The Influence of Antimicrobial Stewardship Measures on Outcome of Patients with Severe Infections treated in Intensive Care Unit

Zjajo, Amela

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Amela Zjajo

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Mentor: Assist. Prof. Vladimir Krajinović, MD

Abbreviations

AI	Artificial intelligence
AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
AMP	Antimicrobial programs
AWaRe	ACCESS, WATCH, RESERVE
BSI	Bloodstream infections
CAUTI	Catheter-associated urinary tract infections
CDCD	Centers for Disease Control and Prevention
CRBSI	Catheter-related bloodstream infections
CVC	Central venous catheter
ESBL	Extended spectrum beta-lactamase
GDP	Gross domestic product
HAI	Hospital-acquired infection
ICU	Intensive Care Unit
ID-IRI	the Infectious Diseases – International Research Initiative
IPC	Infection prevention and control
ML	Machine learning
MRSA	Methicillin-resistant Staphylococcus aureus
PCR	Polymerase chain reaction
SIRS	Systemic Inflammatory Response Syndrome
SSI	Surgical site infections
Strama	Swedish Strategic Program Against Antibiotic Resistance
UNEP	United Nations Environment Program
UTI	Urinary tract infection
VRSA	Vancomycin-Resistant Staphylococcus aureus

VAP	Ventilator-associated pneumonia
WHO	World Health organization
XDR	Extremely drug-resistant

Summary

Antibiotic resistance poses a public health challenge worldwide. The intensive care units (ICUs) are characterized by the highest prevalence of multidrug-resistant microorganisms (MDRs) compared to other units in the hospital. The main reasons can be attributed to multiple factors: the higher average age of patients admitted, the larger number of concomitant diseases, and the more pronounced immunosuppression. In addition, many invasive technologies are used in these departments, which creates an additional risk of infections with MDR microorganisms.

Stewardship was initially introduced into healthcare through antimicrobial stewardship (AMS), as a means of responsibly managing healthcare resources. AMS, an important aspect of healthcare, focuses on optimizing antimicrobial use to combat antimicrobial resistance (AMR). This includes educating prescribers, revising and implementing programs, monitoring antimicrobial use and resistance patterns. Key elements of AMS programs include assessing patient conditions, controlling infection sources, selecting appropriate antimicrobials,following treatment guidelines, and reassessing therapy based on culture results. Inappropriateuse of antibiotics such as prolonged empiric treatment or failure to tailor therapy accordingly contributes to increased resistance.

The future of AMS involves addressing the global threat of multidrug-resistant pathogens by implementing interdisciplinary strategies, educating healthcare workers, and integrating advanced technologies such as artificial intelligence (AI) and rapid diagnostics. Recognizing the connection of animal and environmental health, in the fight against resistance is a key aspect of adopting a One Health approach. Multiple strategies are employed to achieve this goal, including the establishment of dedicated AMS teams, restrictions on the use of broad-spectrum antimicrobials, early termination of treatments, implementation of early warning systems, emphasis on infection control measures and provision of education and feedback to healthcare providers. This review explores the current practices and strategies employed in AMS within ICUs as well as the influence of the AMSs on patient outcomes, underscoring the significance of responsible antibiotic usage to improve patient outcomes and combat AMR effectively.

Keywords: Antimicrobial stewardship, multidrug-resistant, intensive care units, rational antibiotic usage, severe infections, infection control, antibiotics, healthcare-associated infections, surveillance

Sažetak

Otpornost na antibiotike predstavlja izazov za javno zdravlje u cijelom svijetu. Jedinice intenzivnog liječenja (JIL) karakterizira najveća prevalencija multirezistentnih mikroorganizama (MDR) u usporedbi s drugim jedinicama u bolnici. Glavni razlozi mogu se pripisati višestrukim čimbenicima: višoj prosječnoj dobi primljenih pacijenata, većem broju popratnih bolesti i izraženijoj imunosupresiji. Osim toga, na tim se odjelima koriste mnoge invazivne tehnologije, što stvara dodatni rizik od infekcija MDR mikroorganizmima.

Pojam Stewardship (Upravljanje), je prvotno uveden u zdravstvo kroz antimikrobno upravljanje (AMS), kao način odgovornog upravljanja resursima zdravstvene skrbi. AMS, važan aspekt zdravstvene skrbi, usredotočen je na optimizaciju uporabe antimikrobnih sredstava za borbu protiv antimikrobne rezistencije (AMR). To uključuje edukaciju liječnika koji propisuju lijekove, reviziju i provedbu programa, praćenje upotrebe antimikrobnih lijekova i obrazaca rezistencije. Ključni elementi AMS programa uključuju procjenu stanja bolesnika, kontrolu izvora infekcije, odabir odgovarajućih antimikrobnih lijekova, praćenje smjernica za liječenje i ponovnu procjenu terapije na temelju rezultata kulture. Neodgovarajuća uporaba antibiotika, kao što je produljeno empirijsko liječenje ili neuspjeh u prilagođavanju terapije u skladu s tim, pridonosi povećanju otpornosti.

Budućnost AMS-a uključuje rješavanje globalne prijetnje patogena rezistentnih na više lijekova provedbom interdisciplinarnih strategija, edukacijom zdravstvenih radnika i integracijom naprednih tehnologija kao što su umjetna inteligencija (AI) i brza dijagnostika. Prepoznavanje povezanosti zdravlja životinja i okoliša u borbi protiv otpornosti ključni je aspekt usvajanja pristupa „Jedno zdravlje“. Za postizanje ovog cilja koristi se više strategija, uključujući uspostavu namjenskih AMS timova, ograničenja upotrebe antimikrobnih lijekova širokog spektra, rani prekid liječenja, provedbu sustava ranog upozoravanja, naglasak na mjerama kontrole infekcija i pružanje obrazovanja i povratnih informacija osobama pružateljima zdravstvenih usluga. Ovaj pregled istražuje trenutne prakse i strategije koje se koriste u AMS-u unutar JIL-a kao i utjecaj AMS-a na ishode pacijenata, naglašavajući važnost odgovorne upotrebe antibiotika za poboljšanje ishoda pacijenata i učinkovitu borbu protiv AMR-a u JIL-a

Ključne riječi: antimikrobno upravljanje, multirezistentnost, jedinice intenzivnog liječenja, racionalna uporaba antibiotika, teške infekcije, kontrola infekcija, antibiotici, infekcije povezane sa zdravstvenom skrbi, nadzor

Contents

Introduction

In modern healthcare, the management of severe infections in the intensive care unit poses a major clinical challenge, exacerbated by the escalating threat of antimicrobial resistance. With intensive care unit patients often facing complex medical conditions, multiple infections and compromised immune systems, the need for effective antimicrobial therapy is crucial. However, the indiscriminate use of antibiotics in this setting has contributed to the emergence of resistant microorganisms evolving multiple mechanisms of resistance, complicating treatment regimens and jeopardizing patient outcomes.

