Antibiotics are widely recognised for their benefits when used correctly. However, despite the importance of responsible use of antibiotics in good clinical practice, they are often misused. Effective antibiotic treatment is an essential component of universal healthcare, and it is a global responsibility to ensure their proper use. Currently, pharmaceutical companies have little incentive to develop new antibiotics due to scientific, regulatory, and financial barriers, which further emphasises the importance of proper antibiotic use. To address this issue, the Global Alliance for Surgical Site Infection has established an international multidisciplinary working group of 295 experts from 115 countries with diverse backgrounds. The Task Force developed a position statement called WARNING (Worldwide Antimicrobial Resistance National/International Network Group) to raise awareness of antimicrobial resistance (AMR) and improve antibiotic prescribing practices worldwide and published this statement in October 2023 under the title: Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators. Ten golden rules for optimal antibiotic use in hospital settings: the WARNING call to action. World J Emerg Surg. 2023; 18, 50. https://doi.org/10.1186/s13017-023-00518-3.

The above statement is 10 axioms, or “golden rules”, for the correct use of antibiotics. By following these basic principles, healthcare professionals in hospitals (and communities) can support responsible and effective antibiotic use, reduce the risks of adverse events and AMR, and contribute to better patient outcomes in their clinical practice. Antimicrobial resistance is a significant burden for modern medicine, and this section of the review confidently addresses the global challenges associated with it.

Antibiotics are essential, life-saving medicines. Ensuring that antibiotics are prescribed appropriately is a fundamental aspect of good clinical practice [1]. Since the discovery of penicillin by Sir Alexander Fleming in 1928, they have revolutionised medicine and helped to save countless lives [2]. There are significant differences in the use of antibiotics around the world. While some regions face the problem of overuse, others suffer from limited access to antibiotics [3]. This disparity creates a gap that threatens stability and security by making access to effective treatment difficult and leading to suboptimal prescribing practices [4].

Effective antimicrobial treatment is an important component of public health. There is a global collective responsibility to use antibiotics appropriately to maintain their effectiveness. Pharmaceutical companies have little incentive to develop new antibiotics due to numerous scientific, regulatory, and financial barriers [5–8]. It is therefore questionable whether the industry will replace ineffective antibiotics in time.

Antibiotics are commonly used in acute care hospitals to treat both community-acquired infections and surgical prophylaxis [9]. However, when antibiotics are prescribed incorrectly, they fail to benefit patients and put them at risk of adverse events [10]. Studies have shown that adverse events are associated with antibiotic therapy in approximately 20% of patients receiving systemic treatment [11, 12]. These events, in turn, can prolong hospital stays, cause additional clinic or emergency department visits and readmissions, and lead to the need for additional inpatient services [13], increasing the cost of care [14].

Optimising inpatient antibiotic prescribing leads to improved treatment effectiveness and patient safety, minimising the risk of antibiotic-related infections (e.g., Clostridioides difficile infection (CDI)) and the selection and transmission of antimicrobial-resistant bacteria in individual patients within and between hospital, countries and globally [15].

It is suggested that clinical leaders should lead antimicrobial stewardship programmes and education programmes to help standardise and improve prescribing practices. It is also argued that guidance on appropriate antibiotic use from clinical leaders in the speciality is essential to address the global threat of antimicrobial resistance (AMR). Here, we present 10 principles of appropriate antibiotic use that clinicians should always follow in clinical practice (Fig. 1).

In January 2008, the Global Alliance for Surgical Infection [16] established an international multidisciplinary working group to develop a common vision for the appropriate use of antibiotics in hospitals to address the threat of antimicrobial resistance. Two hundred and ninety-five experts from 115
countries on six continents participated, including specialists in anaesthesiology, clinical pharmacology, critical care, emergency medicine, epidemiology, global health, health policy and management, hospital pharmacy, infection prevention and control, infectious diseases, internal medicine, microbiology, nursing, public health, emergency medicine, and general surgery.

Evidence was identified through a comprehensive search of PubMed and Google Scholar. The search identified articles published in English between January 2000 and February 2023. Two experts involved in writing the original manuscript reviewed the selected articles. The first version was then shared with a group of experts and revised by adding additional references. The final document was carefully reviewed by each member of the working group to ensure accuracy, currency and consensus. The project was named WARNING (Worldwide Antimicrobial Resistance National/International Network Group) – a national/international network group on antimicrobial resistance worldwide (Fig. 2).

The global burden of AMR

Antimicrobial resistance (AMR) occurs when bacteria, viruses, fungi and parasites develop antimicrobial defence mechanisms that reduce the effectiveness of treatment and increase the risk of treatment failure, disease progression, serious illness or death. However, inappropriate and excessive use of antimicrobials, combined with ineffective infection prevention and control practices, are recognised as the main factors behind the increasing prevalence of AMR [1] (Fig. 3).

Although antibiotic-resistant infections are a recognised public health threat and a call to action for appropriate antibiotic use, less is known about the burden of AMR fungal infections [1]. It is known that fungal infections are becoming more common, mainly due to the increase in the size of the at-risk population, which includes people with cancer, transplant recipients, people living with human immunodeficiency virus or immunosuppressed by disease or therapy, and critically ill patients. Invasive fungal infections are associated with significant morbidity and mortality. Recently, Candida auris has emerged as a multidrug-resistant (MDR) pathogen worldwide [17–19], and its high transmissibility, wide range of clinical manifestations, and potentially high mortality have led the US Centers for Disease Control and Prevention (CDC) to classify it as one of five pathogens of emerging concern [20]. Data recently published by the CDC indicate that C. auris is spreading at an alarming rate [21], as it was first described as an invasive infection in 2009 [22]. Infections caused by C. auris have increased to a higher prevalence than the common fungal pathogen C. albicans in some centres [24]. Candida auris is a unique problem due to five factors: high transmissibility, leading to massive outbreaks in numerous hospitals worldwide [25,26]; a wide range of clinical manifestations associated with mortality rates of up to 70% [26,27]; environmental resistance, including persistence for weeks on dry surfaces [28,29]; difficulty in identifying C.

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**10 GOLDEN RULES FOR OPTIMAL ANTIBIOTIC USE IN HOSPITAL SETTINGS**

1. Enhancing infection prevention and control
2. Prescribing antibiotics when they are truly needed
3. Prescribing the appropriate antibiotic(s) at the right time
4. Administering antibiotics in adequate doses and routes
5. Initiating, as soon as possible, targeted treatment based on the results of culture and susceptibility testing
6. Using the shortest duration of antibiotics based on evidence
7. Achieving source control by identifying and eliminating the source of the infection or reducing the bacterial load
8. Supporting surveillance of HAIs and AMR, monitoring of antibiotic use, consumption, and the quality of prescribing
9. Educating staff and improving awareness
10. Supporting multidisciplinary ASPs and enhancing collaboration of healthcare professionals from various disciplines

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*Fig. 1.* Ten "golden rules" for optimal use of antibiotics in inpatient settings.
Bacteria can be intrinsically resistant to one or more classes of antibiotics or can acquire such resistance. To avoid the effects of antibiotics, bacteria have developed various resistance mechanisms (Fig. 4). In addition to intrinsic resistance mechanisms, bacterial pathogens can acquire resistance to antibiotics either by mutating existing genes [34] or by acquiring new genes from other strains or species through horizontal gene transfer [34].

«Heteroresistance» describes the presence of subpopulations of bacterial cells with higher levels of antibiotic resistance than the rest of the population in the
same culture [35]. Recent work indicates that heteroresistance is very common across different bacterial species and antibiotic classes. The phenotype of resistance is often unstable and can quickly revert to susceptibility in the absence of antibiotic pressure [36]. Heteroresistance occurs in both Gram– positive and Gram– negative bacteria. Its clinical significance can be significant, as more resistant subpopulations can be identified during antibiotic therapy. However, the use of non– standard methods to determine heteroresistance, which are expensive and require significant labour and resources, does not allow the clinical magnitude and severity of this phenomenon to be assessed [35]. As heteroresistance can have serious consequences in antibiotic therapy, the development of standardised criteria and protocols for the detection and measurement of heteroresistance is important.

