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A Global Declaration on Appropriate Use of Antimicrobial Agents across the Surgical Pathway

Global Alliance for Infections in Surgery Working Group

Abstract

This declaration, signed by an interdisciplinary task force of 234 experts from 83 different countries with different backgrounds, highlights the threat posed by antimicrobial resistance and the need for appropriate use of antibiotic agents and antifungal agents in hospitals worldwide especially focusing on surgical infections. As such, it is our intent to raise awareness among healthcare workers and improve antimicrobial prescribing. To facilitate its dissemination, the declaration was translated in different languages.

Antimicrobial resistance (AMR) has emerged as one of the principal public health problems of the 21st century. This has resulted in a public health crisis of international concern, which threatens the practice of modern medicine, animal health, and food security. The substantial problem of AMR is especially relevant to antibiotic resistance (ABR), although antifungal resistance is increasing at an alarming rate. Although the phenomenon of ABR can be attributed to many factors, there is a well-established relationship between antibiotic prescribing practices and the emergence of resistant bacteria.

This declaration, signed by an interdisciplinary task force of 234 experts from 83 different countries with different backgrounds, highlights the threat posed by AMR and the need for appropriate use of antibiotic agents and antifungal agents in hospitals worldwide especially focusing on surgical infections. This declaration is promoted by the Global Alliance for Infections in Surgery and the World Society of Emergency Surgery (WSES). It is endorsed by the Surgical Infection Society (SIS), the Surgical Infection Society Europe (SIS-E), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Antimicrobial stewardship (ESGAP) and Study Group for Infections in Critically Ill Patients (ESGCIP), the European Confederation of Medical Mycology (ECMM), the World Alliance Against Antibiotic Resistance (WAAR), the British Society for Antimicrobial Chemotherapy (BSAC), the French Society of Anesthesia & Intensive Care Medicine (SFAR), the Italian Society of Anesthesiology, Analgesia, Resuscitation and Intensive Therapy (SIAARTI), the South African Society of Clinical Microbiology (SASCM), the Italian Society of Anti-Infective Therapy (SITA), and the Italian Group for Antimicrobial Stewardship (GISA).

Antibiotic and Antifungal Resistance

Antibiotic resistance is one of the greatest threats to public health, sustainable development, and security worldwide. Its prevalence has increased alarmingly over the past decades. In 2008, the acronym ''ESKAPE'' pathogens, which refers to *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species was proposed to highlight those pathogens about which ABR is of particular concern and to emphasize which bacteria increasingly ''escape'' the effects of antibiotics [1]. These organisms are increasingly multi–drug- (MDR), extensive–drug- (XDR), and pan–drug- resistant (PDR), and this process is accelerating globally [2,3].

Although antibiotic-resistant infections are a widely recognized public health threat, less is known about the burden of antifungal-resistant infections. The frequency of fungal infections has increased in recent years, largely because of the increasing size of the at-risk population, which includes cancer patients, transplant recipients, patients with human immunodeficiency virus infection, and other patients who receive immunosuppressive therapy. In addition, they are relatively common in critically ill patients and are associated with considerable morbidity and death. In this regard, antifungal resistance is becoming increasingly problematic, particularly for *Candida glabrata and Aspergillus fumigatus.* Recently, a new MDR species, *C. auris,* emerged causing persistent multi-regional outbreaks. While some species of *Candida* are inherently resistant to certain antifungal agents, in others, acquired resistance occurs via selection of mutations in existing genes, particularly in units with high

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antifungal consumption [4]. This can impact seriously the outcomes of patients with invasive candidiasis. The problem will likely continue to evolve unless greater attention is given to measures to prevent and control the spread of resistant *Candida* spp.

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 [5]. Antibacterial and antifungal use in animal and agricultural industries aggravates selective pressure on microbes. A One Health approach is required urgently. The burden of ABR is difficult to quantify in some regions of the world, because enhanced surveillance requires personnel, equipment, and financial resources that are not always available [6]. The worldwide impact of ABR is significant, however, in terms of economic and patient outcomes, because of untreatable infections or those necessitating antibiotic agents of last resort (such as colistin) leading to increased length of hospital stay, morbidity, death, and treatment cost.

Misuse and Overuse of Antibiotic Agents

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. Antibiotic resistance is a natural phenomenon that occurs as microbes evolve. Human activities have accelerated the pace at which bacteria develop and disseminate resistance, however. Inappropriate use of antibiotic agents in humans and food-producing animals, as well as poor infection prevention and control (IPC) practices, contribute to the development and spread of ABR.

Raising Awareness to Combat ABR

In line with a One Health approach, raising awareness of ABR by education and dissemination of information to stakeholders is an important factor in changing behaviors. Efforts must be aimed at the general public, healthcare professionals, food producing farmers, civil society organizations, and policy makers. An effective and cost-effective strategy to reduce ABR should involve a multi-faceted approach aimed at optimizing antibiotic use, strengthening surveillance and IPC, and improving patient and clinician education regarding the appropriate use of antibiotic agents. Although the current magnitude of the problem and its extent in both the community and the hospital adds to the complexity of any intervention, these are still necessary because healthcare workers play a central role in preventing the emergence and spread of resistance.