To address this issue, antimicrobial stewardship has emerged as a central strategy aimed at optimizing antibiotic use, preserving their efficacy and combating the spread of antimicrobial resistance. Within the ICU, where antimicrobial use is frequent and diverse, the implementation of antimicrobial stewardship measures holds particular promise in improving patient care and reducing the adverse effects of antimicrobial overuse.

This review aims to explore the complex relationship between antimicrobial stewardship measures and patient outcomes in the context of severe infections treated within the ICU setting as well as incorporating the core elements in AMS. By examining the impact of AMS protocols on antibiotic prescribing practices, resistance patterns, clinical outcomes, and healthcare resource utilization, this review aims to provide valuable insights into the effectiveness of AMS interventions in optimizing the management of severe infections in critically ill patients.

Through a comprehensive review of existing literature, coupled with analysis of various reports and case studies, this review aims to explore the influence of antimicrobial stewardship on patient morbidity, mortality, length of ICU stays, and gaining insight in current implementations of the AMS as well as the future of AMS and the possibilities to incorporate AI and rapid diagnostics.

Multidrug resistant bacteria

Antimicrobial resistance (AMR) refers to a microorganism's ability to withstand the effects of one or more antimicrobial agents. The consequences of AMR are severe, underscoring the necessity for prompt administration of efficient antimicrobial therapies to reduce the potential for negative outcomes in severe infections (1). Globally and within the WHO European Region, AMR stands as a substantial danger to public health, resulting in escalating healthcare expenditures, treatment ineffectiveness and fatalities. (2,3)

AMR can manifest across various microorganisms, encompassing fungi, parasites, viruses, and bacteria. Bacterial resistance is acquired through mutations in chromosomal genes, or the acquisition of external resistance genes transported by mobile genetic elements capable of horizontal transmission between bacteria. As a result, bacteria can accumulate multiple resistance mechanisms, limiting available treatment options for infections.

The primary driver propelling the emergence and dissemination of AMR is the utilization of antimicrobial agents and the transmission of antimicrobial-resistant microorganisms among humans, animals, and the environment. Antimicrobial usage exerts ecological pressure on bacteria, contributing to the emergence and selection of AMR. Meanwhile, suboptimal infection prevention and control (IPC) facilitate the further propagation of these bacteria. Therefore, proper use of antimicrobials and rigorous infection prevention and control protocols in all healthcare settings are components for addressing AMR. (4)

Acinetobacter species

Acinetobacter is a genus of gram-negative bacteria that includes various species. These bacteria are widespread in nature and can be found in soil, water, and on the skin of healthy individuals.

Acinetobacter baumannii typically demonstrates a narrower range of virulence, although it possesses the capability to adhere to surfaces, medical equipment, and personnel hands. Moreover, this species commonly colonizes various regions of patients' bodies, including the oropharyngeal, cutaneous, or gastrointestinal areas within 48 hours of ICU admission (5). The potential for *A. baumannii* to form biofilms enhances its survival in hospital settings. Specifically, genes associated with biofilm formation, such as ompA, bap, and blaPER-1, facilitate the organism's persistence (5). The special characteristics of these bacteria significantly contributes to the adhesion of ICU mechanical ventilators, often necessary for managing acute respiratory failure in recovering patients. While these devices improve patient outcomes, they also correlate with occurrences of *A. baumannii* ventilator-associated pneumonia (VAP). (5)

The prevalence of carbapenem-resistant *Acinetobacter species* exhibited significant variations within the WHO European Region in 2021. Data from 45 countries revealed that three (7%) countries: the Netherlands, Norway, and Sweden—reported percentages of carbapenem resistance below 1% for this microorganism. In contrast, 25 countries (56%) reported percentages equal to or exceeding 50%, being particularly high in southern and eastern Europe (2).

Klebsiella pneumoniae

Klebsiella pneumoniae is a gram-negative, rod-shaped bacterium that belongs to the family *Enterobacteriaceae*. *Klebsiella pneumoniae* is a common cause of bloodstream, urinary, and respiratory tract infections, with a notable risk of nosocomial outbreaks due to its easy transmissibility (6). The prevalence of third-generation cephalosporin resistance in *K. pneumoniae* has significantly increased throughout the WHO European Region. In the year 2021, data from 45 countries indicated that seven (16%) countries: Austria, Denmark, Finland, Iceland, Norway, Sweden, and Switzerland—reported AMR percentages below 10% for the microorganism. In contrast, 19 countries (42%), particularly in the southern and eastern regions, reported high AMR percentages of 50% or more (2).

Carbapenem resistance was frequently reported in *K. pneumoniae.* In 2021, the northern and western parts of the WHO European Region generally exhibited low percentages of AMR, with 14 countries (31% of the total 45) reporting percentages below 1%. However, 15 countries (33%) reported percentages equal to or exceeding 25%, and eight of these countries (18%) reported particularly high AMR percentages equal to or exceeding 50%. These countries include Belarus, Georgia, Greece, Moldova, Romania, Russia, Serbia, and Ukraine. (2)

Resistance can develop through increased efflux mechanisms, drug neutralization, or modifications in target site binding. A considerable number of *K. pneumoniae* strains either generate extended spectrum beta-lactamases (ESBLs) or create biofilms, intensifying the challenge of combating resistance. The antibiotic resistance in *K. pneumoniae* primarily manifests through five mechanisms: enzymatic inactivation and modification of antibiotics, alteration of antibiotic targets, loss and mutation of porins, increased expression of efflux pumps for antibiotics, and the formation of biofilms (7).

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a gram-negative, rod-shaped bacterium often harmless in healthy individuals. *Pseudomonas aeruginosa* is recognized as an opportunistic pathogen causing infections in individuals with weakened immune system.

P. aeruginosa is a frequent cause of hospital-acquired pneumonia, bloodstream infections, and urinary tract infections (8). The rates of carbapenem *P. Aeruginosa* vary significantly across countries in the WHO European Region. In the year 2021, data from 44 countries indicated that two (5%) countries: specifically, Denmark and Finland, reported AMR percentages below5% for this microorganism. In contrast, six countries (14%) reported percentages equal to or surpassing 50%, including Belarus, Georgia, Moldova, Russia, Serbia, and Ukraine. (2)

In general, the primary mechanisms used by *P. aeruginosa* to combat antibiotics fall into three categories: intrinsic, acquired, and adaptive resistance. Intrinsic resistance in *P. aeruginosa* is characterized by factors such as low outer membrane permeability, the expression of efflux pumps that expel antibiotics from the cell and the production of enzymes that deactivate antibiotics. Acquired resistance in *P. aeruginosa* can result from either the horizontal transfer of specific resistance genes or mutational changes. (9)

Escherichia coli

Escherichia coli, is a gram-negative, facultative anaerobic bacterium that predominantly inhabits the lower gastrointestinal tracts of warm-blooded organisms, including humans. While most *E. coli* strains are harmless and contribute to the normal function of the digestive system, certain pathogenic strains can cause various illnesses. *E coli* is the predominant cause of community-acquired bloodstream infections and urinary tract infections (10). In the year 2021, resistance to fluoroquinolones exhibited regional variations within the WHO European Region. Specifically, the lowest resistance rates were generally found in the northern and western parts, while the highest rates were prevalent in the southern and eastern regions. Among the 45 countries providing data on this microorganism, only two, namely Finland and Norway, reported an AMR percentage below 10%. In contrast, 17 countries (38%) reported AMR percentages equal to or exceeding 25%. Notably, four countries (9%), namely Cyprus, North Macedonia, Russia, and Türkiye, reported AMR percentages of 50% or higher (2)...

