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Review

Antimicrobial stewardship in the intensive care unit

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ABSTRACT

High resistance rates to antimicrobials continue to be a global health threat. The incidence of multidrug-resistant (MDR) microorganisms in intensive care units (ICUs) is quite high compared to in the community and other units in the hospital because ICU patients are generally older, have higher numbers of co-morbidities and immune-suppressed; moreover, the typically high rates of invasive procedures performed in the ICU increase the risk of infection by MDR microorganisms. Antimicrobial stewardship (AMS) refers to the implementation of coordinated interventions to improve and track the appropriate use of antibiotics while offering the best possible antibiotic prescription (according to dose, duration, and route of administration). Broad-spectrum antibiotics are frequently preferred in ICUs because of greater infection severity and colonization and infection by MDR microorganisms. For this reason, a number of studies on AMS in ICUs have increased in recent years. Reducing the use of broad-spectrum antibiotics forms the basis of AMS. For this purpose, parameters such as establishing an AMS team, limiting the use of broad-spectrum antimicrobials, terminating treatments early, using early warning systems, pursuing infection control, and providing education and feedback are used. In this review, current AMS practices in ICUs are discussed.

Introduction

An important global health problem is multidrug-resistant (MDR) microorganisms in intensive care units (ICUs) and the infections caused by these pathogens.[1] Antimicrobial resistance and infections in the ICU are influenced by many different variables, including advanced age, immunosuppression, prolonged hospitalization, intense antibiotic treatments, and more invasive procedures.[2] Patients hospitalized in the ICU are 5–10 times more susceptible to infections than other patients outside the hospital.[3] Additionally, nosocomial infections caused by MDR bacteria increase morbidity and mortality rates and treatment costs and prolong ICU hospital stays.[4,5] One of the most crucial steps in preventing colonization and infection by MDR bacteria is to implement infection control procedures in the ICU.[6,7] However, the prolonged and frequent use of antibiotics in ICUs is one of the most significant factors contributing to the higher prevalence of MDR microorganisms in this setting.[8,9] By minimizing the incorrect use of antibiotics, antimicrobial stewardship (AMS) programs can help to minimize the development of antibiotic resistance, improve clinical outcomes, and lower healthcare costs.[1]

MDR Epidemiology in ICUs

The rate of MDR has been rising recently, particularly in ICUs. The emergence of pandrug-resistant bacteria has reduced the variety of treatments available to patients. The rate of *Escherichia coli* resistance to fluoroquinolones and third-generation cephalosporins was >25% across Europe overall in 2020 and >50% in certain areas, including northern Macedonia, Russia, and Turkey, according to 2022 reports from the European Centre for Disease Prevention and Control (ECDC). Resistance rates of *Klebsiella pneumoniae* to third-generation cephalosporin and carbapenem remain >50% in similar countries. Nearly all European nations report carbapenem resistance rates of >50% for *Acinetobacter baumannii*.[10] Methicillin resistance among *Staphylococcus aureus* is also >25% in many European countries.[11] The rate of extended-spectrum β-lactamase (ESBL) producing among Gram-negative bacteria was reported

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to be 72% in a multicenter resistance study that included centers from lower-middle-income, upper-middle-income, and high-income countries, while the rate of carbapenem resistance was found to be 44%. *A. baumannii* has also been found to have a 90% MDR rate.[11] Research indicates the rate of vancomycin resistance among enterococci is as high as 100%, while the rate of methicillin resistance among *S. aureus* was found to be 67% in the same study.[11] In northeast Ethiopia, nosocomial infections caused by *Pseudomonas aeruginosa* and *A. baumannii* were shown to have an MDR rate of >80%.[12] Susceptibility to colistin among *K. pneumoniae* was reported to be 85% in an antibiotic susceptibility investigation of 16,263 ICU isolates in the United States, and the rate of susceptibility to carbapenem was reported to be 76% among *P. aeruginosa*.[13]

Patients who are monitored in ICUs have significantly greater rates of bacterial resistance to medications, and resistance rates among patients who were monitored after having coronavirus disease 2019 (COVID-19) during the pandemic period were found to be even higher. The high co-morbidity burden of ICU patients during this time, the use of immunosuppressive therapies, and poor hand hygiene compliance are all considered to have contributed to the increase in resistance rates.[14,15] Together with MDR bacteria, *Candida* is becoming more prevalent as well. *Candida auris* outbreaks resistant to several antifungal classes have been frequently documented in recent years. The incidence of *C. auris* fungemia was reported to be 17% within 1 year among 157 ICU patients, of whom 59% had COVID-19.[16] Additionally, the prevalence of non-albicans *Candida* in ICUs has increased over the years.[17] According to reports, azole resistance in *C. albicans* detected in ICUs has grown over time.[18] There are additional contributing factors, such as differences in resistance rates between lower-middle-income and high-income countries, an inadequacy of infection control and prevention teams in low- and middle-income countries, and inadequacy in hand hygiene and isolation measures. In an increasingly connected world, the presence of MDR microorganisms poses a threat not only to developing countries but also to developed countries.[19]

What is AMS?

