glomerular hyperfiltration. It should be noted that in critically ill patients, plasma creatinine is an unreliable marker of renal function.

Duration

Duration of therapy should be shortened as much as possible unless there are special circumstances that require prolonging antimicrobial therapy such as immunosuppression, or ongoing infections. Oral antimicrobials, can substitute IV agents as soon as the patient is tolerating an oral diet so as to minimize the adverse effects which are associated with intravenous access devices. Where possible, conversion to oral antimicrobial agents having high oral bioavailability (e.g. fluoroquinolones) should be considered. Patients with surgical infections who have signs of sepsis beyond 5 to 7 days of treatment warrant aggressive diagnostic investigation to determine if an ongoing uncontrolled source of infection or antimicrobial treatment failure is present. In the management of critically ill patients with sepsis and septic shock clinical signs and symptoms as well as inflammatory response markers such as procalcitonin, although debatable, may assist in guiding antibiotic treatment.

Principles of appropriate antibiotic therapy

The source of infection should always be identified and controlled as soon as possible.

Antibiotic empiric therapy should be initiated after a treatable surgical infection has been recognized, because microbiologic data (culture and susceptibility results) may not be available for up to 48–72 hours to guide targeted therapy.

In critically ill patients, empiric broad-spectrum therapy to cover the most likely pathogens should be initiated as soon as possible after a surgical infection has been recognized. Empiric antimicrobial therapy should be narrowed once culture and susceptibility results are available and adequate clinical improvement is noted.

Empiric therapy should be chosen on the basis of local epidemiology, individual patient risk factors for MDR bacteria and Candida spp., clinical severity, and infection source.

Specimens for microbiologic evaluation from the site of infection are always recommended for patients with hospital-acquired or with community-acquired infections at risk for resistant pathogens (e.g., previous antimicrobial therapy, previous infection or colonization with a MDR, XDR, and PDR pathogen) and in critically ill patients. Blood cultures should be performed before the administration of antibiotic agents in critically ill patients.

6. The antibiotic dose should be optimized to ensure that PK-PD targets are achieved. This involves prescribing an adequate dose, according to the most appropriate and right method and schedule to maximize the probability of target attainment.

The appropriateness and need for antimicrobial treatment should be re-assessed daily.

Once source control is established, short courses of antibiotic therapy are as effective as longer courses regardless of signs of inflammation.

Failure of antibiotic therapy in patients having continued evidence of active infection may require a reoperation for a second source control intervention.

Biomarkers such as procalcitonin may be useful to guide duration and cessation of antibiotic therapy in critically ill patients.

Clinicians with advanced training and clinical experience in surgical infections should be included in the care of patients with severe infections.

12. The infection prevention and control measures combined with antimicrobial stewardship programs should be implemented in all hospitals worldwide. These interventions and programs require regular, systematic monitoring to assess compliance and efficacy.

Monitoring of antibiotic consumption should be implemented and feedback provided to all ASP team members regularly along with resistance surveillance data and outcome measures


Which interventions do improve antibiotic prescribing practices?
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Significant data support the importance of antibiotic prescribing practices for patients with surgical infections, in critically ill and non-critically ill patients and in community and hospital-acquired infections. Prescribing practices may influence the outcome and cost of treatment as well as the risk of some emerging infections (such as C. difficile) and resistant pathogens in the individual patient and the broader environment.

The necessity of formalized systematic approaches to the optimization of antibiotics use in the setting of surgical units worldwide, both for prophylaxis and therapy, has become increasingly urgent.

Interventions to improve antibiotic prescribing practices for patients with surgical infections should be directed at two different levels:

Patient level – which includes clinical severity, epidemiological exposures, PK/PD factors, comorbidities, prior antibiotic exposure, prior infection, or colonization with MDROs and infection source.