The increase of carbapenem-resistant *E. coli* raises significant alarm. In the year 2021, percentages of 1% or more were reported by eight countries (18% of the total 44) – being specifically high in Belarus, Cyprus, Georgia, Greece, Russia, Serbia, Türkiye, and Ukraine. (2).

One significant resistance mechanism of *E.coli* involves the production of beta-lactamase enzymes making it resistant to a broad range of beta-lactam antibiotics. These enzymes are capable of hydrolyzing extended spectrum cephalosporins and penicillin, making these antibiotics ineffective. (11)

Proteus Mirabilis

Proteus mirabilis, a gram-negative facultative anaerobe belonging to the *Enterobacteriaceae* family of bacilli with swarming motility and the ability to self-elongate and secrete a polysaccharide. This polysaccharide facilitates its attachment to and movement along surfaces such as catheters, intravenous lines, and other medical equipment and poses an increased risk of infection among patients in hospital settings, those with a history of recurrent infections, structural urinary tract abnormalities, or urethral instrumentation (12). P. mirabilis ranks as the third most prevalent causative agent overall and the second most common in catheter associated UTIs (CAUTIs) among patients with long-term catheterization (13). Specifically, it is implicated in approximately 12% of complicated UTIs (13). Elderly patients undergoing prolonged catheterization have the highest incidence rates of *P. mirabilis*-associated CAUTIs. Patients with hospital-acquired infections, a history of recurrent infections, structural abnormalities of the urinary tract, or urinary catheterization are at increased risk of developing *Proteus* infections.

Staphylococcus aureus

Staphylococcus aureus is a gram-positive, spherical bacterium and is a commensal bacterium commonly found on the skin and mucous membranes of humans and animals. *S. aureus* is an opportunistic pathogen when it enters body areas where it's not normally present causing infections primarily in the skin, bones and soft tissues (14). Some strains of *Staphylococcus* are referred to as Methicillin-resistant *Staphylococcus aureus* (MRSA) and have developed resistance to methicillin and other beta-lactam antibiotics. These resistant strains carry the mecA or mecC gene, for encoding a modified penicillin-binding protein, PBP2a. This altered protein has decreased affinity for beta-lactam antibiotics, resulting in resistance.

In the year 2021, MRSA percentages below 5% were reported in 11 (25%) out of 44 countries that provided data on S. *aureus*. Meanwhile, MRSA percentages equal to or exceeding 25% were reported in 13 (30%) countries (2).

Comparing MRSA rates across different ICUs is challenging due to varying surveillance methods, diagnostic criteria, and systems for assessing illness severity. Studies often show that ICUs exhibit the highest MRSA incidence, followed by surgical and medical wards, while community rates are typically lower. (15)

Enterococcus species

Enterococcal species make up around 6.1–17.5% of isolated strains from recovered patients in Europe, despite their initial presence in the human gut microbiota (16). These percentages primarily pertain to *Enterococcus faecalis* and *Enterococcus faecium*. They commonly cause urinary tract infections, systemic infections, endocarditis, or wound infections following surgical procedures. Additionally, *enterococci* have the potential to colonize medical devices, leading to catheter-related infections (17).

Enterococcus faecium is a gram-positive bacterium and is a facultative anaerobe able to thrive in both oxygenated and hypoxic environments. *E. faecium* is a constituent of the normal bacterial microbiota found in the human gastrointestinal tract. While it is generally mildly pathogenic, under certain circumstances, it can lead to severe diseases such as bloodstream infections, endocarditis, and peritonitis. The resistance to vancomycin in *E. faecium* varies across countries in the European region. In the year 2021, data from 44 countries revealed that six (14%) countries: Finland, France, Luxembourg, the Netherlands, Norway, and Sweden—reported percentages below 1% for this microorganism. On the contrary, 17 countries (39%) reported AMR percentages equal to or exceeding 25%, with five of them (11%of the total 44countries) reporting percentages equal to or exceeding 50%. These countries include Cyprus, Lithuania, Malta, North Macedonia, and Serbia (2).

Enterococcus faecium has developed multiple mechanisms of resistance that make the management of infections particularly difficult. Some prominent mechanisms are efflux pump utilization, plasmid transfer between *E. faecium* strains, biofilm formation and genetic mutations. *E. faecium* is well-known for acquiring resistance to vancomycin via the acquisition of specific genes (e.g., vanA, vanB, or vanC) that modify the structure of the bacterial cell wall, reducing its susceptibility to vancomycin. (18)

Fungal infections in the ICU

In critically ill patients, invasive fungal infections present a growing concern and are linked to increased morbidity and mortality rates. *Candida species*, particularly *Candida albicans*, is responsible for most of these infections (19). Invasive candidiasis includes candidemia, disseminated candidiasis involving deep organ penetration, and chronic disseminated candidiasis. Over recent decades, uncommon pathogenic fungi like *Aspergillus species, Zygomycetes, Fusarium species,* and *Scedosporium* have also been identified as significant contributors to invasive fungal infections.

Bloodstream infections caused by *Candida* represent the most common form of nosocomial fungal infections. According to a comprehensive nationwide surveillance study conducted in the United States, *Candida* species ranked fourth among hospital-acquired BSIs, accounting for 9% of cases, with most of these infections (51%) were observed in the intensive care unit setting. (19). Extended use of azole medications such, as fluconazole frequently prescribed for preventing and treating Candida infections in the ICU may lead to the development ofresistance in yeasts diminishing the effectiveness of the medication. This resistance, widespread, among Candida strains poses a growing concern that adds to treatment challenges.(20).

The majority of *Aspergillus*-related ICU infections are caused *A. fumigatus, A. flavus*, and *A. Niger*. In Western countries, the incidence is estimated to be around 15%, with an associated mortality rate of roughly 80% (20). Factors that increase the risk of developing aspergillosis among patients in the ICU include the use of high doses of corticosteroids and underlying conditions, like kidney failure, chronic obstructive pulmonary disease (COPD) and diabetes. Additionally common comorbidities observed in these patients are acute kidney failure, SIRS, COPD, and septicemia/shock.