AMS refers to the use of coordinated interventions to improve and track the appropriate use of antibiotics while providing the best possible antibiotic prescription (including dose, duration, and route of administration).[20] A number of studies on AMS have emerged recently, at a time when the discovery of new antibiotics has slowed and the frequency of resistant microorganisms has been very high.[20] In AMS programs, there are three crucial phases; the first is a comprehensive evaluation of the patient's condition before treatment, considering the infection parameters, results of the physical examination, and any laboratory results. To start the right antibiotic, physicians should assess patient and environmental factors. The second step is to be careful when it comes to drug toxicity, de-escalation, and daily evaluation of an initiated treatment. The last step is to keep the treatment period short, which can be considered a post-treatment parameter. During all of these processes, infection control procedures should be followed, and feedback regarding therapeutic appropriateness and resistance rates should be provided.[21] AMS programs can be enacted for both community-acquired and hospital-acquired infections. AMS is especially significant in ICUs because of the density of MDR microorganisms in this setting.[22] Table 1 summarizes the parameters and timings of AMS procedures in the ICU.

Before Treatment

Know national guidelines and local resistance rates

Since 2015, AMS projects have been a World Health Organization (WHO) priority, and international action plans are currently being carried out.[23] Antibiotic resistance varies from country to country, hospital to hospital, and even patient to patient within a single ICU. Particularly in poor and developing countries, it is crucial to conduct national surveillance to determine antimicrobial resistance rates and establish national guidelines in accordance with these rates.[24] A national surveillance network was established in Brazil in 2018 in line with the WHO's global action plan, and it was reported that ESBL-producing *K. pneumoniae* is the second-most dangerous microorganism nationwide after *A. baumannii*.[25] Similarly, countries such as Uganda and South Korea have established a national surveillance network and published rates of causative microorganisms and antimicrobial resistance at the national level.[26,27] According to national surveillance data from ICUs in Egypt, the rate of carbapenem resistance among *E. coli, A. baumannii*, and *K. pneumoniae* increased between 2011 and 2017. The increase in the rates of nosocomial infections caused by carbapenem-resistant *K. pneumoniae* is also noteworthy.[28] In light of local data, a significant decrease in antibiotic resistance was demonstrated within 2 years in a trauma ICU where the empirical antibiotic therapy regimen was altered from piperacillin and tazobactam to imipenem–amikacin therapy.[29] Many international guidelines include the step of taking local resistance rates and risk factors into account in treatment protocols.[30] When European and USA hospital-acquired pneumonia and ventilator-associated pneumonia (VAP) guidelines are compared, differences in empirical antibiotic protocols among treatment recommendations can be seen; for example, in the USA guideline, inhaled antibiotics are recommended in cases of unresponsiveness to basic treatments, while, in the European guideline, they are recommended as first-line therapy.[31]

Evaluate patient-specific factors and evaluate possible pathogens

In ICUs, there is a significant rate of colonization with MDR bacteria. Patients with specific risk factors and those who receive more interventions are also at greater risk of infection by these bacteria. When empirical treatment is initiated in these individuals while taking the risk factors into account, a significant impact on clinical response and mortality can be expected.[32] A meta-analysis of 3627 patients and 16 clinical studies investigating risk factors for carbapenem-resistant *K. pneumoniae* infection identified 16 different risk factors, including a longer length of stay (LOS) in the hospital; admission to the ICU; previous hospitalization; more days spent in the ICU; having received a transplant; use of steroids, central venous catheters, and mechanical ventilation; the presence of a tracheostomy; parenteral nutrition; prior antibiotic use; and exposure to carbapenems, amino-

Table 1
AMS parameters and timing for use in the ICU.