Over the past decade, there has been a dramatic increase in both the proportion and absolute number of bacterial pathogens that exhibit multiple antimicrobial resistance. Organisations such as the US Centers for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC) and the World Health Organisation (WHO) consider infections caused by multidrug– resistant bacteria to be an emerging global problem and a serious public health concern [37]. The emergence of resistant microorganisms due to mutations or the acquisition of mobile genetic elements carrying resistance genes can occur independently of the presence of antibacterial agents. It is exposure to these drugs that provides the necessary selective pressure for the emergence and spread of resistant pathogens. Thus, the driving force behind the rise of resistance is the overuse and misuse of antibacterial agents, whether they are used by patients and livestock or released into the environment. Antibiotic resistance has become a global health threat that requires coordinated action by many different stakeholders to tackle it at its root. In 2008, the acronym «ESKAPE» was coined to name the bacteria that can «escape» antibiotics, including Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii– calcoaceticus complex, Pseudomonas aeruginosa, and Enterobacter spp. [38]. In 2012, ECDC and CDC developed a standardised nomenclature to describe acquired bacterial resistance profiles [39]: (1) Multi– drug resistance (MDR). Multidrug resistance (MDR) is an acquired resistance to antimicrobial agents that manifests itself in a given type of micro– organism to at least one antimicrobial agent from three or more categories of antimicrobial agents (e.g. cephalosporins, fluoroquinolones, tetracyclines); (2) extensively drug– resistant bacteria (XDR) is the resistance of a type of bacteria to all antimicrobial agents except for two or fewer antimicrobial categories; (3) pan– drug resistance (PDR) is the resistance of bacteria to all agents of all antimicrobial categories (Fig. 5). This classification provides a standardised nomenclature for bacterial resistance patterns, facilitating surveillance, research and the development of appropriate tactics to combat AMR [40].

Currently, antimicrobial consumption data in the European Union and countries within the European Economic Area/ European Free Trade Association are expressed as the number of prescribed daily doses per 1000 inhabitants per day. Additionally,
the number of packages per 1000 inhabitants per day is reported, depending on the availability of package data from national surveillance networks. Package information is believed to enhance comprehension and interpretation of differences in antimicrobial consumption levels and trends observed both between and within countries. This is because the number of defined daily doses system cannot account for changes in package contents. Furthermore, a drug resistance index has been proposed that combines information on antibiotic resistance and the antibiotic used into a single composite measure [37]. An index of drug resistance, similar to the Dow Jones used in economics, could enable continuous quantification of antibiotic effectiveness over time in specific geographic regions.

Inappropriate prescribing, whether caused by outdated guidelines or pharmaceutical pressure, the availability of antibiotics over the counter, and self-medications reflect a general lack of awareness of the global threat that antibiotic resistance poses to society. To reduce the pressure on prescribers to prescribe antibiotics and decrease antibiotic consumption, it is recommended to implement antibiotic stewardship education programmes targeting primary care physicians, pharmacy providers, and the community. Additionally, prescribing deferred benefits in the event of remission or worsening clinical symptoms can also contribute to this reduction. To improve the situation, local antibiotic prescribing guidelines should be updated, and there should be active reporting of antibiotic prescribing and consumption. Additionally, local AMR surveillance programmes should be implemented. However, implementing these measures requires significant legislative changes and increased funding, which depends on a strong commitment from policymakers at both national and international levels.

Special consideration should be given to the use of antibiotics in low-income countries. In these regions, additional factors contribute to the emergence of resistance, such as the less potent activity of some antibacterial agents (including counterfeit drugs), the overuse of insufficient doses, the lack of diagnostic laboratories, and poor sanitation, which contributes to the spread of resistant microorganisms. Special attention should be given to the worldwide commercialisation of food and international travel.

In 2012, Kadri SS et al. proposed a new category of Gram-negative bacteremia (GNBSI) that includes difficult-to-treat (DTR) resistance due to the lack of susceptibility to first-line antibiotics, typically beta-lactams or fluoroquinolones, which necessitates the use of second-line, often more toxic agents. DTR is a novel antimicrobial resistance classifier that considers the impact of resistance on antibiotic selection and subsequent clinical outcomes. This epidemiological tool reflects the complexity of treating hospital-acquired bacterial infections that are resistant to all first-line antibiotics. For instance, GNBSI exhibits a DTR of one per cent, indicating resistance to all carbapenems, other beta-lactams, and fluoroquinolones. DTR is a category that considers the quantity, efficacy, and toxicity of available antibiotics, providing a more comprehensive understanding of the key aspects of antimicrobial resistance that impact mortality risk.

Antimicrobial resistance is a multifaceted problem that affects not only humans but also animals and the environment [42, 43]. On 17 March 2022, four international agencies: The Food and Agriculture Organization of the United Nations, the World Organisation for Animal Health, the United Nations Environment Programme, and the World Health Organization established the One Health alloy of the International Health Regulations (IHR) to better address global health security.

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signed an agreement to strengthen collaboration and promote sustainable practices that balance and optimize the health of humans, animals, plants, and the environment. The concept of ‘One Health’ recognizes the interconnectedness of human, animal, and environmental health [44]. To address antimicrobial resistance [45–48], global collaboration across sectors and in various health areas is necessary (Fig. 6).

In May 2015, the World Health Assembly adopted a global action plan against antimicrobial resistance (AMR) [49]. The plan includes five goals: (1) The aim is to enhance awareness and comprehension of antimicrobial resistance through effective communication, education, and training. (2) The objective is to strengthen the knowledge and evidence base through surveillance and research. (3) The goal is to decrease the incidence of infection through effective sanitation and infection control measures. (4) The focus is on optimising the use of antimicrobials in human and animal health. (5) The aim is to develop a business case for sustainable investment that considers the needs of all countries and increases investment in new medicines, diagnostics, vaccines, and other measures. Member States have committed to developing comprehensive, funded, and monitored National Action Plans (NAPs) on antimicrobial resistance. The aim is to learn lessons and change priorities. However, cross-country variability in economic and political resilience, as well as resource constraints, pose significant barriers to NAP implementation [50, 51]. Although there is a strong commitment to addressing antimicrobial-resistant infections, the endorsement and implementation of the NAP have been hindered by the prioritisation of issues related to the COVID-19 pandemic [52]. There is increasing evidence that the pandemic has expedited the emergence and spread of antimicrobial resistance (AMR), particularly in hospital settings [53]. Langford et al. reported that over 60% of COVID-19 patients with bacterial infections had highly resistant microorganisms [54]. However, accurately quantifying the impact of COVID-19 on the global epidemiology of AMR is challenging due to limitations in interpreting COVID-19 data [55, 56].

AMR has been reported at alarming levels in all countries, regardless of their average income [57]. According to a 2019 pre-pandemic analysis published in 2022 by Murray et al. [57], bacterial AMR is the leading cause of death worldwide, with 4.95 million deaths attributable to it, including 1.27 million directly caused by bacterial AMR. Out of the 23 bacteria that were studied, six (E. coli, S. aureus, K. pneumoniae, S. pneumoniae, A. baumannii and P. aeruginosa) caused 929,000 deaths related to AMR and 3.57 million deaths overall. It is worth noting that MRSA alone was responsible for over 100,000 deaths in 2019. In Africa, AMR bacterial infections had the highest rates of infection-related mortality, with 99 deaths per 100,000 people. In high-income countries, AMR was associated with 56 deaths per 100,000 people, in comparison. However, it is possible that Murray et al. underestimated the true burden of AMR [58]. Effective antibiotics are necessary to prevent and treat infections in modern medical treatments,
such as trauma care, cancer surgery and chemotherapy, organ transplants, and other invasive procedures. Untreated infections decrease the value of medical interventions. Modern medical treatments, such as trauma care, cancer surgery, chemotherapy, organ transplants, and other invasive procedures, require effective antibiotics to prevent and treat infections. Untreated infections reduce the value of these medical interventions by negatively impacting their efficiency, although quantifying this impact is difficult [58].

The extent of AMR in low- and middle- income countries will remain unknown unless surveillance is adequately resourced [59]. Bacterial identification and susceptibility testing are not routinely performed in these countries due to a lack of personnel, equipment, and supplies. Additionally, in some healthcare systems, patients may have to pay out-of-pocket for testing [60]. Antibiotic therapy is often empirical, leading to inappropriate prescription of broad-spectrum antibiotics. This can result in suboptimal care of infections, leading to clinical failure, higher mortality rates, and increased antimicrobial resistance. In low- and middle- income countries, progress has been made in collecting data to inform antimicrobial resistance and monitor antibiotic use, but more needs to be done.