Hospital level – which includes presence of in-hospital antimicrobial stewardship programs, availability of local guidelines and updated microbiological data, infection and control control policy, educational activities, and structural resources (like computer-assisted order entry).

Components of antibiotic prescribing practices at patient level that may influence outcome and the risk of developing emerging infections and antibiotic resistant infections include:

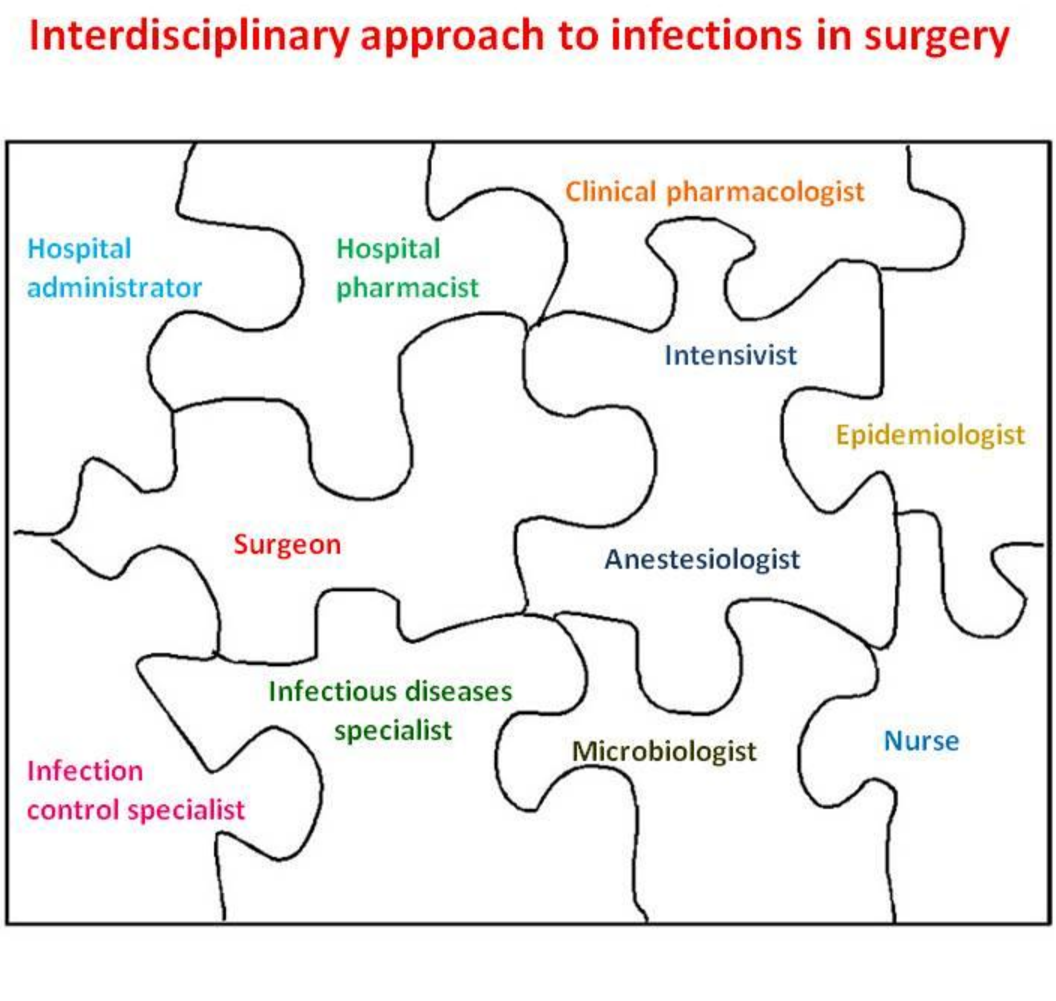
Adequacy of antibiotic therapy/prophylaxis,
Time to initial antibiotic therapy/prophylaxis,
Appropriate pharmacokinetic dosing,
Reassessment of antibiotic therapy,
Length of treatment, and
Avoidance of unnecessary antibiotic therapy.

