MANIFESTO

for the appropriate use

of antibiotics

in healthcare facilities

Global Alliance for Infections in Surgery

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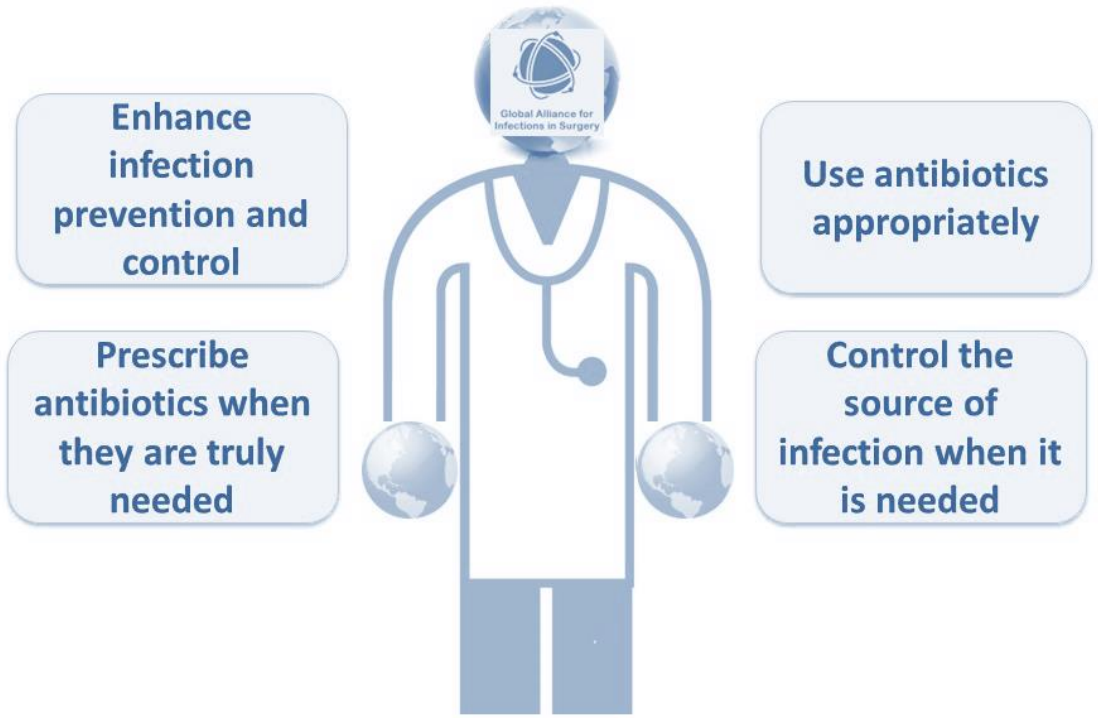

All together we can impact millions of people

Preface

Antibiotics have well-known benefits when used appropriately. However, it has been estimated that up to 50 percent of antibiotic usage in hospitals may be inappropriate.
Physicians regularly have to make complex decisions about antibiotic use. On one hand they 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 adverse effects, the selection of opportunistic bacteria such as *Clostridioides difficile* and of antibiotic-resistant bacteria.
The problem of antibiotic resistance (ABR) is widespread worldwide. ABR poses a global challenge. No single country, however effective it is at containing resistance within its boundaries, can protect itself from the importation of ABR through travel and trade.
The global nature of ABR calls for a global response, both in the geographic sense and across the whole range of sectors involved. Nobody is exempt from the problem.
ABR is a growing public health concern worldwide, and it is now regarded as a critical One Health issue. One Health's interconnected domains contribute to the emergence, evolution, and spread of antibiotic-resistant bacteria on a local and global scale. The drivers of ABR include antibiotic use and abuse in human, animal, and environmental sectors and the spread of antibiotic-resistant bacteria and resistance determinants within and between these sectors and around the globe. Given the important and interdependent human, animal, and environmental dimensions of ABR, it is logical to take a One Health approach when addressing this problem.
Despite an increasing prevalence of antibiotic-resistant bacteria worldwide, the impact of ABR is often underestimated.
In the face of such problem, everyone must contribute.
This document aims to actively raise awareness of healthcare workers (HCWs) and improve antibiotic prescribing practices worldwide.
The document highlights the threat posed by ABR and the need for the appropriate use of antibiotics in healthcare facilities worldwide. As such, it is our intent to raise awareness among HCWs and improve antibiotic prescribing practices.
The document reports the 10 commandments for the appropriate use of antibiotics in healthcare facilities, which all HCWs should always respect in their clinical practice around the World.
Join us now in this global cause, by supporting this document and accepting the responsibility for maintaining the effectiveness of current and future antibiotics.