The COVID-19 pandemic has highlighted the disproportionate impact of infectious diseases on certain populations [61]. To control the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), measures such as social distancing and frequent hand washing have been recommended. However, these measures pose challenges for individuals living in densely populated communities with inadequate housing, poor sanitation, and limited access to clean water. Individuals living in poverty are at a higher risk of contracting infectious diseases and being exposed to antibiotics, making them particularly vulnerable to AMR. A systematic review conducted by Alividza et al. [62] in 2018 highlighted the intricate relationship between AMR and various aspects of poverty, such as education, income, and the quality of housing and water. Addressing these disparities is crucial in reducing the burden of AMR and improving health outcomes in vulnerable communities.

In November 2012, India published an important report known as the ‘Chennai Declaration’. This report represents a significant national step forward in antibiotic stewardship, with international significance and global implications [63]. Although India has had a national antibiotic policy since 2011, implementing the recommendations has been challenging due to the lack of a clear action plan. In August 2012, a meeting of Indian medical societies and national authorities was held to develop a roadmap containing urgent actions in response to the lack of impact of a well-intentioned but difficult-to-implement policy. The final declaration, released in November 2012, is a remarkable example of national consensus and commitment that recognises the clinical and public health challenges associated with AMR.

Aware of the seriousness of AMR, the United Kingdom commissioned a comprehensive analysis of this global problem in 2014 [64]. The staggering conclusion of this report was that, if no action is taken, AMR is projected to cause 10 million deaths by 2050. Separately, the World Bank warned that «under a high-impact scenario, an additional 24 million people could become ill by 2030» [65]. While there is undoubtedly a large clinical and public health burden associated with AMR, it is difficult to quantify the excess morbidity and mortality associated with it. Detailed, reliable data, preferably based on comprehensive population-based surveillance in low- and middle- income countries and high- income countries [66], will be needed to strengthen antimicrobial resistance control measures.

In 2022, the Group of Seven countries (Canada, France, Germany, Italy, Japan, the United Kingdom, and the United States) issued the G7 Health Ministers' Declaration [67]. Their communiqué covered several topics but focused on four priority areas: (1) overcoming COVID-19; (2) preparedness for a future pandemic; (3) AMR; and (4) health risks from climate change [67]. In a subsequent communiqué, G7 health ministers called the response «an urgent public health and socio-economic challenge» that could have global implications but may have a greater impact on low- and middle- income countries. Recognising AMR as a shared responsibility, they pledged together to take further urgent and tangible action to address the problem. Among the actions, they pledged to establish new or improved national integrated surveillance systems for antimicrobial resistance and use in the human, livestock, agricultural and environmental sectors; promote the appropriate use of antimicrobials through stewardship; strengthen the implementation of one-health infection prevention and control programmes; and strengthen research and development of new antibiotics. This approach aims to achieve optimal health outcomes for humans, animals and the environment, taking into account the diverse socio-economic, political and cultural contexts that affect AMR [68], including limited technical expertise, insufficient clinical and research laboratory infrastructure, other financial constraints, and the necessary political commitment [69]. Since effective antibiotics are a global public good that is on the verge of scarcity, antimicrobial resistance is rightly considered a serious threat [70], and antibiotic conservation is a collective responsibility [8, 71].

On 13th June 2023, the European Council adopted a resolution urging the EU to take enhanced action to combat antimicrobial resistance in human and animal health and the environment. The resolution advocates for a ‘one health’ approach to antimicrobial resistance and encourages the judicious use of antimicrobials for human and animal health through a series of voluntary measures to reduce antimicrobial resistance [72].

**Antibiotic use in hospital and community settings**

Healthcare professionals (HCPs) play a crucial role in the fight against AMR. Unfortunately, antibiotics are often prescribed inappropriately in human and animal healthcare...
When prescribing antibiotics, understanding the differences between (1) prophylactic, (2) empiric, and (3) targeted therapy can help ensure appropriate use and prevent antimicrobial resistance. Antibiotic prophylaxis is the prescription of antibiotics to patients with no signs of infection to prevent it from occurring. Empirical antibiotic therapy is prescribed to treat known or suspected infections based on the patient’s symptoms and likely pathogens before definitive diagnostic test results, including antimicrobial susceptibility testing, are available. Targeted antibiotic therapy is initiated on the basis of microbial identification and susceptibility test results to identify the specific pathogen and to ensure that the most effective (ideally also the most cost-effective), least toxic antibiotic with the narrowest spectrum of activity is used as therapy. Optimal targeted therapy requires early identification and characterisation of bacteria. However, despite advances in rapid microbial diagnostics, turnaround times for microbiological testing and reporting can be up to 72 hours or even longer, if available at all. Clinicians often initiate empirical antibiotic therapy, which can have negative health outcomes for patients and increase the risk of antimicrobial resistance [74]. Antibiotic prescribing practices in hospitals worldwide are often inadequate [76]. A survey of 33 hospitals across five Latin American countries (Cuba, El Salvador, Mexico, Paraguay, and Peru) found that prescribing guidelines were followed in 68.6% of cases. The most commonly prescribed antibiotic group was third-generation cephalosporins (26.8%), followed by carbapenems (10.3%) and fluoroquinolones (8%). Targeted therapy was only achieved in 17.3% of cases [77].

Clinicians should aim to improve their daily practice by implementing antimicrobial stewardship principles [78]. Antimicrobial stewardship programmes (ASPs) [79–81] should be integrated into all hospital quality improvement programmes globally. ASPs aim to promote responsible antibiotic use by improving diagnostic decision-making, emphasising the importance of prescribing antibiotics only when necessary, at the correct dose, interval, and duration, for the appropriate patient and clinical situation [82–84]. Additionally, ASPs play a crucial role in raising awareness of AMR among healthcare professionals and community members [85, 86]. Diagnostic guidelines are an essential component of ASPs. They emphasise the significance of selecting appropriate diagnostic tests for each patient at the correct time [87]. The guidelines encourage the use of rapid molecular diagnostics to initiate targeted antibiotic therapy as soon as possible. It is important to avoid the overuse of broad-spectrum antibiotics when they are no longer necessary. It is important to accurately interpret test results to prevent overdiagnosis and unnecessary costs [88] and to improve diagnostic decision-making by integrating all relevant clinical, biological, and imaging information.

Although joint recommendations for the development of institutional ASPs were published by the CDC, the Society for Healthcare Epidemiology of America (SHEA), and the Infectious Diseases Society of America (IDSA) 15 years ago, best practices are still being defined. These practices may vary depending on local policies, practice patterns, and available resources [89]. A comprehensive programme involving collaboration between professionals and support staff in the facility is the preferred means of improving antimicrobial stewardship. Direct involvement of all prescribers in ASP can be of great importance [90].

Therefore, we present the following 10 principles for the correct use of antibiotics. These principles are essential for all healthcare professionals to follow in their clinical practice and should be considered core components of ASP activities.

1. To prevent hospital-acquired infections (HAIs), it is crucial for healthcare workers to adhere to evidence-based infection prevention and control (IPC) practices. IPC education and training have been shown to significantly reduce healthcare-associated infections (HAIs) [91–94]. The most common types of HAIs include surgical site infections (SSIs), catheter-related urinary tract infections, central bloodstream infections, hospital-acquired infections, ventilator-associated pneumonia, and Clostridioides difficile infections [95] (Fig. 7).

2. Hospital-acquired infections (HAIs) can lead to additional diagnostic and therapeutic procedures, prolonged hospital stays, increased costs, and high complication and mortality rates. Moreover, MDR bacteria are responsible for many HAIs [96, 97]. Therefore, preventing HAIs is crucial for ensuring quality healthcare and mitigating antimicrobial resistance (AMR). These infections are linked to worse outcomes and often necessitate the use of broad-spectrum antibiotics [98].

3. The European Centre for Disease Prevention and Control (ECDC) reports that the six major types of hospital-acquired infections in the European Union/European Economic Area caused more disability-adjusted life years than all 32 other infectious diseases monitored by the ECDC combined, based on data from 2011 to 2012 [99]. It is important to note that many hospital-acquired infections are preventable. Implementing multimodal prevention and developing a safety-focused approach has been documented to reduce hospital-acquired infections by 35–55%, regardless of country income [100]. However, healthcare workers exhibit poor adherence to evidence-based infection prevention and control (IPC) measures [95]. Hand hygiene is a prime example of an indicator of patient safety and quality of care, and a cornerstone of infection prevention and control (IPC) in all healthcare settings. Specific recommendations for improving hand hygiene practices are provided to healthcare professionals by many organizations, including the World Health Organization (WHO) [101] and the Centers for Disease Control and Prevention (CDC) [102]. Recently, practical guidelines for preventing hospital-acquired infections through hand hygiene have been published by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Association of Professionals in Infection Control and Epidemiology (APIC).
WHO published five basic rules for hand hygiene to encourage healthcare workers to follow hand hygiene guidelines and minimize the risk of infection and transmission [104] (Fig. 8).