MDR epidemiology in the ICU

According to reports from the European Centre for Disease Prevention and Control (ECDC) in 2022, the rate of *E.coli* resistance to fluoroquinolones and third generation cephalosporins exceeded 25% across Europe, with rates surpassing 50% in specific regions such as northern Macedonia, Russia, and Turkey. Similarly, resistance rates of *Klebsiella pneumoniae* to third-generation cephalosporins and carbapenems remain above 50% in comparable countries. Additionally, nearly all European countries report carbapenem resistance rates exceeding 50% for *Acinetobacter baumannii*. Methicillin resistance among *Staphylococcus aureus* is also documented to be over 25% in multiple European countries. (21)

A multicenter study on resistance involving centers from various income brackets found extended-spectrum β-lactamase producing gram-negative bacteria to have a reported rate of 72%, with a 44% rate of carbapenem resistance (21). *A. baumannii* has exhibited an alarming

90% MDR rate. Furthermore, research indicates a vancomycin resistance rate of up to 100% among *enterococci*, while the methicillin resistance rate among *S. aureus* was found to be 67%. In northeast Ethiopia, nosocomial infections caused by *Pseudomonas aeruginosa* and *A. baumannii* demonstrated an MDR rate exceeding 80%. Among ICU isolates in the United States, susceptibility to colistin among *K. pneumoniae* was reported to be 85%, with a 76% susceptibility rate to carbapenems among *P. aeruginosa*. (21)

Alongside MDR bacteria, *Candida species* are also becoming increasingly prevalent, with documented outbreaks of *Candida auris* resistant to multiple antifungal classes. A prospective cross-sectional study was conducted by the Infectious Diseases – International Research Initiative (ID-IRI), encompassing fifty-seven participating ICUs representing 24 countries, found that the incidence of *C. auris* fungemia was reported to be 17% among 157 ICU patients within one year, a substantial portion of whom had COVID-19. (22)

Intensive care units

Intensive care units (ICUs) play an important role in the healthcare system by providing specialized and advanced care to patients facing life-threatening illnesses or injuries. These critical care units offer around-the-clock monitoring, specialized medical interventions, and comprehensive support for patients requiring close attention due to the severity of their medical conditions. (23)

These patients often have severe medical conditions, such as trauma, organ failure, sepsis, respiratory distress, or post-surgical complications, requiring close observation and immediate access to advanced medical technology and expertise. While an ICU is physically situated within a specific area of a hospital, its operations often extend beyond the confines of its physical boundaries, encompassing the emergency department, hospital ward, and post-treatment clinic. (23)

ICUs are divided into three main levels: a Level 1 ICU is equipped to deliver oxygen, noninvasive monitoring, and heightened nursing care compared to a standard ward. Conversely, a Level 2 ICU can provide brief periods of invasive monitoring and fundamental life support. At the highest tier, a Level 3 ICU offers a wide range of monitoring and life support technologies for critically ill patients and may actively contribute to the advancement of intensive care through research and educational initiatives. Establishing a precise definition and a descriptive framework for ICUs serves to guide healthcare decision-makers in both planning and assessing capacity. (24)

Types of infections in the intensive care unit

In critically ill patients, infections are prevalent and often arise due to the severity of the patient's condition. Recent data shows that 51% of individuals in ICUs are affected, with 71% undergoing antimicrobial therapy (25). While bacterial infections are the primary concern, opportunistic fungal infections also occur. Infections significantly increase the mortality rate in ICUs (25).

Leading types of infections acquired in the ICUs include pneumonia, such as ventilator-associated pneumonia (VAP), surgical site infection (SSI), catheter-related bloodstream infection (CRBSI), and catheter-associated urinary tract infections (CAUTI).

Among patients hospitalized in the ICU for more than two days, annual epidemiological report from ECDC in 2019, revealed that 4% were diagnosed with pneumonia, 3% with bloodstream infection, and 2% with urinary tract infection (UTI). Notably, 96% of pneumonia cases were linked to intubation, 44% of BSI cases were catheter-related, and 94% of UTI cases were associated with urinary catheterization. The predominant microorganisms isolated were *Klebsiella spp*. in cases of ICU-acquired pneumonia, coagulase-negative *staphylococci* in cases of ICU-acquired bloodstream infections and *E.coli* in cases of ICU-acquired urinary tract infections (26). Blood stream infections are a common and potentially life-threatening occurrence in hospital environments. Critically ill patients are especially vulnerable to developing BSIs, with an incidence of approximately 7% within the initial month of hospitalization in the ICU. (27)

CRBSIs, defined as the presence of the same pathogen in both the catheter tip and peripheral blood culture, constitute approximately 30% of cases. Additionally, primary BSIs, making up about 35% of cases, are prevalent in ICUs. VAP, a common complication during mechanical ventilation, is associated with bacteremia in approximately 15% of cases and stands as the primary source of secondary bacteremia in critically ill patients. Secondary BSIs, primarily originating from lower respiratory tract and abdominal infections (including those evolving from urinary tract infections), constitute most BSI cases acquired either in the community or in the hospital, necessitating ICU admission (28,29). Infections such as bloodstream infections, pneumonia, surgical site infections, and other healthcare-associated infections have a higher impact on patients in the ICU compared to those in other healthcare settings. Reports indicate a global ICU infection rate ranging from 12% to 49%, with the median time to infection being around 4 days. Notably, a significant proportion of patients in the ICU typically experience the onset of infection within the first 6 days of admission. (30)

Ventilator-associated pneumonia

Ventilator-associated pneumonia is characterized by infection of the lung tissue in patients who have been subjected to invasive mechanical ventilation for a minimum of 48 hours and is categorized as a subset of ICU-acquired pneumonia (31). It remains among the most prevalent infections in individuals necessitating invasive mechanical ventilation. The incidence of VAP ranges widely from 5% to 40% in patients receiving invasive mechanical ventilation for over 2 days, with significant disparities depending on geographical location, ICU type, and the criteria used to diagnose VAP (32).

North American hospitals have reported relatively low rates, ranging from 1 to 2.5 cases per 1000 ventilator-days (33). Conversely, European centers have reported substantially higher rates, as evidenced by the EU-VAP/CAP study, which documented an incidence density of 18.3 VAP episodes per 1000 ventilator-days (33). The risk of VAP peaks between days 5 to 9 of mechanical ventilation, while the overall incidence is closely linked to the total duration of mechanical ventilation (34).

The causative organisms associated with VAP exhibit variability influenced by factors such as the duration of mechanical ventilation, length of hospital and ICU stays preceding VAP occurrence, timing and cumulative exposure to antimicrobials, local microbial ecology, and the potential for epidemic occurrences within a given ICU. Common gram-negative microorganisms implicated in VAP include *P. aeruginosa*, *E. coli*, *K. pneumoniae*, and various *Acinetobacter species*, while *S. aureus* predominates among Gram-positive microorganisms. (35,36)

Conventionally, early-onset VAP (manifesting within the initial 4 days of hospitalization) in previously healthy patients not receiving antibiotics typically involves the normal oropharyngeal flora. Conversely, late-onset VAP (occurring after at least 5 days of hospitalization) and VAP in patients possessing risk factors for MDR pathogens are more likely to be attributed to MDR organisms (37).