Timing	Parameters*
Before treatment	Know national guidelines and local resistance rates
	Evaluate patient-specific factors (catheter use, immunosuppression, colonization, etc.)
	Evaluate possible pathogens
	Do not use antibiotics as a treatment tool for high fever
	Shorten the time to diagnosis
During treatment	Consider pharmacokinetic and pharmacodynamic properties
	Provide source control
	Daily assessment of clinical symptoms and culture results of infection
	Discontinue antibiotics at the appropriate time and de-escalation
After treatment	Use automatic early warning systems
	Cooperate and communicate

AMS: Antimicrobial stewardship.
* The infection control procedures should be followed, and the feedback should be provided during these processes.

glycosides, glycopeptides, quinolones, and anti-pseudomonal penicillins.[33] The administration of fluoroquinolones, a history of hospitalization, cephalosporin use, and piperacillin–tazobactam use were identified to be significant risk factors for MDR *P. aeruginosa* infection. Exposure to carbapenem and vancomycin was found to be a risk factor for infections brought on by these microorganisms.[34] In a multicenter study in which risk factors for hospital-acquired MDR *A. baumannii* infection were determined, advanced age, days of mechanical ventilation, presence of a central catheter, presence of cancer, staying in the ICU for >15 days, and use of third-generation cephalosporins were documented.[35] The presence of a central catheter, the presence of nephropathy, a history of hemodialysis, the use of vancomycin or carbapenem, and a history of vancomycin-resistant enterococcus colonization were reported as the main risk factors for vancomycin-resistant enterococcus infection caused by Gram-positive microorganisms.[36,37]

Immunosuppressive patients are always at risk in terms of colonization and infection by resistant microorganisms.[38] Because mortality may be high in these patients, early diagnosis and treatment are even more important. Other risk factors include advanced age, co-morbidities, and the presence of a foreign body — such as a central catheter, urinary catheter, or mechanical ventilator.[34,35,37–39] Risk factors for infection by resistant microorganisms commonly seen in ICUs are shown in Table 2. Analyzing the risk factors for MDR bacteria and *Candida* infections reveals that the majority of them are similar; for example, major risk factors include advanced age, antibiotic exposure, and a history of prolonged hospitalization. In this context, empiric treatment should be planned based on the patient's understanding of these risk factors, the potential focus of infection, a past infection or colonization agent, antibiotic susceptibility, and the flora of the ICU where the patient is being monitored.[37,38]

Do not use antibiotics as a treatment tool for high fever

In ICU patients with high fevers, the origin of the fever is non-infectious in 3–52% of cases.[33] Fever, also known as pyrexia, is an adaptive reaction to a physiologic stressor that is closely regulated by endogenous pyrogenic and anti-pyretic pathways and is related to an increase in the hypothalamic set point.[46] Therefore, fever may not always be a sign of infection. Especially at temperatures exceeding 41 °C, there is a pathological increase that is not related to the hypothalamic adjustment center. These criteria are also valid for laboratory parameters. Findings such as an elevated C-reactive protein level and white blood cell count without signs of infection should not be considered an indication to start antibiotics.[33] Acute infections, including those due to *Coronaviridae* and other viruses, often stimulate a febrile response. In these patients, mostly unnecessary antibacterial treatments are administered.[47] It is important to evaluate patients comprehensively as a whole entity. Also, daily assessment of patients for alternative diagnoses and discontinuing empiric antimicrobials if a non-infectious cause is demonstrated is suggested. The causes of non-infectious fever in the ICU are shown in Table 3.

Shorten the time to diagnosis

The patient should be carefully examined, and a microscopic examination and culture should be obtained from the potential infection focus to speed up the diagnosis. After the infection focus has been detected, revealing Gram-staining features of the microorganism during microscopic examinations will be useful in empirical treatment.[32] Apart from this, not every positive culture result is an indication to start antibiotics. Colonization with resistant microorganisms and *Candida* is very common in ICUs. Isolation of *Candida* in a urine culture usually does not require antifungal therapy.[48] Other positive colonization results should also be evaluated together with the patient's clinic and other acute-phase reactants.[49] Additionally, accurate culture sampling algorithms must be established for use in ICUs to avoid contamination.

Another method to shorten the time to diagnosis is the use of rapid molecular tests. Within hours of a positive test result, molecular diagnostic procedures, such as polymerase chain reaction, microarray technology, fluorescent in situ hybridization (FISH), or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS), can identify an organism and, in some cases, test its susceptibility to an antibiotic by looking for known genetic resistance determinants (such as *K. pneumoniae* carbapenemase).[49] For example, it was found that MALDI-TOF-MS could make an accurate diagnosis 21.5 h earlier than Vitek 2 (BioMérieux, Inc., Marcy-l'Étoile, France) in a 2-year study that compared the times required for each instrument to detect the causative microorganism.[50] A bundle program, in which MALDI-TOF-MS was used as one of the rapid

Table 2
Risk factors for infection and colonization by MDR microorganisms in the ICU.