Massimo Sartelli
Director Global Alliance for Infections in Surgery

Abbreviations

AMR	Antimicrobial resistance
ABR	Antibiotic resistance
AFR	Antifungal resistance
HAIS	Healthcare-associated infections
ARB	Antibiotic-resistant bacteria
MDR	Multi-drug resistance
XDR	Extensive Drug Resistance
PDR	Pan-drug resistance
HCWs	Healthcare workers
ASP	Antimicrobial stewardship program

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Introduction

Prescribing appropriately antibiotics is an integral part of good clinical practice. Optimizing this attitude can maximize the efficacy of patient treatment, and minimize the risks associated with opportunistic infections (such as *Clostridioides difficile*), the selection of antibiotic-resistant bacteria (ARB) in individual patients, and the spread of antimicrobial resistance (AMR) globally.

Prescribing appropriately antibiotics is vital to addressing the threat of AMR, which is deemed to be one of the most urgent threats to global health.

AMR occurs when bacteria, viruses, fungi, and parasites no longer respond to antimicrobials. AMR is emerging as one of the global public health threats of the 21st century.

A global action plan to tackle the threat of AMR was endorsed at the Sixty-eighth World Health Assembly in May 2015. One of the five key objectives of the plan is to improve awareness and understanding of AMR through effective communication and education [1].

Although antibiotic resistance (ABR) is a widely recognized public health threat, less is known about the burden of antifungal resistance (AFR). Fungal infections are relatively common in critically ill patients and are associated with considerable morbidity and death and represent an under-recognized component of AMR. Resistance to antifungal agents is an emerging concern around the World, including novel resistant variants of previously susceptible fungi such as the ubiquitous *Aspergillus fumigates*. Recently, a new resistant species, *Candida Auris,* has emerged causing persistent multi-regional outbreaks. The problem of AFR will likely continue to evolve unless greater attention is given to measures to prevent and control its spread [2].

Beginning in the late 1920s when Alexander Fleming discovered penicillin, antibiotics have revolutionized the field of medicine. Antibiotics have saved millions of people each year. However, bacteria are acquiring the ability to resist the effect of antibiotics which they were initially sensitive. This is resulting in a public health crisis, threatening the practice of modern medicine.

In 2008, the acronym "ESKAPE", referring *to Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter*, species was proposed to focus on those bacteria that increasingly "escape" the effects of antibiotics [3].

Many different definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria have been used to define the different patterns of resistance found in healthcare-associated infections.

A group of international experts from European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), created in 2012 [4] a standardized international terminology with which to describe acquired resistance profiles in all bacteria often responsible for healthcare-associated infections and prone to AMR.

MDR (Multi-Drug Resistance) was defined as acquired non-susceptibility to at least one antibiotic in three or more antibiotic categories.

XDR (Extensive Drug Resistance) was defined as non-susceptibility to at least one antibiotic in all but two or fewer antibiotic categories (bacterial isolates remain susceptible to only one or two categories).

PDR (Pan Drug Resistance) was defined as non-susceptibility to all antibiotics in all antibiotic categories.

ABR is a complex, multifaceted problem threatening human and animal health, the global economy, and national and global security. It should be now regarded as a critical One Health issue, recognizing that the health of people, animals and the environment, are closely linked and interdependent.

Given this complexity and the multiple routes of exposure, it is difficult to determine the relative contribution of different sectors to ABR in humans.

Despite the importance of approaching ABR through a One Health vision—as an issue impacting humans, animals, and the environment, healthcare workers (HCWs) in healthcare facilities play a central role in preventing the emergence and spread of ABR [2]. Hospitals are ideal locations for the transmission of ARB.

Many HCWs underestimate the burden of ABR in their hospitals, and thus, many antibiotics are prescribed unnecessarily or incorrectly.

By far, the most important reason for inappropriate prescribing practices in hospitals is a lack of knowledge, but cultural and social reasons may also play a role.

ABR is a natural phenomenon occurring as bacteria evolve. Human activities have accelerated the development and dissemination of ABR. Misuse and overuse of antibiotics, as well as inadequate infection prevention and control measures, have contributed to the development and spread of ABR in healthcare [2].