Catheter-related bloodstream infection

Catheter-related bloodstream infection occur when there is bacteremia originating from an intravenous catheter. This type of infection is a serious and costly complication linked to venous and arterial catheters and is the leading cause of nosocomial bacteremia (38).

Intravascular catheters are frequently used in practices especially in critically ill patients for administering fluids, medications, blood products, nutritional solutions and for monitoring hemodynamics. Among various types of medical devices, central venous catheters (CVCs) pose an increased risk of device-related infections and are significant contributors to morbidity and mortality rates. They serve as the primary source of bacteremia and septicemia among hospitalized patients (38).

The majority of CRBSIs are linked to CVCs, and prospective studies have revealed that the relative risk for CRBSI is up to 64 times greater with CVCs compared to peripheral venous catheters (38).

Every year around 250,000 people in the United States deal with bloodstream infections. It has been found that 60% of catheter related bloodstream infections occur due to microorganisms from patient's skin. CRBSIs frequently originate in emergency rooms and intensive care units, where there are reported occurrences of 5.3 bloodstream infections per 1000-days of central venous catheter insertion. (39,40)

The main pathogens responsible for CRBI are gram-positive bacteria, in particular *S. aureus* and coagulase negative staphylococci such as *S. epidermidis*, which is the most common. However, infections can be caused by a wide range of microorganisms including *Enterococci*, *Candida spp*, Acinetobacter *spp*, *Pseudomonas spp*, and *Klebsiella spp*. (41)

Catheter-associated urinary tract infection

Catheter-associated urinary tract infections are urinary tract infections occurring in individuals who have a urinary bladder catheter or have had one within the past 48 hours. They represent the most prevalent nosocomial infections, amounting to approximately 1 million cases annually in the United States (42). Additionally, they are the primary cause of secondary bloodstream infections. In the intensive care unit where infection rates are 3–5 times higher than in other hospital patient care areas, the incidence of CAUTI is 7.78 per 1000 catheter days (43). CAUTIs in ICUs are linked with prolonged lengths of stay, increased healthcare costs, and excessive use of antibiotics (44).

The main mechanism of colonization of catheters is via the production of biofilm. The pathogenic biofilm responsible for CAUTI can colonize either the inner (intraluminal infection) or outer (extraluminal infection) surfaces of a catheter. Gram-negative rods, especially, *E. coli*, are the most common type of isolated pathogens, with other bacteria and candida being less frequent (45).

Surgical site infection

As per the Centers for Disease Control and Prevention definition, surgical site infection refers to an infection associated with a surgical procedure, manifesting at or near the surgical incision within 30 days post-operation, or within 90 days if prosthetic material is implanted during surgery. SSIs represent one of the most common preventable complications following surgical procedures. They occur in approximately 2% to 4% of all patients undergoing inpatient surgical interventions. Notably, SSIs rank as the primary cause of hospital readmissions after surgery, and roughly 3% of patients who develop SSI do not survive. (46)

The specific pathogens responsible vary depending on the surgical procedure, with *S. aureus*, coagulase-negative *Staphylococci*, and *Enterococcus spp*. being the most frequently identified organisms. (46)

Antimicrobial stewardship

Definition

Stewardship, which involves the responsible management of entrusted resources was initially applied in healthcare to promote antimicrobial use, known as "antimicrobial stewardship". Over time, the concept of stewardship has expanded to encompass the broader governance within the health sector, involving the responsibility for the overall health and well-being of populations and guiding health systems on national and global scales. (47)

In today's healthcare environment, AMS constitutes one of the three integral "pillars" essential for an integrated approach to health systems strengthening. The other two pillars include IPC and medicine-patient safety. When combined with antimicrobial use surveillance and the World Health Organization's essential medicines list- Access, Watch, Reserve (AWaRe) classification, AMS plays a vital role in combating antimicrobial resistance by optimizing antimicrobial usage. (48)

The interconnectedness of these three pillars with other key components, such as AMR surveillance and ensuring a sufficient supply of quality-assured medicines, promotes equitable and high-quality healthcare, aligning with the goal of achieving universal health coverage.

Moreover, the principles of AMS also extend to the use of antimicrobials in the animal and agriculture sectors, emphasizing the responsible and sensible use of these agents.

AMS stands for the organized effort to educate and guide healthcare providers who prescribe antimicrobials promoting the use of evidence based prescribing methods. The main objective is to restrain antimicrobial overuse and, consequently, reduce the development of antimicrobial resistance. Since the late 1990s, AMS has been a coordinated initiative involving infectious diseases specialists in Internal Medicine and Pediatrics, alongside their respective peer organizations, hospital pharmacists, and the broader public health community. (49)

Initially implemented in hospital settings, AMS, within the United States, operated as voluntary self-regulation, relying on policies and appeals to encourage prescribing discipline among physicians. In 2017, the Joint Commission mandated hospitals to establish an Antimicrobial Stewardship team, and this obligation extended to outpatient settings in 2020. (50)

Core elements of antimicrobial stewardship programs

There are three core phases of the AMS programs, firstly, there is a comprehensive assessment of the patient's condition before treatment initiation. This evaluation includes reviewing infection indicators results, from examinations and any relevant laboratory test findings. Physicians must carefully consider patient and environmental factors to initiate the appropriate antibiotic therapy. The second phase emphasizes caution regarding drug toxicity, de-escalation of treatment when appropriate, and regular evaluation of the initiated therapy. Lastly, there is an emphasis on minimizing the duration of treatment, which can be viewed as a post-treatment consideration. Throughout these processes, strict adherence to infection control procedures is imperative, and ongoing feedback regarding the appropriateness of therapy and resistance patterns should be provided. (21)

In the ICU where the prevalence of resistant microorganism colonization and infection is increased as well as increased usage of antibiotics, it is important to decrease the resistance rates as patients admitted to the ICU face a significantly higher susceptibility to infections, ranging from 5 to 10 times greater compared to patients in non-ICU hospital settings (21). By implementing stewardship protocols alongside treatments there has been a noticeable decrease in inappropriate antibiotic use and a reduction in resistance rates especially when starting antibiotic therapy in ICUs. These measures help improve the critically ill patients and reduce spread of MDR organisms between patients in the ICU. (21)

Core measures of infection prevention and control programs

AMS and IPC are directly interconnected, and an integral part of IPC is to reduce the risk of healthcare-associated infections (HAIs) and reduce the emergence of antimicrobial resistance and therefore, infection control must be efficient. Implementing effective hygiene measures serves as the foundation for preventing the transmission of infections and managing disease outbreaks. The practice of effective infection control not only reduces the spread of diseases but also diminishes the necessity for antimicrobials. Inadequate infection control within any environment can significantly amplify the dissemination of drug-resistant infections, particularly during disease outbreaks. (52)

The selected IPC practices for the prevention of spread and emergence of AMR microorganisms is presented on Figure 1.(52):