Improving Antibiotic Prescribing Behaviors

Appropriate use of antibiotic agents should be integral to good clinical practice and standards of care [7,8]. Physicians should be aware of their role and responsibility for maintaining the effectiveness of current and future antibiotic agents specifically by:

- Following locally developed customized antibiotic guidelines and clinical pathways
- Supporting and enhancing IPC including correct hand hygiene protocols
- Supporting and enhancing surveillance of ABR and antibiotic consumption
- Prescribing and dispensing antibiotic agents only when they are truly required
- Identifying and controlling the source of infection
- Prescribing and dispensing appropriate antibiotic agents with adequate dosages—i.e., administration of antibiotic agents according to pharmacokinetic-pharmacodynamic (PK-PD) principles
- Re-assessing treatment when culture results are available
- Using the shortest duration of antibiotic agents based on evidence
- Educating healthcare workers and staff how to use antibiotic agents wisely

Antibiotic Stewardship Programs

Hospital-based programs dedicated to improving antibiotic use, commonly referred to as Antimicrobial Stewardship Programs (ASPs), can both optimize the management of infections and reduce adverse events associated with antibiotic use [8,9]. Of note, a recent systematic review and meta-analysis demonstrated that ASPs significantly reduce the incidence of infections and colonization with antibiotic-resistant bacteria and *Clostridium difficile* infections in hospital inpatients [10]. Therefore, every hospital worldwide should utilize existing resources to create an effective multidisciplinary team. The preferred means of improving antibiotic stewardship should involve a comprehensive program that incorporates collaboration between various specialties within a healthcare institution including infectious disease specialists, hospital pharmacists, clinical pharmacologists, administrators, epidemiologists, IPC specialists, microbiologists, surgeons, anesthesiologists, intensivists, and underutilized but pivotal stewardship team members—the surgical, anesthetic, and intensive care nurses in our hospitals.

The ASP policies should be based on both international/national antibiotic guidelines and tailored to local microbiology and resistance patterns. Facility-specific treatment recommendations, based on guidelines and local formulary options promoted by the APS team, can guide clinicians in antibiotic agent selection and duration for the most common indications for antibiotic use. Standardizing a shared protocol of antibiotic prophylaxis should represent the first step of any ASP. Because physicians are responsible primarily for the decision to use antibiotic agents, educating them and changing the attitudes and knowledge that underlie their prescribing behavior are crucial for improving antibiotic prescription.

Education is fundamental to every ASP. A range of factors such as diagnostic uncertainty, fear of clinical failure, time pressure, or organizational contexts can complicate prescribing decisions. Because of cognitive dissonance (recognizing that an action is necessary but not implementing it), however, changing prescribing behavior is extremely challenging [11]. Efforts to improve educational programs are thus required, and this should be complemented preferably by active interventions such as prospective audits and feedback to clinicians to stimulate further change [12]. It is also crucial to incorporate fundamental ASP [13] and IPC principles in under- and post-graduate training at medical faculties to equip young physicians and other healthcare professionals with the required confidence, skills, and expertise in the field of antibiotic management.

The principles for appropriate prophylactic and therapeutic use of antibiotic agents in surgical procedures are summarized below.

Please, use antibiotics appropriately and play an active role in combating antibiotic resistance. Join us now, as we embark on this global cause, by pledging support for this declaration and accepting responsibility for maintaining the effectiveness and longevity of current and future antibiotic agents.

Principles of Appropriate Antibiotic Prophylaxis in Surgical Procedures

1. 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
2. Antibiotic prophylaxis should be administered for operative procedures that have a high rate of postoperative surgical site infection, or when foreign materials are implanted.
3. 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.
4. 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.
5. 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).
6. There is no evidence to support the use of postoperative antibiotic prophylaxis.
7. Each institution is encouraged to develop guidelines for proper surgical prophylaxis.

Principles of Appropriate Antibiotic Therapy in Surgical Procedures

1. The source of infection should always be identified and controlled as soon as possible.
2. 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.
3. 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.
4. 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.
5. 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.
7. The appropriateness and need for antimicrobial treatment should be re-assessed daily.
8. Once source control is established, short courses of antibiotic therapy are as effective as longer courses regardless of signs of inflammation.
   - Intra-abdominal infection—four days are as effective as eight days in moderately ill patients [14]
   - Blood stream infection—five to seven days are as effective as seven to 21 days for most patients [15]
   - Ventilator associated pneumonia—eight days are as effective as 15 days [16,17].
9. Failure of antibiotic therapy in patients having continued evidence of active infection may require a reoperation for a second source control intervention.
10. Biomarkers such as procalcitonin may be useful to guide duration and cessation of antibiotic therapy in critically ill patients.
11. Clinicians with advanced training and clinical experience in surgical infections should be included in the care of patients with severe infections.
12. The IPC measures combined with ASPs should be implemented in surgical departments. These interventions and programs require regular, systematic monitoring to assess compliance and efficacy.

13. Monitoring of antibiotic consumption should be implemented and feedback provided to all ASP team members regularly (e.g., every three to six months) along with resistance surveillance data and outcome measures.

The documents translated into French, Spanish, Portuguese, Chinese, Arabic, Russian, German, Japanese, Italian and Greek are included in the Supplementary Material; see online only supplementary material at www.liebertpub.com/sur.

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