We propose that clinical leaders drive antimicrobial stewardship and education programs to improve prescribing practices. Furthermore, we argue that endorsement and guidance on the appropriate use of antibiotics from clinical leaders within a specialty are crucial to combat the global threat of ABR and to provide support to policymakers.

This document aims to actively raise awareness of healthcare workers (HCWs) and improve antibiotic prescribing practices worldwide.

The document highlights the threat posed by ABR and the need for the appropriate use of antibiotics in healthcare facilities worldwide. As such, it is our intent to raise awareness among HCWs and improve antibiotic prescribing practices.

The document reports the 10 commandments for the appropriate use of antibiotics in healthcare facilities, which all HCWs should always respect in their clinical practice around the World.

1

Enhance infection prevention and control

Hospitalized patients may have multiple risk factors for the acquisition of ARB, and acute care facilities are incubators for their spread. The intensity of patient care in acute care facilities can create an environment facilitating both the emergence and spread of ARB. It is important that all HCWs respect evidence-based measures of infection prevention and control, preventing the occurrence of healthcare-associated infections (HAIs), and, then making every effort to prevent the transmission of microorganisms including ARB.

HAIs are very common adverse events in healthcare. Patients at high risk of HAIs are those who undergo surgical procedures and patients with medical devices such as central lines, urinary catheters, and ventilators. HAIs are linked with high morbidity and mortality, can require additional diagnostic and therapeutic procedures, prolong hospital stay, and necessitate additional cost. Moreover, many HAIs are caused by ARB.

However, the importance of the phenomenon is not yet sufficiently perceived among HCWs, resulting in a poor level of responsiveness.

Hand hygiene is the cornerstone of infection prevention and control in any healthcare setting Worldwide. It is an important indicator of safety and quality of care. There is evidence demonstrating the correlation between appropriate hand hygiene practices and low HAI rates [4]. Failure to perform appropriate hand hygiene is considered the main cause of HAIs and spread of ARB and has been recognized as an important contributor to outbreaks. Improvement of hand hygiene through multimodal implementation approaches can reduce HAI rates. In addition, several studies showed a sustained decrease in the incidence of ARB isolates and patient colonization following the implementation of improved hand hygiene [5].

Effective hand hygiene is the single most effective action to reduce health care associated infections. Since Semmelweis' observation, there have been many studies to confirm the role that HCW hands play in transmission of pathogens in the health care setting. Various organizations, including both World Health Organization (WHO) [5] and the US Centers for Disease Control and Prevention [6], have published guidelines providing to HCWs specific recommendations for improving hand hygiene practices.

Starting from 2009, every year, WHO promotes the campaign "SAVE LIVES - clean your hands", to support the improvement of hand hygiene at a global level, making available tools useful to implement multimodal strategies and interventions with the aim of improving and supporting hand hygiene in healthcare.

The 5 Moments for Hand Hygiene were designed by WHO to minimize the risk of transmission of microorganisms between the HCWs, the patients, and the environment

The 5 Moments for Hand Hygiene includes the following:

Moment 1 - before touching a patient

Moment 2 - before a procedure

Moment 3 - after a procedure or body fluid exposure risk

Moment 4 - after touching a patient

Moment 5 - after touching a patient's surroundings.

Any HCWs, caregiver or person involved in direct or indirect patient care needs to be concerned about hand hygiene and should be able to perform it correctly and at the right time.

Hands should be cleaned by rubbing them with an alcohol-based formulation, as the preferred mean for routine hand hygiene if hands are not visibly soiled. It is faster, more effective, and better tolerated by your hands than washing with soap and water.

Hands should be washed with soap and water when hands are visibly dirty or visibly soiled with blood or other body fluids or after using the toilet. If exposure to potential spore-forming pathogens is strongly suspected or proven, including outbreaks of *Clostridioides difficile*, hand washing with soap and water is the preferred means.

The use of gloves does not replace the need for cleaning hands.

2

Control the source of infection

Source control aims to eliminate the source of infection, reduce the bacterial inoculum and correct the anatomic derangements to restore normal physiologic function. Source control is of outmost importance in the management of infections. Intra-abdominal infections and soft tissue infections are the settings where source control is more impactful. In these settings appropriate control of the source of infection can improve patients' outcomes and can reduce antibiotic pressure allowing short course of antibiotic therapy. However, also in other settings, the role of source control should not be underestimated.