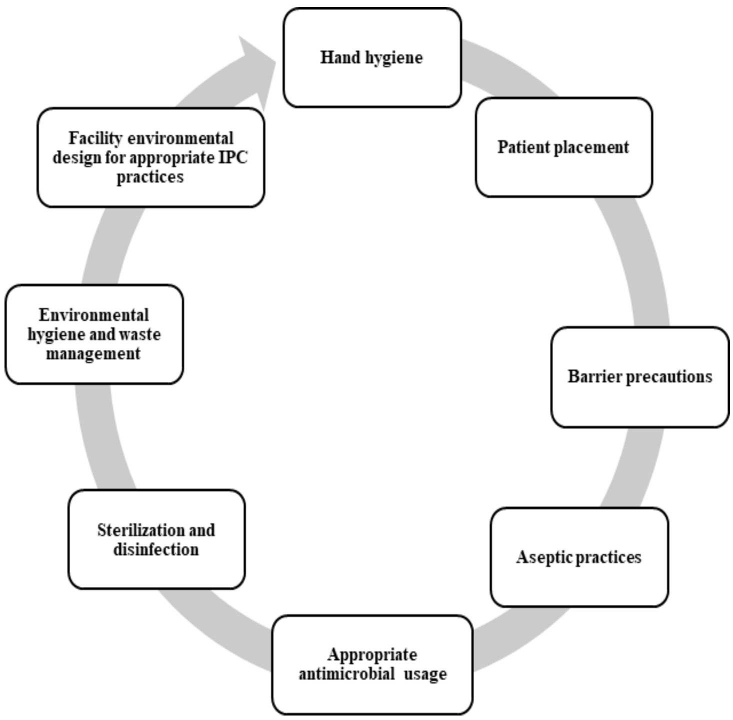

Figure 1: Core IPC features

Controlling the source of infection

Managing the source of infection involves a range of strategies aimed at preventing and minimizing the transmission of infectious agents. The concept of "source control" refers to the various physical interventions employed to manage a center of invasive infection and restore optimal functionality to the affected region. These measures can be categorized into three groups: drainage, which manages the liquid component of an infection by transforming a closed space infection into a controlled sinus or fistula; debridement, involving the physical removal of solid necrotic tissue and definitive measures, aimed at restoring optimal function to the affected area. (53)

The process of source control typically involves draining abscesses or infected fluid collections, debriding necrotic or infected tissues, and definitively managing the source of contamination. Early intervention for septic sources can be achieved through both operative and non-operative techniques, with operative intervention remaining the most viable therapeutic strategy for managing surgical infections in critically ill patients. (54)

Prescribing antibiotics when indicated

Strategies to enhance the sensible use of antibiotics in routine clinical practice and reducing the risk of bacterial resistance include implementing rapid microbiological diagnostics for prompt identification and susceptibility testing, utilizing inflammation markers to guide the initiation and duration of therapies, shortening standard durations of antibiotic courses, tailoring antibiotic therapies and dosages based on individual characteristics and pharmacokinetics/pharmacodynamics targets, and avoiding antibiotic classes associated with a higher risk of inducing bacterial resistance (55). It's essential to highlight the importance of focusing on enhancing prescribing practices and promoting stewardship initiatives. The key is to support decision making and enhance the prescription process by addressing any obstacles that may hinder effective prescribing methods. (56).

Selecting appropriate antimicrobials and rational usage

Adhering to specific guidelines when selecting and prescribing antibiotics is vital, by identifying the exact microorganism that is the cause of the infection, the proper antimicrobial can aid in the treatment against specific microbes. Appropriate antimicrobial treatment is defined as the utilization of at least one medication with in vitro activity against the causative pathogen(s) of the infection. (57)

Once a particular infectious agent has been identified through assessment it's crucial to monitor infection outcomes by examining laboratory results, inflammatory markers and the patient's overall condition. If there are no improvements in the patient's well-being or if inflammatory markers show no change or worsen, it suggests that either the prescribed antimicrobial is ineffective, an incorrect diagnosis has been made or further laboratory testing is necessary. (58).

Another important aspect is the timing for starting initial treatment which should be determined by the urgency of the situation. For critically ill patients, like those experiencing septic shock, febrile neutropenia, or bacterial meningitis, it's crucial to begin empiric therapy promptly, either immediately after or concurrently with obtaining diagnostic samples (58, 59). In less urgent cases, antimicrobial treatment should be deliberately postponed until appropriate specimens have been obtained and sent for analysis at the microbiology laboratory (58).

Following antibiotic duration guidelines

Every type of infection whether complicated or uncomplicated, has its own treatment recommendations tailored to the specific pathogen, clinical manifestations of the infection and patient age. Some antibiotics need to be taken a few times per day for weeks while others require less frequent dosing. Before administering an empiric antibiotic, the treatment guidelines must be reviewed and adhered. This will help preventing that antibiotics are taken too short or too long time and minimizes the risks of side effects and antimicrobial resistance. (58)

Reassessment after culture and sensitivity report

Since microbiological test results typically take 24 to 72 hours to become available, the initial treatment for infections is often empirical, based on the clinical presentation. Studies demonstrate that inadequate treatment for infections in critically ill, hospitalized patients leads to unfavorable outcomes, such as higher morbidity, mortality rates and longer hospital stays (58, 60). Consequently, a common strategy involves employing broad-spectrum antimicrobial agents initially, aiming to cover various potential pathogens linked with the specific clinical syndrome.

A microbial susceptibility report provides important information regarding the effectiveness of antimicrobial agents against specific pathogens. It outlines the susceptibility or resistance of a microbial isolate to various antibiotics, helping clinicians make informed decisions about appropriate treatment options for infections. (61)

This report is typically created following the isolation and identification of a pathogen from clinical specimens, such as blood, urine, trachea or wound swabs. Laboratory testing, including methods like agar diffusion or broth dilution, determines the susceptibility profile of the microorganism to different antibiotics. (61)

Interpretation of the susceptibility report involves understanding key terms such as "susceptible," "intermediate," and "resistant." The susceptibility of an organism to an antibiotic indicates that the drug is likely to inhibit its growth at standard dosage levels. Intermediate susceptibility suggests that the antibiotic may have limited effectiveness and should be used cautiously. Resistance implies that the microorganism is not inhibited by the antibiotic at achievable concentrations, making it ineffective for treatment. Additionally, the regular monitoring of resistance trends helps healthcare facilities adjust empiric treatment guidelines and make changes when needed, contributing to effective antimicrobial stewardship. (61)

AMR surveillance

AMR surveillance and monitoring serve to detect and monitor shifts and patterns in microbial communities, including those resistant to drugs, and the genetic components underlying resistance. Surveillance involves collecting, organizing, analyzing data and sharing it with relevant stakeholders. This surveillance can be conducted on a global, regional, local country, or healthcare facility basis. (62)

Educating staff

In order to prevent MDR organism emergence and spread, its essential that the staff is up-to-date and have the necessary knowledge and skills to prevent it. Education about aseptic practices, hand-hygiene and how to minimize the spread of infections in hospitals is vital. Physicians must be trained and educated about the various protocols and guidelines, so the inappropriate usages of antimicrobials minimize. (63)