Although hand hygiene is widely recognised as a cost-effective infection prevention and control (IPC) measure, compliance remains unacceptably low. The systematic review [105] reported a compliance rate of approximately 40%, which is significantly lower than the WHO benchmark of 80%. Compliance varied among hospital departments and healthcare workers, necessitating multifaceted mitigation measures to promote consistency. All healthcare workers involved in direct or indirect patient care should be aware of the importance of hand hygiene and the need to follow basic rules. Hand hygiene during care is recognised as a best practice to promote compliance at times when it is most important. According to current best practice, hand hygiene products should be easily accessible and ideally within arm’s reach at the point of patient care or treatment [106].

Surgical site infections (SSIs)

Surgical site infections are the most common healthcare-associated infection among surgical patients and pose a significant clinical problem due to their impact on morbidity, mortality, length of hospital stay, and overall direct and indirect costs worldwide. To reduce the occurrence of SSIs (107–109), measures should be taken before, during, and after surgery.

In 2016, the World Health Organization (WHO) published evidence-based recommendations on the main components of effective Infection Prevention and Control (IPC) programmes that should be implemented at both national and hospital levels [110, 111]. The IPC interventions were summarised in eight ‘core components’ (Fig. 9). Since the landmark Study of the Effectiveness of Hospital Infection Control (SENIC) programme in the 1970s [112], which demonstrated the effectiveness of IPC in reducing Healthcare-Associated Infections (HAIs), a dedicated IPC programme is considered essential in every hospital. The leadership of IPC experts must collaborate closely with healthcare professionals in all relevant areas [113].

The World Health Organization (WHO) has confidently published the results of a global survey that assessed the implementation of infection prevention and control (IPC) programmes in health facilities worldwide. The survey provides a comprehensive overview of IPC programme implementation in 4,440 health facilities across 81 countries, spanning all six WHO regions and income levels. The findings reveal strengths and gaps in the implementation of infection prevention and control (IPC), as well as key opportunities for improvement. This information can inform ongoing global efforts to improve IPC, particularly in low- and middle-income countries (LMICs), which have shown significantly lower levels of IPC implementation [114].

IPC and antimicrobial stewardship programmes (ASPs) must work together as partners in reducing healthcare-associated infections (HAIs) to achieve the common goal of reducing antimicrobial resistance. Institutional leadership support is crucial for the success of each programme. An effective microbiology laboratory is necessary to ensure
rapid diagnosis, effective communication, and appropriate use of technology, such as electronic health records. The IPC and ASPs programmes are based on similar interdisciplinary models of work and activities, such as training, monitoring, and feedback. Integrating these interventions reduces redundancy and aligns forces to maximize their impact on health workers. Antimicrobial Stewardship Programs are significantly more effective in reducing the development and spread of Multidrug-Resistant (MDR) bacteria when implemented in conjunction with Infection Prevention and Control (IPC) interventions in hospitals, such as hand hygiene, than ASPs alone [115].

Containing the spread of antibiotic-resistant bacteria is a challenging task due to their high propensity for human-to-human transmission [116]. However, with the right approach, it is possible to tackle even the most difficult bacteria to treat, such as carbapenem-resistant Enterobacterales (CRE), A. baumannii (CRAB) and P. aeruginosa (CRPA). The WHO has already published recommendations for the prevention and control of these bacteria in acute care settings in 2017 [117], which were further supported by a systematic literature review in 2019 [118]. The most frequently reported interventions were contact precautions, active surveillance cultures, monitoring, auditing and feedback of interventions, patient isolation or cohorting, hand hygiene, and environmental cleaning.

Vaccination is unequivocally the most effective and cost-efficient prevention measure available. Vaccines serve primarily as prophylactic measures, including post-exposure prophylaxis, to significantly reduce the incidence of infectious diseases. This, in turn, leads to a reduction in the use of antibiotics and the spread of antimicrobial resistance. Furthermore, vaccines are being developed to combat resistant bacterial pathogens that cause a significant burden of disease, such as MRSA and P. aeruginosa [119, 120, 121]. Vaccines affect the antimicrobial response both directly and indirectly. Directly, they prevent infections, which reduces the prevalence of resistant pathogens and the need for antibiotics. Indirectly, they prevent non-bacterial primary infections, such as viral infections, which are often inappropriately treated with antibiotics [119]. The effectiveness of vaccines in reducing antibiotic use and AMR is well-documented. Examples include the Haemophilus influenzae serotype B (HiB), influenza, and pneumococcal conjugate vaccines [122–124]. Vaccination against S. pneumoniae (which is increasingly resistant to penicillin), HiB, and Neisseria meningitidis after splenectomy has been proven to be highly effective in preventing significant infection caused by encapsulated microorganisms [125]. Measles immunisation prevents measles virus infection, thereby reducing the available antibodies that provide protection against other pathogens [126]. Furthermore, the development and evaluation of new vaccines offer opportunities to address life-threatening diseases and further curb antibiotic use, effectively mitigating AMR [127].

It is crucial to avoid prescribing antibiotics when they are not needed. Clinicians must provide patients with the best possible treatment while also preserving the efficacy of...
antibiotics, minimizing opportunistic infections such as CDI, reducing the selection of resistant pathogens in individual patients, and preventing further global increases in AMR. Assessing and balancing any conflicts (Fig. 10) is crucial before prescribing antibiotics.

The intestinal microbiota plays a vital role in maintaining human health and protecting against colonisation by harmful intestinal bacteria [128]. This is known as colonisation resistance. The indigenous bacteria of the microbiome provide a vital defence mechanism by preventing colonisation by potentially pathogenic bacteria. In certain circumstances, the patient's microbiota may become compromised, no longer providing protection against colonisation by opportunistic organisms. Antibiotics exert selection pressure on the human microbiome, contributing to antimicrobial resistance. The unintended consequences of antibiotic use can compromise the gut commensal microbiota. The destruction of susceptible bacteria by antibiotics can create an ecological vacuum that promotes the overgrowth of pathogenic bacteria, which may already be resistant to antibiotics [129, 130]. Additionally, antibiotics aid in the transfer of resistance genes that provide resistance to other bacteria [131, 132] (Fig. 11), thereby elevating the likelihood of cross-transmission between patients [133, 134] and outbreaks of multidrug-resistant (MDR) infections.

Several studies have assessed the long-term effects of antibiotics on the intestinal microbiota [135–137]. These antibiotics were administered at appropriate doses and frequencies, and the results showed significant changes in the gut microbiota composition. To demonstrate these effects on a healthy microbiome, healthy humans were evaluated after taking amoxicillin, ciprofloxacin, and cefprozil for 5–7 days. Microbiota changes persisted for up to 12 weeks after treatment. The changes were characterized by incomplete restoration of microbial balance and the emergence of MDR strains. Oral drugs lead to higher antibiotic concentrations in the intestine and a higher number of MDR bacteria in the intestinal microbiota compared to parenteral antibiotics [141].

A one-year study was conducted to investigate the effects of ciprofloxacin (500 mg twice daily for 10 days) or clindamycin (150 mg four times daily for 10 days) on the faecal microbiota of healthy individuals. The study unequivocally demonstrated a significant impact on microbiome diversity [141]. The changes in microbial balance were most noticeable during the first month after treatment and persisted until month 20.

The gut microbiota plays a crucial role in protecting against CDI [142]. A correlation between antibiotic exposure and CDI has been demonstrated [144]. Antibiotics disrupt the normal intestinal flora, allowing C. difficile to proliferate and produce toxins [145]. Research has unequivocally demonstrated that the normal gut microbiota effectively prevents the multiplication and persistence of C. difficile [146]. Antibiotics have a significant impact on an individual's microbiota, which can be observed during and for a few days after treatment [147]. The risk of CDI is estimated to increase up to six times during and in the month following antibiotic therapy [34]. The antibiotics that pose the greatest risk for CDI are clindamycin, amoxicillin–clavulanic acid, third- and fourth-generation cephalosporins, fluoroquinolones, and carbapenems [34].
It is important to note that surgical antibiotic prophylaxis (SAP) plays a crucial role in preventing infections during perioperative procedures, especially in clean and contaminated surgeries with a high risk of infection. SAP is necessary in clean procedures where SSI could have severe consequences, such as those involving prosthetic implants. It is important to consider patients with medical conditions that increase the risk of SSI, including compromised immune systems (e.g. neutropenia), those with an ASA score $\geq 3$, and obese patients. Although SAP is not necessary for all surgical procedures, it is often overused, leading to a significant contribution to overall antibiotic consumption in surgical services. Prophylactic antibiotic use is not justified in patients undergoing elective uncomplicated laparoscopic cholecystectomy, as elective laparoscopic cholecystectomy carries a low risk of SSI. The role of SAP in patients undergoing herniorrhaphy or open groin surgery remains uncertain due to conflicting results of generally low quality evidence [150–155]. International guidelines [156] recommend SAP for open groin mesh repair in any high-risk patient.