A challenging problem in daily care is the management of central venous catheters associated catheter-related bloodstream infection. In most patients, it is clearly necessary to remove the central venous catheter, although there may be fear of complications caused by inserting a new catheter.

The level of urgency of treatment is determined by the affected organ(s), the relative speed at which clinical symptoms progress and worsen, and the underlying physiological stability of the patient.

Although an accurate understanding of the precise relationship between time-to-source control and mortality for patients with sepsis and septic shock is a challenge, there is no reason to delay source control even for a few hours in the majority of the patients with sepsis [7-9].

The 2021 Surviving Sepsis Campaign Guidelines [10] recommend to identifying the anatomical source of infection that may require source control and implementing this as soon as logistically and medically possible.

In principle, in patients with sepsis, the source control intervention should be performed as soon thereafter as is medically and logistically practical. Delays of as little 6 h in patients with sepsis or septic shock have been associated with increased mortality [11-12].

For many infections, the need to control the source of infection may not reach the same level of urgency such as diffuse peritonitis and necrotizing infections. However, also in other infections, prompt source control may be important [13].

Some patients are prone to persisting sepsis regardless of eradication of the source of infection and timely re-intervention provides the only surgical option that significantly improves outcome.

Failure of source control can occur and may be caused by ongoing infection, incomplete source control or ongoing contamination [14]. Failure of source control is usually difficult to diagnose. Most often the diagnosis is based on the lack of clinical improvement, persistent signs and symptoms of inflammation. Therefore, monitoring the success of source control, with a low index of suspicion if a patient does not improve, is of crucial importance.

3

Prescribe antibiotics when they are truly needed

Physicians prescribing antibiotics have two potentially conflicting responsibilities. On one hand, physicians should offer the best therapy for the individual patient under their care by offering appropriate antibiotics. On the other hand, they should preserve the efficacy of antibiotics and minimize infections of opportunistic bacteria such as *Clostridioides difficile*, the selection of resistant pathogens in individual patients, and the continued spread of AMR globally. These conflicting responsibilities should be properly evaluated and balanced before prescribing antibiotics.

The intestinal microbiota has an important role in human health and can protect the patient against invading enteric bacteria. The indigenous bacteria of the colon provide an important host-defence mechanism by inhibiting colonization by potentially pathogenic bacteria. This defence mechanism is named "colonization resistance". This is particularly important in the hospital setting where the intestinal microbiota can protect the patient from HAIs originating from the gastrointestinal tract excluding invading bacteria from colonizing the intestinal tract. However, in certain circumstances, the patient's microbiota can be compromised and no longer protects the patient against colonization by exogenous bacteria, including ARB. Consequently, these patients can become colonized with ARB, such as *Enterobacterales* species, *Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterococcus* spp. which can then proliferate to high densities. The gastrointestinal tract thus serves as an important reservoir for ARB. This poses two important concerns. First, densely colonized patients serve as reservoirs for patient-to-patient transmission, contributing to the endemic persistence of ARB in hospitals. Second, the pathogen can cause potentially life-threatening diseases, especially in immunocompromised patients [15].

Antibiotics exert a well-known selective pressure on bacteria in the intestine in two different ways. First, antibiotics kill susceptible bacteria from the commensal intestinal microbiota favouring invading bacteria within the intestine that are already resistant, because of translocation across the intestinal lining or as a consequence of faecal contamination [16-17]. Second, antibiotics promote the overgrowth of resistant bacteria present in the intestinal microbiota [18-19], thereby increasing the risks of cross-transmission between patients [20-21] and increasing the risk of untreatable or difficult-to-treat infectious outbreaks. Antibiotic pressure combined with inadequate infection control practices accelerates the spread of AMR.

Antibiotics are life-saving when treating bacterial infections but are often used inappropriately, when they are not necessary.

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.

The first step in prescribing appropriately antibiotics is to give them to the right patient, identifying which patient really needs antibiotics.

Antibiotics should be used after a treatable bacterial infection has been recognized or when there is a high degree of suspicion of bacterial infection.

4

Prescribe the appropriate antibiotic(s) at the right time

Most antibiotics are prescribed as empiric therapy, before knowing the pathogen and its susceptibility to antibiotics because microbiologic data (both the detection and the characterization of microbial pathogens) may not be available for up to 48–72 hours to guide targeted therapy.