Promotion of interdisciplinary strategy

Encouraging an interdisciplinary strategy in AMS involves advocating for collaboration across various fields and specialties to optimize antimicrobial use. This approach recognizes that addressing AMR requires efforts from various healthcare providers such as infectious disease specialist, clinical microbiologists, pharmacists, researchers, policymakers, veterinarians, pharmacists, agricultural experts, environmental scientists and other stakeholders. (63)

Inappropriate usage of antimicrobials

Prolonged empiric treatment

One of the most inappropriate treatment errors in antimicrobial usage involves persisting with the addiction or change of antibiotics even when a patient does not seem to respond to the treatment, despite lacking clear evidence of an infectious disease. It is important to note that many non-infectious, inflammatory, or neoplastic conditions can manifest with symptoms and signs resembling infectious diseases. Various illnesses can lead to a fever, making it challenging for doctors to decide whether antibiotics are necessary. For example, adult-onset Still disease and certain connective tissue disorders can present with high fever despite giving antibiotics (58).

In critically ill patients in the ICU presenting with elevated body temperatures, non-infectious causes account for around 3–52% of cases (64). Fever represents an adaptive response to physiological stressors, tightly regulated by endogenous pyrogenic and anti-pyretic pathways, and associated with an elevation in the hypothalamic set point. Therefore, fever may not invariably indicate the presence of an infection and thus antibiotics are not always indicated if there is no evidence of bacterial infection (64).

Failure to tailor treatment when causative organism is identified

While initial therapy is typically empirical, relying on broad-spectrum agents until culture or other tests establish the microbiological cause. Transition to a narrow-spectrum antibiotic once culture and susceptibility data are available is recommended. However, this transition often does not occur, especially if the patient has shown improvement with empirical therapy and the physician is hesitant to change treatment despite clinical progress (58).

Prolonged prophylactic treatment

In certain cases, infection can be prevented with prophylactic antimicrobial use (e.g., pre-surgical prophylaxis). However, guidelines generally recommend a single preoperative dose of an antimicrobial agent. Prolonged prophylaxis increases the risk of antimicrobial resistance development. For instance, the common practice of continuing antimicrobial therapy until surgical drains are removed lacks evidence-based support. (58)

Excessive usage of specific antibiotics

Overutilization of certain agents or classes of antimicrobials in healthcare settings can lead to the selection of resistant organisms. For instance, the widespread use of fluoroquinolones over the past decade has contributed to the emergence of fluoroquinolone-resistant strains of *C. difficile*, a common cause of nosocomial infectious diarrhea, especially in susceptible populations like the elderly. (58)

One of the essential ways to prevent excessive usage of antibiotics is antibiotic de-escalation. This encompasses various strategies intended to reduce antibiotic exposure, including opting for monotherapy over combination therapy, narrowing the antimicrobial spectrum, and conserving broad-spectrum antibiotics such as carbapenems and new beta-lactams. (65)

The initial step in de-escalation involves discontinuing antibiotics when there is no clear evidence of infection. While initiating antibiotics for suspected sepsis may be warranted, especially in cases of shock, ceasing antibiotic therapy once infection is ruled out is equally important. This necessitates the ability to confirm the absence of infection, which underscores the importance of obtaining adequate bacteriological samples before initiating antibiotic treatment. (65)

Implementation of antimicrobial stewardship program

A recent report released by the CDC indicates a significant increase in the number of U.S. hospitals implementing antibiotic stewardship programs that adhere to all recommended core elements. Between 2014 and 2017, the count nearly doubled to 3,816 hospitals. (61)

As of the latest report, more than 7,600 outpatient facilities have partnered with the Centers for Medicare & Medicaid Services' Quality Innovation Network-Quality Improvement Organizations to integrate all core elements of outpatient antibiotic stewardship, as advised by the CDC. Noteworthy resources include the CDCs toolkit from 2018 aimed at assisting hospitals in monitoring and improving usage for sepsis treatment. (67)

The responsibility for surveillance of resistance and sales of antibiotics in human medicine lies within the jurisdiction of Sweden's Public Health Agency (Folkhälsomyndigheten) supported by local and regional professionals. Information is routinely communicated to clinical microbiology laboratories, Strama groups, healthcare professionals, policymakers, and the media.

Sweden has been at the forefront in adopting a strategy for antimicrobial stewardship, across various sectors including veterinary medicine. The Strama initiative, which originated as a network in 1995 was formally established as a governmental entity in 2006. Collaborating closely with hospital stewardship programs, local Strama groups play an important role in formulating guidelines that are reviewed, analyzed and changed annually. (68)

Despite a surge in the use of antibiotics in hospitals the overall usage remains relatively low compared to other European countries with outpatient antibiotic consumption ranking among the lowest. (68)

France ranks among the European countries with the highest rates of outpatient antibiotic consumption (69). Over the past decade, France has implemented three national action plans (2001-2005, 2007-2010, and 2011-2016) aimed at safeguarding the efficacy of antibiotics. These efforts included a public awareness campaign called "Antibiotics are not automatic " which started in 2002 and led to a reduction of over 25% in antibiotic prescriptions per 100 individuals during its initial years (70).

The influence of antimicrobial stewardship in the intensive care unit

In ICUs, where the prevalence of resistant microorganism colonization and infection is elevated, antibiotic utilization tends to be correspondingly high. Implementing antimicrobial stewardship strategies is crucial to maintaining the effectiveness of antibiotics and addressing the emergence of pathogens in ICUs.

The key components of AMSs; controlling source of infection, rational antibiotic usage and proper selection, following guidelines and reassessment after culture and sensitivity report is established, tailored treatment and AMR surveillance are essential to implement to reduce the incidence of inappropriate antibiotic utilization and subsequent rates of antibiotic resistance. This is particularly important when initiating antibiotic treatment in the ICU where patients with the most severe infections can be treated in the most appropriate way.

Recent research suggests that there is a need for studies on stewardship. Current evidence shows that implementing programs in the ICU leads to use of antibiotics reduced rates of antibiotic resistance and fewer adverse events. However further research and increased public awareness about stewardship are necessary. Importantly, these benefits are achieved without compromising short-term clinical outcomes. (71).