Confirmation of a bacterial infection is necessary before prescribing antibiotic therapy. Patients with indwelling urinary catheters, mechanical ventilation endotracheal tubes, or chronic wounds may be colonised with potential pathogens without showing signs of infection, but this should not lead to unnecessary antibiotic use. To ensure appropriate assessment, cultures must be obtained only from the indicated sites, without contamination from the collection methodology itself. This involves avoiding surface swab cultures and drainage tract cultures [157], and refrain from antibiotic treatment of a 'positive' culture result without symptoms or evidence of active infection [158]. Asymptomatic bacteriuria is a common scenario in which antibiotics are not recommended, but it is often treated regardless. Positive urine culture results in these patients may be due to the formation of biofilm on the device. Asymptomatic bacteriuria in patients with a urinary catheter that drains should not be treated with antibiotics, except in special circumstances such as pregnancy or the use of transurethral instruments. This is because antibiotic therapy may increase the likelihood of further urinary tract infections that may become resistant to conventional antibiotics [159, 160].

The appropriateness of antibiotic use in the treatment of mild uncomplicated diverticulitis is being questioned due to a growing body of evidence suggesting that it is more likely to be an inflammatory rather than an infectious condition [161]. All three randomised trials and two prospective cohort studies have shown that antibiotic treatment does not prevent complications or recurrence, reduce symptoms or length of hospital stay [161–165]. Despite some opposition from experts, these findings suggest that the regular use of antibiotics may not be necessary [166, 167].

**Timely administration of the appropriate antibiotic(s)**

Once the decision to treat has been made, it is crucial to choose the most appropriate antibiotic(s) for the...
individual patient (Fig. 12). The antibiotic chosen for SAP should be active against the common bacteria that cause SSI in a particular procedure. SSIs during clean procedures are usually caused by skin flora, including S. aureus or coagulase–negative staphylococci. Depending on the flora of the mucous membranes on which the incision is made, clean and contaminated procedures may involve other bacteria such as E. coli, other Enterobacterales or anaerobes. The most common antibiotics used for SAP have been first– and second– generation cephalosporins (e.g., cefazolin, cefuroxime) [148, 149]. Cefazolin is the drug of choice for SAP before most procedures. It has proven efficacy, appropriate duration of action, activity against bacteria commonly encountered in SSI, an acceptable safety profile, and low cost. Routine use of vancomycin in SAP is not recommended. Vancomycin may be considered for SAP in patients with known MRSA colonisation or those at high risk, such as those in facilities with a high incidence of MRSA infections, patients after recent hospitalisation, dialysis patients and patients admitted from skilled nursing facilities, taking into account national guidelines and local epidemiology.

With regard to empirical therapy before the causative bacteria and their susceptibility are known, the choice of the optimal antibiotic should be based on the source of infection, expected pathogens, the patient's clinical condition, local epidemiology and individual patient risk factors for MDR bacteria [1]. Treatment guidelines based on local epidemiology and resistance patterns should be developed and implemented consistently in accordance with ASP principles. Determining the right antibiotic(s) for a particular patient can be challenging. Although the susceptibility of bacteria involved in community–acquired infections is typically much higher and broader than that of HAIs, clinicians often recommend broad–spectrum antibiotics for severe community–acquired infections to «leave nothing to chance». While the spectrum of action may be appropriate for this, overtreatment is likely, as narrow–spectrum antibiotics are equally effective in most cases. In contrast, for HAIs, the best course of action is empirical broad–spectrum therapy, including an antifungal agent in some circumstances [170, 171], followed by de–escalation to dedicated therapy once microbiological evidence is available [172, 173].

The WHO Expert Committee on the Selection and Use of Essential Medicines introduced the A WaRe (Access, Watch, Reserve) classification for antibiotics in 2017 to encourage efficient use of antibiotics worldwide at all levels of care. The A WaRe classification system categorises antibiotics into three groups based on their effectiveness in treating common bacterial infections and their impact on antimicrobial resistance. This comprehensive classification system highlights the importance of appropriate antibiotic use and demonstrates the significant impact it can have on combating antimicrobial resistance. The 2021 update of the classification includes 78 additional antibiotics, bringing the total number of classified antibiotics to 258 (Fig. 13).

The Access category recommends the use of specific antibiotics for the 25 most common infections. These antibiotics are widely available, affordable, and acceptable.
The Watch category includes the majority of the 'highest priority, critical antibiotics' that are recommended only for specific indications. The 'Reserve' category comprises antibiotics that should be used as a last resort, specifically to treat MDR bacteria, and only after all other antibiotics have failed. To reduce the global overuse of piperacillin–tazobactam, a ureidopenicillin antibiotic commonly used to treat community– acquired infections, the World Health Organization (WHO) recommends increasing access and use of antibiotics in the Access group while reducing the use of antibiotics in the Watch and Reserve groups. To reduce the global overuse of piperacillin–tazobactam, a ureidopenicillin antibiotic commonly used to treat community– acquired infections, the World Health Organization (WHO) recommends increasing access and use of antibiotics in the Access group while reducing the use of antibiotics in the Watch and Reserve groups.

Assessing infection severity is a critical step in evaluating patients for antimicrobial therapy. Early introduction of appropriate empirical antibiotic therapy has a significant positive impact on septic shock outcomes, irrespective of the infection location [175]. Although critically ill patients benefit from early antibiotic therapy, clinicians managing less severely ill patients can take the time to carefully consider and determine appropriate antibiotic treatment before initiating therapy [175]. Delayed antibiotic prescribing, which involves a wait– and– see approach with reassessment of the patient, is a useful tactic to help reduce antibiotic use, especially for respiratory tract infections [176]. It is important to note that hasty antibiotic therapy may be harmful for critically ill surgical patients, where adequate source control is a critical factor in survival. A before– and– after study [177] compared universal early antibiotic therapy (an aggressive approach) with a second period when immediate antibiotic therapy was prescribed only to patients with hypotension. The aggressive approach was associated with a shorter time interval between the onset of fever and haemoculture collection and the start of treatment, while the conservative approach was associated with a higher likelihood of initial appropriate therapy, shorter therapy duration, and lower mortality. It is clear that the conservative approach is a viable option that should not be overlooked. The aggressive approach was associated with a shorter time interval between the onset of fever and haemoculture collection and the start of treatment, while the conservative approach was associated with a higher likelihood of initial appropriate therapy, shorter therapy duration, and lower mortality. Distinguishing between infection and inflammation is challenging, especially in critically ill patients. However, in patients without shock,
postponing the administration of antibiotics to determine the cause of sepsis can be advantageous.

Delayed antibiotic prescribing is a useful strategy for reducing antibiotic use, particularly for community–acquired respiratory tract infections [178], which are often of viral origin. Delaying antibiotic prescription has been found to result in similar symptom duration as compared to no antibiotics, according to a meta–analysis. Withholding antibiotics until pathogen identification and susceptibility testing is performed may be a suitable approach to minimize unnecessary antibiotic use in cases of viral respiratory tract infections.

Delaying appropriate empirical antibiotic therapy can be harmful for patients with shock associated with sepsis and organ dysfunction [179, 180]. Early initiation of antibiotic treatment is crucial for good outcomes. Each hour of delay in starting antibiotic treatment shows a strong correlation with mortality rates in patients with septic shock [181, 182]. The 2021 Surviving Sepsis Campaign guidelines recommend prompt administration of antibiotics to adults with possible septic shock or probable sepsis, ideally within 1 hour of symptom onset [183]. For adults with possible sepsis without shock, a rapid assessment of infectious and non–infectious causes of acute illness should be made, and antimicrobials should be given within 3 hours of the first detection of sepsis [183].