Empiric antibiotic therapy should be based on local epidemiology, individual patient risk factors for difficult-to-treat bacteria, clinical severity of infection, and infection source.

In patients with organ dysfunction from sepsis, early appropriate empiric antibiotic therapy has a significant impact on the outcome, independent of the site of infection [22-24].

Based on the available data, there is a strong relationship between each hour until antibiotics and mortality in patients with septic shock but a less pronounced relationship in patients with sepsis and without shock [25-27].

Given the high risk of death with septic shock and the strong association between antibiotic timing and mortality, it should fundamental to administer antibiotics immediately, in all patients with septic shock. In patients with sepsis without shock, the association between time to antibiotics and mortality within the first few hours from the presentation is less consistent. Therefore, antibiotics in patients with possible sepsis without shock should be administered as soon as sepsis appears to be the most likely diagnosis [10].

in 2017 the WHO Expert Committee on Selection and Use of Essential Medicines developed The AWaRe Classification of antibiotics in order to support antibiotic stewardship efforts at local, national and global levels. Antibiotics were classified into three groups, Access, Watch and Reserve, taking into account the impact of different antibiotics on AMR, to emphasize the importance of their appropriate use. In 2021 the AWaRe classification was updated and included other 78 antibiotics not previously classified, bringing the total to 258.

Access, refers to the antibiotic of choice for each of the 25 most common infections. These antibiotics should be available at all times and in all places.

Watch, includes most of the “highest-priority critically important antibiotics”. These antibiotics are recommended only for specific, high-priority indications

Reserve, indicates antibiotics that should only be used as a last resort and only when all other antibiotics have failed.

The overall goal is to reduce the use of antibiotics in the Watch Group and in the Reserve Group (the antibiotics most crucial for human medicine and at higher risk of resistance), and to increase the use of antibiotics in the Access group where availability is low [28].

5

Prescribe antibiotics with adequate dosages

It is well known that optimization of antibiotic administration is necessary to preserve our current antibiotic armamentarium. The dose and duration of dosing intervals of antibiotics are determined according to their pharmacokinetic and pharmacodynamic properties.

Antibiotic pharmacodynamics (PD) refers to the relationship between the concentration of an antibiotic and its ability to inhibit the growth of bacteria. The most important pharmacodynamic parameter is the minimal inhibitory concentration (MIC) of the target bacteria for an antibiotic. The antibiotic concentration at the site of the infection must exceed the MIC for the target bacteria in order to obtain an adequate effect.

Antibiotic pharmacokinetics (PK) integrates the fundamental processes of absorption, distribution, metabolism, and elimination of the antibiotics, describing the time course of antibiotic concentrations in both serum and the site of infection.

Knowledge of the pharmacokinetic and pharmacodynamic properties of each antibiotic may provide a more rational determination of optimal dosing regimens in terms of the dose and the dosing interval.

Critically ill patients are at high risk for development of life-threatening infections leading to sepsis and multiple organ failure. Adequate antibiotic dosing is pivotal for optimizing the chances of survival.

The pathophysiologic changes occurring in patients with sepsis can have a major effect on pharmacokinetic parameters, which in turn may result in failure to achieve pharmacodynamic targets for antibiotic thus adversely affecting clinical outcome.

A deep understanding of the pathophysiologic changes, and their effects on the overall drug PK/PD relationship is essential in critically ill patients with sepsis or septic shock.

Optimal use of the PK/PD relationship of antibiotics is important to obtain good clinical outcomes and reduction of risk for AMR. Dosing frequency is strictly related to the concept of time-dependent versus concentration-dependent activity. Some antibiotics such as beta-lactams exhibit time-dependent activity and have optimal bactericidal activity when antibiotic concentrations are maintained above the MIC. Therefore, the serum concentration should exceed the MIC for the duration of the dosing interval. Higher frequency dosing, prolonged infusions and continuous infusions have been proposed to achieve this effect.

On the contrary, 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.

Therefore, with these antibiotics, the peak serum concentration, and not the time the concentration remains above the MIC, is more closely associated with their efficacy [23].