A growing body of evidence demonstrates that hospital based programs dedicated to improving antibiotic use, commonly referred to as "Antibiotic Stewardship Programs" (ASPs), can both optimize the treatment of infections and reduce adverse events associated with antibiotic use.
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 antibiotic 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 antibiotic use within an institution. The preferable means of improving antimicrobial stewardship is to involve a comprehensive program that incorporates collaboration among various specialties within a healthcare institution.

Successful ASPs should focus on collaboration between all healthcare professionals to shared knowledge and widespread diffusion of practice. Involvement of prescribing physicians in ASPs may rise their awareness on antimicrobial resistance.

It is essential for an ASP to have at least one member who is an infectious diseases specialist. Pharmacists with advanced training or longstanding clinical experience in infectious diseases are also key actors for the design and implementation of the stewardship program interventions. In any healthcare setting, a significant amount of energy should be spent on infection prevention and control. Infection control specialists and hospital epidemiologists should be always included in the ASPs to coordinate efforts on monitoring and preventing healthcare-associated infections. Microbiologists should actively guide the proper use of tests and the flow of laboratory results. Being involved in providing surveillance data on antimicrobial resistance, they should provide periodic reports on antimicrobial resistance data allowing the multidisciplinary team to determine the ongoing burden of antimicrobial resistance in the hospital. Moreover, timely and accurate reporting of microbiology susceptibility test results allows selection of more appropriate targeted therapy, and may help reduce broad-spectrum antimicrobial use. Surgeons with adequate knowledge in surgical infections and surgical anatomy when involved in ASPs may audit antibiotic prescriptions, provide feedback to the prescribers and integrate best practices of antimicrobial use among surgeons, and act as champions among colleagues implementing change within their own sphere of influence. Infections are the main factors contributing to mortality in intensive care units (ICU). Intensivists have a critical role in treating multidrug resistant organisms in ICUs in critically ill patients. They have a crucial role in prescribing antimicrobial agents for the most challenging patients and are at the forefront of a successful ASP. Emergency departments (EDs) represent a particularly important setting for addressing inappropriate antimicrobial prescribing practices, given the frequent use of antibiotics in this setting that sits at the interface of the community and the hospital. Therefore also ED practitioners should be involved in the ASPs. Without adequate support from hospital administration, the ASP will be inadequate or inconsistent since the programs do not generate revenue. Engagement of hospital administration has been confirmed as a key factor for both developing and sustaining an ASP.

Finally, an essential participant in antimicrobial stewardship who has been often unrecognized and underutilized is the "staff nurse." Although the role of staff nurses has not formally been recognized in guidelines for implementing and operating antimicrobial ASPs they perform numerous functions that are integral to successful antimicrobial stewardship. Nurses are antibiotic first responders, central communicators, as well as 24-hour monitors of patient status.