Knowing about colonisation by multidrug–resistant bacteria through reference cultures improves the likelihood of appropriate initial antibiotic therapy for subsequent healthcare–associated infections (HAIs) in critically ill patients with bloodstream infections or ventilator–associated pneumonia (VAP) [184, 185]. Moreover, the tested cultures exhibit a high negative predictive value for MDR bacteria. Therefore, early and appropriate antibiotic therapy has the potential to conserve antibiotics by reducing the use of carbapenems and other antibiotics in comparison to guideline–based prescribing [185–188]. This approach can effectively alleviate the pressure of antibiotic selection on the local environment. According to a meta–analysis of diagnostic test accuracy, twice–weekly sampling frequency is the most effective. Additionally, recent culture observations demonstrate a higher positive predictive value for bacterial pathogens in VAP [185].

The administration of antibiotics in adequate doses and by appropriate routes

The prescription of antibiotics must be based on the inherent pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of each antibiotic class and agent, as well as the specific pathophysiological characteristics of the patient. It is important to note that the PD of antibiotics is directly related to the concentration of the drug and its ability to inhibit bacterial growth. To evaluate the effectiveness of an antibiotic against target bacteria, the primary in vitro parameter used is the minimum inhibitory concentration (MIC). For a therapeutic effect, the concentration at the site of infection should exceed the MIC against the target bacteria by at least 40% of the dosing interval, and ideally longer if the killing is time–dependent, or ten times if the killing of these bacteria is concentration–dependent [189]. Understanding the pharmacokinetics of antibiotics is crucial as it determines their concentration and duration in the body, including at the site of infection. Failure to achieve optimal concentrations can lead to therapeutic failure and promote antimicrobial

Fig. 13. WHO AWaRe classification.
resistance, particularly when dealing with clinical isolates that have borderline susceptibility in vitro [190].

Therefore, it is crucial to consider clinical and antibiotic-related factors that may affect the distribution of antibiotics at the target site. Understanding the pharmacokinetics/pharmacodynamics (PK/PD) of each antibiotic can aid in determining the most suitable dosing regimens in terms of both dose and interval. By doing so, we can confidently determine the most effective dosing regimens for each patient. The concentration gradient between plasma and the site of action may be particularly significant in cases of bacterial infection with multidrug-resistant (MDR) strains. Higher doses of ceftazidime, meropenem, and imipenem-clastatin are required to achieve target values in patients with severe intra-abdominal infections [193–195].

The pathophysiology of sepsis and septic shock can significantly affect pharmacokinetic parameters in seriously ill patients who are at high risk of infection, life-threatening sepsis, and multiple organ dysfunction syndrome. Understanding the pathophysiological impact on PK/PD is crucial for optimizing antibiotic treatment in critically ill patients with sepsis or septic shock [196, 197]. Impaired liver or renal function may require a change in PK and dose reduction.

To achieve optimal bactericidal activity, it is important to maintain the antibiotic concentration above the minimum inhibitory concentration (MIC) for a prolonged period of time. Beta-lactam antibiotics exhibit time-dependent activity, which means that the serum concentration of antibiotics should be at least 40% higher than the MIC (optimally 70%) [196]. To optimise beta-lactam activity, it is recommended to use higher dosing rates, prolonged infusions, and continuous infusions [196]. It is important to achieve a high peak plasma concentration when administering antibiotics that have a concentration-dependent effect. The efficacy of these antibiotics is more closely related to the peak serum concentration (MIC, not time above MIC, fT>MIC) [196]. Although aminoglycosides are ideally administered once daily for most therapeutic indications, particularly in critically ill patients [198], restricting administration to once daily can reduce the risk of nephrotoxicity [34, 199].

In patients with septic shock, timely administration of antimicrobial agents, including the first 'loading' dose, is crucial. It is important to note that the volume of distribution (VD) of hydrophilic agents, such as beta-lactams, aminoglycosides, and glycopeptides, may increase in patients with septic shock due to increased microvascular endothelial permeability and extracellular fluid expansion. Administering loading doses of beta-lactams, aminoglycosides (especially when dosed once daily), or glycopeptides [196] is recommended to enhance the therapeutic effect.

It is crucial to review antibiotic therapy daily after initiating treatment, as fluctuating organ function in critically ill patients can significantly impact antibiotic exposure. For example, in the presence of renal impairment, lower doses of urinary excreted antibiotics should be administered, while patients with increased renal clearance (such as those with burns or obesity) should receive higher than standard doses [34]. Antibiotic therapy is challenging for obese patients due to altered FFR/FD [200]. Obesity increases VD, particularly for lipophilic antibiotics, resulting in lower than expected plasma antibiotic concentrations. Increased renal clearance is often experienced by patients, and fatty infiltration of the liver can impair liver function. In general, the dosage of lipophilic antibiotics should be based on total body weight or adjusted body weight for hydrophilic antibiotics, regardless of body weight. Individualised dosing, supported by laboratory tests, is crucial due to patient heterogeneity and clinical variability.

The American Society of Health-System Pharmacists, the Society for Paediatric Infectious Diseases, and the Society of Infectious Disease Pharmacists have published a revised consensus guideline and review of therapeutic monitoring of vancomycin for serious MRSA infections. This guideline is a comprehensive and authoritative resource for healthcare professionals who treat patients with MRSA infections, and it provides clear and concise recommendations for the use of vancomycin in these cases. This review confidently evaluates the scientific evidence and controversies surrounding vancomycin dosing and serum concentration monitoring for serious MRSA infections, such as bacteremia, sepsis, infective endocarditis, pneumonia, osteomyelitis, and meningitis. It decisively provides new recommendations based on the latest available data [201].

Several studies have shown that oral antibiotics can confidently reduce hospitalization costs and duration [202, 203]. Guidelines suggest that the switch can be made if the gastrointestinal tract is functional and there is a decrease in temperature and clinical improvement with or without improvement in laboratory markers [204]. To switch from intravenous to oral antibiotics, several antibiotics with high oral bioavailability can be considered, and it is not necessary to switch to the same drug. Partial oral antibiotic therapy has been shown to successfully treat many serious infections [205]. The switch to oral antibiotics does not result in longer antibiotic therapy than parenteral therapy. The use of oral antibiotics can affect the dynamics of the intestinal microbiome, leading to stronger antibiotic resistance [206].

The results of culture and susceptibility testing must be used to initiate the fastest and most appropriate treatment possible

Microbiological testing plays a crucial role in selecting targeted antibiotic therapy. Clinicians should narrow the spectrum of an empirical regimen that was too broad, known as de-escalation, rather than broadening the antibiotic spectrum if the initial choice was too narrow. De-escalation of antibiotic therapy based on microbiological culture and susceptibility testing supports antimicrobial stewardship programmes (ASP) and improves outcomes in severe infections [34].
De-escalation tactics involve switching to narrower-spectrum regimens or reducing the number of antibiotics used in combination therapy [207], or to monotherapy. De-escalation aims to avoid the use of broad-spectrum antibiotics whenever possible, reducing selection pressure and ultimately the prevalence of multidrug-resistant (MDR) bacteria. The evidence is most convincing for patients with ventilator-associated pneumonia (VAP), with several studies reporting higher survival rates. Obtaining sputum samples before administering antibiotics is crucial for enabling de-escalation. De-escalation has been widely adopted as part of ASPs.

The MIC, the lowest concentration of an antimicrobial agent that inhibits microbial growth, can be determined by various methods such as broth or agar dilution, disc or gradient diffusion. The MIC value, expressed as µg/ml, is often translated by clinical microbiology laboratories as «sensitive», «intermediate» or «resistant» according to defined «cut-off points» established by the Clinical and Laboratory Standards Institute (CLSI, Wayne, PA, USA) or «sensitive», «resistant, susceptible» or «resistant» according to the criteria of the European Committee for Antimicrobial Susceptibility Testing (EUCAST, Vaxjo, Sweden) [34].

Rapid diagnosis can facilitate further development by limiting the unnecessary initiation of broad-spectrum therapy, thereby reducing the need for subsequent de-escalation [211, 212]. Most commercially available methods for rapid detection of MDR bacteria include genotyping, which is based on the detection of resistance genes [213] based on DNA sequencing. Genotypic methods can be used in conjunction with phenotyping [214], but genotypic methods in current clinical use should be considered as a complement to traditional phenotypic antimicrobial susceptibility testing due to several limitations. Genotyping can effectively predict AMR but does not inform susceptibility testing. In addition, the panel of resistance determinants is small, so other resistance determinants may not be detected. In addition, genotypic methods are likely to overestimate AMR, as the presence of a resistance gene is not necessarily associated with phenotypic expression of resistance (the gene may be inactivated or not expressed).