Most systematic reviews indicate that the existing evidence on antimicrobial stewardship in critical care patients is predominantly derived from uncontrolled before-and-after studies conducted in individual ICUs. Studies have demonstrated significant heterogeneity concerning the outcomes evaluated and the interventions implemented in the ICU setting, ranging from antibiotic restriction to formal infectious diseases physician consultation and implementation of protocols for de-escalation and antibiotic prophylaxis or treatment. Despite this variability, several consistent trends have emerged. (71)

The majority of stewardship interventions have been linked to a reduction in either targeted or overall antibiotic usage among critical care patients. However, strategies that involve restricting the use of specific antibiotic classes have been associated with a compensatory increase in the utilization of unrestricted antibiotics, a phenomenon often referred to as 'squeezing the balloon'. Additionally, while most stewardship interventions have resulted in decreased resistance rates among key ICU pathogens after six months, policies focused on restriction have led to reduced susceptibility rates to unrestricted antibiotic agents. Consequently, active interventions, as opposed to passive restriction policies, may yield more favorable outcomes. (71)

There have been reductions in drug costs by approximately US$ 5–10 per patient day. However further cost effectiveness evaluations considering costs and savings are necessary to gauge their overall effectiveness. Various stewardship interventions have been correlated with shortened durations of antimicrobial therapy, although the impact on antibiotic appropriateness has been extensively studied and documented only in programs utilizing computer-assisted decision support. Similarly, adverse events have been evaluated primarily in the context of computer-assisted decision support programs, and the most crucial antimicrobial adverse event, *C. difficile* colitis, has not been adequately evaluated for any stewardship intervention in the ICU setting. (71)

Importantly, the reductions in antimicrobial utilization associated with stewardship interventions have not been linked to worsening nosocomial infection rates, prolonged length of stay, or increased mortality among intensive care patients. (71)

The future of antimicrobial stewardship measures

Looking ahead as the threat of multidrug microbes continues to grow it is essential to use antibiotics wisely to prevent the spread of more resistant bacteria.

Concerns are mounting over the rising levels of resistance in gram negative bacteria leading to the prevalence of multi drug resistant (MDR) and extremely drug resistant (XDR) pathogens (72). The presence of these bacteria in water sources and food supplies well as their colonization in patients and communities poses a significant risk for causing various infections.

Respiratory infections like pneumonia are particularly concerning due to their association with MDR and XDR gram bacteria often resulting in higher mortality rates (72)

Recent data from UNEP and WHO indicates that drug resistant infections directly caused 1.27 million deaths in 2019 and indirectly contributed to 4.95 million deaths. By 2050 it is estimated that, up to 10 million deaths annually could be attributed to drug resistant infections. (73)

Apart, from the loss of lives and disabilities AMR also brings about financial challenges. As per the World Bank AMR could result in a $1 trillion in healthcare costs by 2050 along with GDP declines ranging from $1 trillion to $3.4 trillion by 2030. (74)

In order to effectively slow down the emergence of MDR organisms, antimicrobial stewardship measures must be implemented in countries where resistance is high. This entails a systematic strategy aimed at educating and assisting healthcare professionals in adhering to evidence-based guidelines and protocols when prescribing and administering antimicrobials. The education of healthcare workers holds significant importance, as they serve as the primary guardians of antimicrobial efficacy. The WHO advises countries to establish and execute antimicrobial stewardship programs (ASP) as one of the most cost-effective measures to optimize antimicrobial use, enhance patient outcomes, and reduce antimicrobial resistance healthcare-associated infections. (73)

One avenue of advancement lies in the integration of advanced technologies, such as artificial intelligence (AI) and machine learning (ML), into ASPs. AI and ML algorithms can analyze large amounts of clinical data to provide real-time insights into antimicrobial prescribing patterns, identify trends in resistance patterns, and offer personalized treatment recommendations tailored to individual patient characteristics and pathogen profiles (75). By controlling the power of predictive analytics, ASPs can anticipate outbreaks, optimize empiric therapy selection, and minimize the risk of treatment failure due to antimicrobial resistance.

Moreover, the advent of rapid diagnostic technologies promises to revolutionize ASPs by enabling rapid pathogen identification and antimicrobial susceptibility testing at the point of care. Techniques such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and polymerase chain reaction (PCR) can provide clinicians with actionable information within hours, allowing for targeted antimicrobial therapy and de-escalation strategies. As these technologies become more accessible and cost-effective, they have the potential to enhance the timeliness and accuracy of antimicrobial decision-making in diverse clinical settings. (76)

Furthermore, the future of ASPs lies in fostering interdisciplinary collaboration and adopting a One Health approach that recognizes the interconnectedness of human, animal, and environmental health. By engaging healthcare providers, veterinarians, environmental scientists, policymakers, and other stakeholders, ASPs can address the complex factors driving antimicrobial resistance across different sectors and implement holistic strategies for AS. (77)

Conclusion

The emergence of multidrug resistant organism remains a public health concern with millions of people suffering the consequences of inadequate and inappropriate prescribing of antibiotics as well as the inappropriate usage in both the agricultural and veterinarian industry. The importance of adhering to up-to date guidelines and evidence-based studies emerging from annual surveillance of MDR organisms and their mechanism of resistance is essential to establish further changes that may be needed.

The AMS program is an essential and cost-effective tool in the fight against MDR organisms and emergence of new XDR organisms. Fewer antibiotics can fight against infections by XDR organisms and the production of new antibiotics that must undergo clinical trials are extensive. The AMS provides a cheap and evidence-based approach to reduce the emergence and the core elements are simple to follow by both physicians and other healthcare personnel. The battle against these organisms continues and the fight must be multidisciplinary across all different industries and sectors as this is a large-scale public health threat.

In the ICU, where infection rate is high, AMS provides a cost-effective way to reduce the emergence of infections caused by MDR organism which significantly impacts patient outcomes in the ICU, leading to delays in appropriate treatment, prolonged hospitalizations, increased healthcare costs, and the potential for outbreaks and clusters of infections. While stewardship interventions generally lead to decreased resistance rates among key ICU pathogens within six months, policies focused solely on restriction may inadvertently reduce susceptibility rates to other antibiotics. Therefore, active interventions are preferred over passive restriction policies for more favorable outcomes. Additionally, these interventions have demonstrated significant reductions in overall drug acquisition costs, showcasing their potential economic benefits alongside clinical advantages.

Looking ahead, the future of AS lies in interdisciplinary collaboration, technological advancements, and a One Health approach. Integration of artificial intelligence and rapid diagnostic technologies can enhance antimicrobial decision-making, while holistic strategies that involve healthcare providers, veterinarians, policymakers, and other stakeholders can address the complex drivers of AMR across different sectors.

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Biography

Amela Zjajo, born on the 23rd of April 1998 in Zenica, Bosnia and Herzegovina, grew up in Sweden where she finished her primary and secondary education with a focus on natural science. During her high school years, she participated in scientific and research projects and thus developed her passion for science and medicine. Before attending medical school at the University of Zagreb, School of Medicine, she completed a pre-medical course in Stockholm in January of 2018.

During her studies at the university, she received the Deans Commendation for the best 3rd year student in the academic year 2020/2021. In the same academic year, she received the Certificate of Excellence in Pathophysiology, awarded to students who demonstrated exceptional performance in the pathophysiology course.

With fluency in six different languages and valuable work experience with medical practitioners and patients, she all possesses the qualities, skills, and enthusiasm required to make a meaningful impact in the medical field.

In the summer of 2024, she will successfully graduate from medical school after completing her clinical rotations in Family Medicine in Sweden and plans on starting her career in the same field.