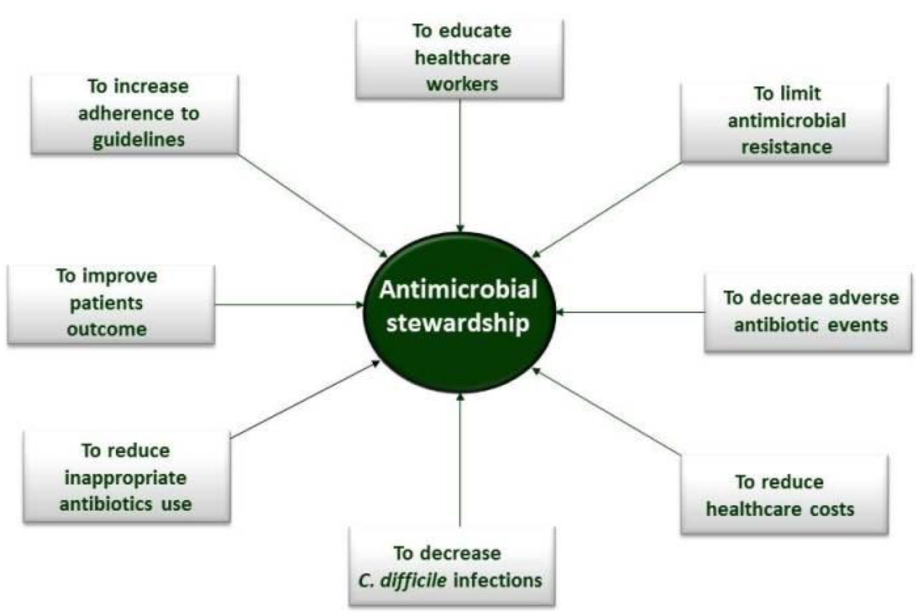


Multifaceted interventions are more likely to improve antibiotic prescribing practices than simple, passive interventions. Although didactic educational programs alone are generally ineffective, education is crucial in implementing antibiotic prescribing practices among prescribers. Since physicians are primarily responsible for the decision to use antibiotics, educating them and changing the attitudes and knowledge that underlie their prescribing behavior may be crucial for improving antibiotic prescription.

Education of all health professionals involved in antibiotic prescribing should begin at undergraduate level and be consolidated with further training throughout the postgraduate years. Hospitals are responsible for educating clinical staff about their local antimicrobial stewardship programs.

Active education techniques, such as academic detailing, consensus building sessions and educational workshops, should be implemented in each hospital worldwide according to its own resources. Efforts to improve active educational programs raising awareness of the correct use of antibiotics are strongly required. The direct involvement of the prescribers in these programs may be a way to fight the cognitive dissonance that blocks prescribers in this process.

The 8 goals of the antimicrobial stewardship programs



Best practices to combat antimicrobial resistance in surgery

Follow locally-developed antibiotic guidelines and clinical pathways	Enhance infection prevention and control	Control the source of infection
Prescribe antibiotics only when they are truly required	Prescribe appropriate antibiotics(s) with adequate dosages	Reassess treatment when culture results are available
Use the shortest duration of antibiotics based on evidence	Educate staff	Support surveillance of antibiotic resistance and antibiotic consumption

Enhance infection prevention and control

Use antibiotics appropriately

Prescribe antibiotics when they are truly needed

Control the source of infection when it is needed

Together we can impact millions of people!

References

Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis. 2008;197:1079–1081.

Sartelli M, Weber DG, Ruppé E, Bassetti M, Wright BJ, Ansaloni L, et al. Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA). World J Emerg Surg. World J Emerg Surg. 2016 Jul 15;11:33.

Sartelli M, Labricciosa FM, Barbadoro P, Pagani L, Ansaloni L, Brink AJ, et al. The Global Alliance for Infections in Surgery: defining a model for antimicrobial l stewardship-results from an international cross-sectional survey. World J Emerg Surg. 2017 Aug 1;12:34.

Goff DA, Kullar R, Goldstein EJC, Gilchrist M, Nathwani D, Cheng AC, et al. A global call from five countries to collaborate in antibiotic stewardship: united we succeed, divided we might fail. Lancet Infect Dis. 2017 Feb;17(2):e56-e63.

Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51–e77.

Sartelli M, Weber DG, Ruppé E, Bassetti M, Wright BJ, Ansaloni L, et al. Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA). World J Emerg Surg. 2016;11:33.

A Global Declaration on Appropriate Use of Antimicrobial Agents across the Surgical Pathway. Surg Infect (Larchmt). 2017 Nov/Dec;18(8):846-853.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Let's act now
Awareness
Knowledge
Attitude

Appropriate use of antibiotic agents should be integral to good clinical practice and standards of care. Physicians should be aware of their role and responsibility for maintaining the effectiveness of current and future antibiotic agents.