The greatest advantage of genotyping is undoubtedly its speed, with a turnaround time of 1–4 hours. The use of comparative genomics, probes, microarrays, nucleic acid amplification and deoxyribonucleic acid sequencing should allow for the detection of several genes or resistance variants simultaneously. However, a logistical challenge in practice is that when new antibiotics enter the market, there may be a delay before in vitro susceptibility assays are validated for clinical use, which may limit the initial clinical use of new agents [215].

Rapid diagnostic testing for possible pathogens is considered indispensable for ASP. When combined with rapid, appropriate treatment, antibiotic use is reduced, mortality is reduced, hospital stays are reduced, and costs are reduced [216–218]. The lack of modern diagnostic tests is an important barrier in resource-limited settings [219].

Use the shortest possible duration of antibiotics based on evidence

The duration of antibiotic therapy prescribed in routine practice is often longer than recommended [220]. The WHO recommends against prolonging SAP after surgery to prevent SSIs, based on a meta-analysis [220] of 69 randomised controlled trials investigating the optimal duration of SAP. For clean and cleanly contaminated procedures, CDC guidelines recommend that no additional doses of prophylactic antibiotics should be given after the surgical incision is closed in the operating room, even if drainage is present [109]. The updated IDSA and SHEA guidelines recommend discontinuing all SAP after incision closure, regardless of procedure type or duration [221]. de Jonge SW et al. (2020) investigated the effect of prolonging SAP on the rate of SSI [222]. They evaluated 83 RCTs; 52 (19 275 participants) were included in the primary meta-analysis. There was no convincing evidence of a benefit of postoperative continuation of antibiotic prophylaxis (compared with discontinuation). In combination with a comprehensive approach to best practice in SSI prevention, postoperative continuation of SAP did not provide additional benefits in reducing the incidence of SSI in any surgical setting. In a 2019 multicentre retrospective cohort study [223], an increase in the duration of antibiotic prophylaxis was associated with a higher risk of acute kidney injury and CDI, but without a reduction in SSI.

A study of 34 urban and rural hospitals in South Africa demonstrated that the implementation of institutionally focused process improvement initiatives and principles involving pharmacists effectively improved SAP adherence and sustainable patient outcomes [224]. Efforts to reduce the duration of antibiotic therapy in hospital practice are an increasing area of focus for ASPs [225]. However, Langford BJ et al. (2020) showed that ASP advice to stop or reduce antibiotic duration was less commonly accepted than advice to start or increase antibiotics [226].

Reducing the duration of antibiotic therapy is a crucial tactic to reduce unnecessary inpatient antibiotic use where antibiotic pressure is intense [227]. Although there are circumstances that may require prolonged antibiotic therapy (e.g. endocarditis, osteomyelitis, etc.), the duration of antibiotic therapy should always be as short as possible. In the case of intra-abdominal infections, the STOP-IT trial [228] in 2015 demonstrated that 4 days of antibiotic therapy is as effective as 8 days of therapy when the source is adequately controlled. In the randomised clinical trial DURAPAP [229], critically ill patients with postoperative intra-abdominal infections who received a short course of antibiotics (8 days) showed similar results compared to patients who received treatment for 15 days.

Antibiotic therapy for up to 21 days for VAP and community-acquired pneumonia (CAP) was historically used until several prospective studies demonstrated the efficacy of shorter (7–8 days) therapy with no difference in mortality, ICU stay, ventilator-free days, or days without organ failure [230, 231]. The 2017 European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and
2016 IDSA guidelines [232] recommend 7 days of therapy for CAP/VAP. An ongoing study [233] will determine whether the duration of therapy can be further reduced.

Bacteraemia caused by Enterobacterales has traditionally been treated with 2 weeks of antibiotics. Recent RCTs and meta– analyses investigating shorter (7– 8 days) versus longer courses of antibiotics (14– 15 days) in patients with Gram– negative bacteremia, mostly originating from the urinary tract, have demonstrated no less efficacy [234– 239]. For acute uncomplicated cellulitis, evidence also suggests that prolonged courses may not be necessary and that 5 days of treatment may be sufficient [240]. The IDSA guidelines recommend a 5– day duration of antibiotic therapy for uncomplicated cellulitis, but it can be extended if the infection has not improved during this period [241].

Generally, for critically ill patients, the decision on the duration of antibiotic therapy should be made on an individual basis, taking into account patient parameters such as disease severity, location and type of infection, whether source control has been achieved, whether the FC has been optimised and clinical response [242]. Procalcitonin (PCT) may be useful for guiding antibiotic therapy in the intensive care unit. PCT– guided treatment can reduce the duration of therapy and length of hospital stay in critically ill adult patients with sepsis [243, 244]. Based on the clear benefit and lack of obvious adverse effects, the Surviving Sepsis 2021 guidelines suggest using PCT together with clinical assessment to decide when to stop antibiotics in adults with an initial diagnosis of sepsis or septic shock and an adequate source of control, if the optimal duration of therapy is not clear and PCT measurement is available [185].

Achieving source control by identifying and eliminating the source of infection or reducing the bacterial load

Source control aims to eliminate the source of infection, reduce the bacterial inoculum and correct anatomical abnormalities to restore physiological homeostasis. It also involves draining abscesses or accumulations of infected fluid, cleaning necrotic tissue or removing contaminated medical devices, etc. These are all situations where antibiotics alone are of limited effectiveness.

Source control is crucial in the treatment of surgical infections, especially intra– abdominal and soft tissue infections. Adequate source control achieved by surgery allows for a shorter course of antibiotic therapy, thereby improving patient outcomes, including a lower risk of organ dysfunction [245, 246]. In the case of uncomplicated intra– abdominal infections, such as uncomplicated appendicitis or cholecystitis, postoperative antibiotic therapy is not required if the source is adequately controlled [246]. In the case of complicated intra– abdominal infections, a short course of antibiotic therapy is always suggested, even if the source is adequately controlled [228, 229].

In some circumstances, organisational determinants may influence the overuse of antibiotics. For example, acute cholecystitis should be treated with early cholecystectomy [247]. Nevertheless, because operating theatre availability is critical in many centres, cases of acute cholecystitis are sometimes treated with percutaneous drainage or delayed cholecystectomy, which requires a longer duration of antibiotic therapy.

Some patients are prone to persistent or recurrent sepsis despite initial attempts at source control [254]. Source control procedures can be ineffective in up to 25% of cases of abdominal sepsis with shock [255]. Timely reoperation is the only option that significantly improves outcomes. Failure of source control can be caused by incomplete initial source control, especially if contamination is ongoing [256], and source control failure can be difficult to diagnose. Monitoring the success of source control is thus crucial, with a high index of suspicion if the patient does not improve. Most often, the diagnosis is based on a lack of clinical improvement (persistent signs and symptoms of inflammation) and is confirmed by imaging.

Support surveillance of HAI s and AMR, monitoring antibiotic use, consumption and prescribing quality

Surveillance and prevalence surveys to determine the incidence of HAIs are a crucial tactic in the strategy to reduce HAIs and contain AMR. HAI prevalence data allow hospitals to measure the effectiveness of IPC activities; inspections and feedback are used to drive change, improve quality and safety. The European Healthcare– Associated Infection Surveillance Network (HAI– Net) [257], coordinated by the ECDC, provides surveillance of HAIs. The main priorities of the HAI– Net are the coordination of European point– of– care surveys of HAI prevalence and antimicrobial stewardship in acute and long– term care hospitals, surveillance of SSI s and HI A in intensive care units. In the United States, the CDC’s National Healthcare Safety Network (NHSN) [258] is the most widely used HAI surveillance system. The NHSN provides facilities and government agencies with the data they need to identify problem areas, measure progress in prevention efforts, and ultimately eliminate HAIs. Additionally, NHSN allows for the tracking of transfusion safety errors and important healthcare process metrics such as staff flu vaccination status and IPC compliance rates. MDR bacterial surveillance provides the basis for taking action to control AMR. Consistent data on the incidence and prevalence of MDR bacteria and geographic patterns associated with AMR guide patient care and monitor the effectiveness of interventions.