Aminoglycosides nephrotoxicity is caused by a

direct effect on the renal cortex and its uptake saturation. Thus, an extended interval dosing strategy limits the exposure of renal cortex to aminoglycosides reducing the risk of nephrotoxicity

In patients with septic shock, administering an optimal first dose is probably as important as the timing of administration [29]. The optimal first dose described as the loading dose, is calculated from the volume of distribution (Vd) of the antibiotic and the desired plasma concentration. The Vd of hydrophilic agents such as beta-lactams, aminoglycosides and glycopeptides, dispersing mainly in water, in critically ill patients with septic shock may be altered by changes in the permeability of the microvascular endothelium with consequent alterations in extracellular body water. This may lead to lower-than-expected plasma concentrations at the beginning of the therapy resulting in sub-optimal achievement of antibiotic levels [29].

In patients with sepsis or septic shock loading doses and/or a higher overall total daily dose of beta-lactams, aminoglycosides, or glycopeptides are often required to maximize the pharmacodynamics ensuring optimal drug exposure to the infection site [29].

Another important aspect is tissue penetration because high concentrations at the site of infection can potentially overcome “resistance”.

Protein binding is a relevant property of antibiotics as only their unbound fraction is pharmacodynamically active and can achieve antibiotic efficacy or cause toxicity. Hypoalbuminemia frequently occurs in critically ill patients [30].

In these patients, lower serum protein concentrations result in greater proportions of unbound drug and may therefore temporarily result in high antibiotic concentrations and optimal bacterial killing activity. As hypoalbuminemia is usually associated with increased Vd and drug clearance of highly protein bound hydrophilic antibiotics, the free fraction after administration can soon be diluted over the increased total body water and more rapidly cleared. As such hypoalbuminemia may contribute to initial target concentrations but failure to maintain sufficient drug concentrations throughout the dosing interval necessitating a shorter dosing interval [29].

Once an appropriate initial loading dose is achieved, the antibiotic regimen should be reassessed, at least daily, because pathophysiological changes may significantly affect antibiotic availability especially in critically ill patients. Lower than standard dosages of renally excreted antibiotics should be administered in the presence of impaired renal function, while higher than standard dosages of renally excreted antibiotics should be administered, for optimal activity, in patients with glomerular hyperfiltration [29]. It is important to note that in critically ill patients, plasma creatinine is not a reliable marker of renal function.

6

Reassess treatment basing on microbiologic culture and susceptibility testing

Reassessment of antibiotic therapy based on microbiologic culture and susceptibility testing not only promotes antimicrobial stewardship but may be associated with improved outcomes in serious infections. The patient should be always reassessed when the results of microbiological testing are available. The results of microbiological testing may have great importance for the choice of therapeutic strategy of every patient, in particular in the adaptation of targeted antibiotic treatment. They provide an opportunity to expand the antibiotic regimen if the initial choice has been too narrow but also allow de-escalation of antibiotic therapy if the empirical regimen has been too broad.

The need to speed up diagnostic testing is a central theme in recent initiatives to combat ABR. One of the major goals for combating ABR is to develop rapid diagnostic tests for identifying and characterizing ARB as soon as possible. Thus, the need for rapid, highly sensitive, affordable, and cost-effective detection platforms for ABR diagnostics has become urgent. The utilization of such platforms can significantly reduce the turnaround time for antibiotic susceptibility determination, thus enabling the selection of enhanced, target-specific therapies [31]. Diagnostic tests are considered an essential weapon in any strategy against ABR. Rapid diagnostic tests (RDTs) related to infectious diseases are considered indispensable tools for antimicrobial stewardship programs. RDTs have been shown to reduce mortality, lessen hospital stay, and shrink healthcare costs. Indeed, such diagnostic tests have proven to be more cost-effective, not only by providing a significant cost reduction, but also by decreasing antibiotic use [32–35].

7

Use the shortest duration of antibiotics based on evidence

Shortening the duration of antibiotic therapy is a crucial strategy for reducing unnecessary antibiotic use in the hospital setting, where antibiotic pressure is very intense. Shorter courses of antibiotics may reduce antibiotic-related adverse events, duration of hospitalization, the emergence of AMR and *Clostridioides difficile* infections

Duration of therapy should be shortened as much as possible unless there are special circumstances that require prolonging antibiotic therapy such as immunosuppression, or ongoing infections. There is good evidence that shorter durations of antibiotics can reduce adverse effects associated with their use. Furthermore, many studies have found that clinical outcomes are similar between short and long courses for many common infections. Given the relatively high rates of prescribing, we can all play a significant role in reducing the burden of inappropriate antibiotic use by prescribing short-course therapy when appropriate. In the setting of intra-abdominal infections. The STOP-IT trial [36] demonstrated that in patients with complicated intra-abdominal infections undergoing adequate source control, the outcomes after approximately 4 days of fixed-duration antibiotic therapy were similar to those after a longer course of antibiotics that extended until after the resolution of physiological abnormalities.

Short-course antibiotics were demonstrated also in patients with post-operative intra-abdominal infections too [37].

Historically, antibiotic therapy for ventilator-associated pneumonia and hospital-acquired pneumonia was prolonged, up to 21 days, until several studies and meta-analyses demonstrated the relative efficacy of shorter (7-8 days) versus longer therapy and showed no difference in mortality, intensive care unit stay, mechanical ventilation free days or organ failure free days [38,39]. European (2017) and IDSA guidelines (2016) [40] both recommend durations of 7 days for ventilator-associated pneumonia (moderate quality evidence) and hospital-acquired pneumonia (very low-quality evidence).

Bacteraemia caused by *Enterobacterales*, has been traditionally treated with 14 days to 15 days of antibiotics. Recent meta-analyses and several RCTs investigating shorter course (7 to 8 days) versus longer course (14 to 15 days) of antibiotics in patients with Gram-negative bacteraemia (of which the majority had a urinary tract source) demonstrated that the shorter course was non-inferior to the longer course [41-46]. In the setting of acute cellulitis evidence suggests that prolonged courses may be unnecessary, and that 5 days treatment may be sufficient in cases of uncomplicated cellulitis [47].

The IDSA guidelines recommend a duration of antibiotic therapy of 5 days, but treatment should be extended if the infection has not improved within this time period [48].

8

Support surveillance of heal and AMR and monitor of antibiotic consumption

HAIs are patient safety and quality of healthcare issue which contributes to poor patient outcomes and additional costs to the healthcare system. Surveillance to determine the incidence of HAIs is an important part of the strategy to minimise the occurrence of these infections.

Surveillance allows hospitals and HACWs to measure the effectiveness of infection prevention and control strategies that are implemented to decrease infection rates. Infection rate data should be used to improve the quality and safety of healthcare and should be fed back be used to drive change.

Surveillance of ARB provides a basis for taking action to control AMR. It is a core pillar in the global action plan on AMR.

Consistent and high-quality data on the incidence, prevalence, range across pathogens and geographical patterns related to AMR are needed to guide the treatment of patients, to inform local, national and regional actions, and monitor the effectiveness of interventions.

A recent document published jointly by the European Centre for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe reported AMR data from invasive isolates in Europe [49]. The report shows that, although the AMR situation depends on the bacterial species, antibiotic group and geographical region, AMR is widespread in the WHO European Region. A north-to-south and west-to-east gradient was generally observed, with higher AMR percentages in the southern and eastern parts of Europe. Overall, in the EU/EEA, AMR percentages for the bacterial species–antimicrobial group combinations under surveillance continue to be high, with carbapenem resistance in Escherichia coli and Klebsiella pneumoniae and vancomycin resistance in Enterococcus faecium showing a significant increase during 2016–2020. High percentages of resistance to third-generation cephalosporins and carbapenems in K. pneumoniae and high percentages of carbapenem-resistant Acinetobacter species and Pseudomonas aeruginosa in several countries in the European Region are of concern.

On 22 October 2015, WHO launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS), the first global collaborative effort to standardize AMR surveillance Worldwide.

Since its launch, GLASS has expanded in scope and coverage and as of May 2021, 109 countries and territories worldwide have enrolled in GLASS [50].

Most countries reported high rates of AMR in bloodstream, urinary and gastroenteric infections. High rates of resistance to last resort antibiotics, such as carbapenems, or first-line antibiotics, such as cotrimoxazole, were reported.

Globally, of most crucial concern is the emergence of carbapenem resistant organisms.

The very high rates of carbapenem resistant *Acinetobacter spp,* as well as the non-negligible carbapenem resistance rates in *K. pneumoniae*, represent a scenario to keep under close monitoring. Carbapenem resistance is particularly important as the pipeline for effective antibiotics against this type of AMR is poor.

The majority of antibiotics targeting the priority bacteria are beta-lactam and beta-lactamase inhibitor combinations and do not sufficiently address the problem of XDR or PDR Gram negative bacteria. In particular, critical priority bacteria such as *carbapenem-resistant A. baumannii* and *Pseudomonas aeruginosa* are insufficiently addressed in the clinical pipeline.