A recent joint publication by the ECDC and the WHO Regional Office for Europe reported on AMR rates in Europe using data from invasive bacterial isolates [259]. Carbapenem resistance in K. pneumoniae and vancomycin resistance in E. faecium increased during 2016– 2020. In addition, high rates of resistance to third– generation cephalosporins and high rates of carbapenem resistance in Acinetobacter spp. and P. aeruginosa in several countries in the European region.
In 2015, the WHO launched the Global Antimicrobial Resistance and Surveillance System (GLASS) as a collaborative effort to standardise antimicrobial resistance surveillance worldwide. Since its launch, GLASS has expanded its coverage, and as of 2021, 109 countries and territories have reported data to GLASS [260]. Most countries have reported high rates of antimicrobial resistance to first-line antibiotics, and in some countries even to antibiotics of last resort. The GLASS data show that carbapenem-resistant bacteria are a major concern worldwide. The high rates of carbapenem-resistant Acinetobacter spp. and K. pneumoniae, third-generation cephalosporin resistance in Enterobacterales, multidrug-resistant and extensively drug-resistant tuberculosis and MRSA will require ongoing close monitoring.

Inappropriate antibiotic use is a major driver of AMR [261]. Data on antibiotic use (volume and appropriateness) are important for assessing the impact of ASP. Antibiotic use and appropriateness can be measured at different levels, from the national level to the prescribing level, allowing for informed, targeted efforts to reduce unnecessary or inappropriate use [262]. The most common metric used to monitor antibiotic use is based on the concept of the defined daily dose (DDD). The DDD is the average maintenance dose of an antibiotic per day used in adults for the main indication. Expressing antibiotic consumption in DDD/1000 patient days allows for comparisons to be made regardless of differences in the choice of individual antibiotics, and for changes to be measured over time to assess the impact of ASP interventions. Between 2000 and 2015, antibiotic consumption, expressed in DDD, increased by 65% from 21.1 to 34.8 billion DDD, while antibiotic use increased by 39%, from 11.5 to 15.7 DDD/1000 inhabitants/day in 76 countries [263]. Of particular concern was the rapid increase in the use of last resort compounds in both high-income and low-income countries, such as glycyclines, oxazolidinones, carbapenems and polymyxins.

Staff training and awareness raising

One of the goals of the WHO Global Action Plan on Antimicrobial Resistance [49] is to increase awareness and understanding of antimicrobial resistance through effective communication, education, and training. To address antimicrobial resistance, all prescribers should prescribe antibiotics appropriately and educate colleagues and patients on their proper use. The goal of raising awareness is to change the behaviours that fuel AMR. Not only may behaviours, beliefs, and practices regarding antibiotic use be inappropriate, but there are misconceptions about the concept of antibiotics and its emergence, spread, and impact. Clinic leaders should promote awareness by encouraging an institutional culture of patient safety and responsible use, where clinicians are persuaded, rather than forced, to follow antibiotic stewardship measures. A strong patient safety culture promotes education, collaboration, and engagement. Patients should also be informed about the social cost of AMR and the individual benefits of targeted therapy.

The ultimate goal of any stewardship programme should be to encourage behavioural change in prescribing practices [264]. It is important to include basic antimicrobial stewardship, diagnostic and IPC principles in pre- and postgraduate training and education to ensure confidence, skills, and experience in infection management [265]. Antibiotic prescriber education is essential to persuade clinicians to use antibiotics appropriately [1], following good prescribing practices and adhering to IPC guidelines. There is an urgent need to integrate antimicrobial stewardship education at the undergraduate medical education level to educate future prescribers on this important aspect of public health. Adequate undergraduate education on antibiotic stewardship will enable healthcare graduates to enter clinical practice with the appropriate competencies to prescribe antibiotics rationally [266]. However, although education to enhance antimicrobial stewardship is fundamental, without accompanying interventions, education alone is of little value. Diagnostic uncertainty, fear of clinical failure or potential litigation, time constraints, or organisational circumstances may complicate the decision to prescribe antibiotics.

A cross-sectional study of physicians' and pharmacists' perceptions and practices regarding antibiotic misuse in primary care centres in the Middle East reported a number of misconceptions and inappropriate practices regarding antibiotic use in Qatar by patients and healthcare providers [267]. Interestingly, the study found that about a third (29.2%) of doctors felt that they were often pressured by patients to prescribe antibiotics. Physicians who are overworked, underinformed or under pressure from patients are more likely to prescribe excessive amounts of antibiotics and thus contribute to the spread of antibiotic resistance. Patients often expect to be prescribed antibiotics, and it is difficult for doctors to ignore this pressure. However, physicians' communication with patients affects patient satisfaction more than the actual receipt of antibiotics, especially when patients are asked by their doctor to contact them if symptoms do not improve [268]. Thus, these findings suggest that educating patients about their diagnosis and course of treatment may lead to a reduction in the demand for unnecessary antibiotics [267].

Supporting a multidisciplinary antimicrobial stewardship programme (ASP) and improving collaboration between healthcare professionals from different disciplines

Promoting ASPs is key to ensuring more standardised and responsible antibiotic use in the healthcare setting [269]. ASPs publicise and implement best practices for antibiotic prescribing, administration, monitoring, and disposal. However, ASP implementation practices may vary depending on local culture, policies, and resources. Some hospitals still do not have formal ASPs, but even well-established programmes may struggle to be adequately resourced and...
The axiom “if you want to go fast, go alone; if you want to go far, go together” reminds us that we need global solidarity not only to reduce health inequalities, but also to be united against all global health challenges, including antimicrobial resistance.

Supporting a cohesive and multidisciplinary approach.
Due to the challenges associated with the development of new antibiotics, the emergence of MDR bacteria is likely to outpace the introduction of new drugs to combat them. Thus, it may be important to focus on alternative non-antibiotic measures to address antimicrobial resistance [279]. Health information technology is an emerging approach to optimising antibiotic use in the healthcare setting, although computerised decision support for antibiotic use in hospitals may not work in all settings [280]. Curtis CE et al. (2017) demonstrated the usefulness of computerised decision support for antibiotic use and even in reducing mortality in the hospital setting [281].

While clinical research should work to develop new treatments and cures for antibiotics, physicians should continue to use antibiotics as much as possible. In addition, public health campaigns aimed at raising awareness of responsible antibiotic use and IPC measures can also be crucial to reducing the spread of MDR bacteria. This document reaffirms the mission of the Global Alliance for Surgical Infection by advancing standards for the management of surgical infections through a cohesive and interdisciplinary approach. The axiom «if you want to go fast, go alone; if you want to go far, go together» reminds us that we need global solidarity not only to reduce health inequalities, but also to come together to address all global health challenges, including antimicrobial resistance (Fig. 14).

Conclusions

The appropriate use of antibiotics should be an integral part of good clinical practice and treatment standards. The inappropriate use of antibiotics, as well as poor infection prevention and control practices, contribute to the development and spread of antibiotic resistance. Antibiotics should be viewed as a global public good that is on the verge of scarcity; there is a global collective responsibility to conserve them to avoid the countless future victims of multi-drug resistant infections. Infections, especially multidrug-resistant bacteria, threaten the success of all healthcare practitioners, including surgeons. A technologically competent operation will fail if a patient develops a hospital-acquired infection that cannot be treated. Through joint initiatives and a united front, we can imagine the future of effective antimicrobial therapy for future generations.

Abbreviations

AMR: Antimicrobial resistance
ASPs: Antimicrobial Stewardship Programs
CDC: Centers for Disease Control and Prevention
CDI: Clostridioides difficile infection
COVID—19: Coronavirus disease 2019
CRAB: Carbapenem-resistant Acinetobacter baumannii
CRE: Carbapenem-resistant enterobacteriales
CRPA: Carbapenem-resistant Pseudomonas aeruginosa
DDD: Defined daily doses
ECDC: European Centre for Disease Prevention and Control
EDs: Emergency departments
GLASS: Global antimicrobial resistance and use surveillance system
HAIs: Hospital-acquired infections
HAP: Hospital-acquired pneumonia
HCWs: Healthcare workers
Hib: Haemophilus influenzae type B
ICU: Intensive care unit
IDSA: Infectious Diseases Society of America
IPC: Infection prevention and control
LMICs: Low- and middle-income countries
MDR: Multidrug-resistant
MIC: Minimal inhibitory concentration
MRSA: Methicillin-resistant Staphylococcus aureus
NAPs: National action plans
PCT: Procalcitonin
PD: Pharmacodynamics
PDR: Pan-drug-resistant
PK: Pharmacokinetics
RCTs: Randomized controlled trials
SAP: Surgical antibiotic prophylaxis
SARS—CoV—2: Severe acute respiratory syndrome coronavirus—2
SSIs: Surgical site infections
VAP: Ventilator-associated pneumonia
WHO: World Health Organization
XDR: Extensively drug-resistant

References


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