The link between AMR and the use antibiotics is well documented.

Monitoring of antibiotic consumption should be implemented and feedback provided to all prescribers.

Antibiotic consumption can be measured at many different levels, for example at country, region, hospital and prescriber levels. It allows for informed decisions on where to focus efforts to reduce unnecessary use.

The most common method to monitor antibiotics consumption is based on the concept of defined daily doses (DDD). The DDD is the assumed average maintenance dose per day of an antibiotic used for its main indication in adults. Expressing antibiotic consumption in DDD per 1000 patient-days can allow hospitals to compare their consumption with other hospitals regardless of differences in quality and quantity of antibiotics.

9

Educate staff

The ultimate goal of any stewardship program should be to stimulate a behavioural change in prescribing practices. In this context, education of prescribers is crucial to convince clinicians to use antibiotics judiciously.

Education to improve antibiotic prescribing practices is fundamental even if without concurrent interventions education alone is of little value. A range of factors such as diagnostic uncertainty, fear of clinical failure, time pressure or organisational contexts can complicate antibiotics prescribing decisions. However, due to cognitive dissonance (recognising that action is necessary but not implementing it), changing prescribing practices is extremely challenging.

Efforts to improve educational programs are thus required and this should preferably be complemented by active interventions such as prospective audits and feedback to stimulate further change. It is also crucial to incorporate fundamental antimicrobial stewardship and infection prevention and control principles in under and post graduate training at medical faculties to equip young doctors and other healthcare professionals with the required confidence, skills and expertise in the field of antibiotic management.

10

Support a multidisciplinary approach

The promotion of antimicrobial stewardship across the clinical practice is crucial to ensure standardization of antibiotic use within a healthcare facility.

Antimicrobial stewardship is the healthcare response to this – developing better ways to prescribe, use, and dispose of antibiotics.

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

Of note, many studies demonstrated that Antimicrobial Stewardship Programs (ASPs) significantly reduce the incidence of infections and colonization with ABR and *Clostridioides difficile* infections in hospital inpatients [1]. Therefore, every hospital worldwide should utilize existing resources to create an effective interdisciplinary team. We propose that the best means of improving antimicrobial stewardship should create collaboration among all the specialties within a healthcare facility including prescribing physicians [51].

Successful antimicrobial stewardship should be based on the collaboration between all healthcare professionals to share knowledge and widespread diffusion of practice.

ASPs have been promoted to optimize antimicrobial usage and patient outcomes and reduce the emergence of ARB. However, the best strategies for an ASP are not definitively established and are likely to vary based on local culture, policy, routine clinical practice, and available resources.

Successful ASP should focus on collaboration between healthcare professionals in order to share knowledge and best practices.

ASP should be coordinated by an infectious disease specialist. Pharmacists with advanced training or clinical experience in infectious diseases are also key actors in designing and implementing stewardship program interventions. Infection control specialists and hospital epidemiologists should grant efforts on monitoring and preventing healthcare-associated infections and in analysing and reporting the data. Microbiologists should actively guide the proper use of tests and the flow of laboratory results. Being involved in providing surveillance data on AMR, they should provide periodic reports on AMR data allowing the multidisciplinary team to determine the ongoing burden of AMR in the hospital. Moreover, timely and accurate reporting of microbiology susceptibility test results allows the selection of more appropriate targeted therapy, and may help reduce broad-spectrum antimicrobial use.

Surgeons with adequate knowledge in surgical infections when involved in ASP may audit antibiotic prescriptions, provide feedback to the prescribers and integrate best practices of antibiotics use among surgeons, and act as champions among colleagues.

Infections are the main factors contributing to mortality in intensive care units (ICU).

Intensivists have a critical role in preventing and treating ARB in ICUs in critically ill patients. They have a crucial role in prescribing antimicrobial agents for our most challenging patients and are at the forefront of successful ASPs. 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. The 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 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.

Conclusions

Prescribing appropriately antibiotics is an integral part of good clinical practice. Optimizing this attitude can maximize the efficacy of patient treatment, and minimize the risks associated with opportunistic infections (such as *Clostridioides difficile*), the selection of resistant bacteria in individual patients, and the spread of antimicrobial resistance (AMR) globally.

Join us now in this global cause, by supporting this document and accepting the responsibility for maintaining the effectiveness of current and future antibiotics.

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