Microorganism	Risk factors
MDR *K. pneumoniae*[33,40]	Long-term hospitalization
	History of ICU admission
	Transplant patients
	Corticosteroid use
	Presence of a central venous catheter
	Mechanical ventilation
	Tracheostomy
	Parenteral nutrition
	Exposure to anti-pseudomonal penicillins, carbapenems, glycopeptides, aminoglycosides, and quinolones
	Continuous renal replacement therapy
MDR *P. aeruginosa*[34,41]	Quinolone exposure
	Having a history of hospitalization
	Cephalosporin and piperacillin tazobactam exposure
	Total parenteral nutrition
	Carbapenem exposure
MDR *A. baumannii*[35,42]	Carbapenems and penicillins + β-lactamase inhibitor exposure
	Advanced age
	History of hospitalization
	Corticosteroid use
VRE[36,37,43]	VRE colonization
	Vancomycin exposure
	Third-generation cephalosporin exposure
	Presence of a central venous catheter
	History of hemodialysis
MRSA[44]	MRSA colonization
	Age >65 years
	Trauma or medical patient
	Transferred from a long-term care facility
	Presence of a urinary catheter
	Previous antibiotic exposure
	Skin/soft tissue infections or superficial skin infections after surgery
Colistin resistance[45]	Increased age
	Prior antibiotic use
	Pre-admission stay in a skilled nursing facility
	Use of carbapenems within the last 90 days
	Previous carbapenem-resistant bacterial infection
	History of ventilatory support
Candida spp.[39]	Acute necrotizing pancreatitis
	Abdominal surgery and anastomotic leak or repeat laparotomy
	Exposure to broad-spectrum antibiotics
	Presence of a central venous catheter
	Hematopoietic stem cell transplantation
	Immunosuppression with chemotherapy and corticosteroids
	Hemodialysis
	Multifocal *Candida* colonization
	Prolonged ICU stay
	Total parenteral nutrition
	Low birth weight

ICU: Intensive care unit; MDR: Multidrug-resistant; MRSA: Methicillin-resistant Staphylococcus aureus; VRE: Vancomycin-resistant enterococcus.

Table 3
Non-infectious causes of high fever in patients monitored in the ICU.

High fever (38–41 °C)	Hyperthermia (>41 °C)
Drug reaction	Drug reaction, such as malignant hyperthermia, neuroleptic malignant syndrome and serotonin syndrome
Venous thromboembolism	Endocrine, such as thyrotoxicosis, adrenal crisis and Ppeochromocytoma
Pulmonary embolism	
Central nervous system	Environmental heat stroke
Subarachnoid hemorrhage	
Pancreatitis	Viral infections, such as COVID-19, SARS, MERS, German measles, influenza, rabies
Systemic lupus erythematosus	
Malignancy	
Transfusion reactions	

COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; MERS: Middle East respiratory syndrome; SARS: Severe acute respiratory syndrome.

molecular diagnostic methods to target the early treatment of MDR Gram-negative microorganisms, was also found to be effective in terms of rapid diagnosis and earlier initiation of the correct treatment.[51] Using the microarray and FISH methods, the infectious agent can be identified from direct blood samples within 0.5–1 h in cases of bloodstream infections.[52] This period is also very short compared to that required for MALDI-TOF-MS to work. With the use of rapid diagnostic methods in ICUs, the appropriateness of empirical treatment can quickly be evaluated, allowing time to be saved in the revision of treatment. In this way, the broad-spectrum antibiotics started as part of empirical treatment can be altered appropriately, and unnecessary antibiotic use can be prevented.

Another method used to initiate treatment in the early period is daily procalcitonin monitoring. During the COVID-19 pandemic period, intensive antibiotic use was also observed in ICUs where patients with a diagnosis of COVID-19 were treated. Inappropriate antibiotic treatment was prevented by performing C-reactive protein and procalcitonin tests at admission and during follow-up of these patients.[53] In an observational study comparing the effect of initiating antibiotics and using procalcitonin in the discontinuation of treatment in surgical patients treated in the ICU, a significant improvement in both total antibiotic density and the antimicrobial spectrum was observed.[54] Furthermore, the initiation and termination of procalcitonin-guided treatment in severe sepsis patients do not change the mortality rate or the LOS.[55] For this reason, the use of procalcitonin together with the patient's clinical findings is recommended in the sepsis diagnosis and treatment guide at both the beginning and end of treatment, with a low level of recommendation.[56]

During treatment

Consider pharmacokinetic and pharmacodynamic properties

It is important to consider whether the antibiotics depend on time activity or concentration activity when determining the appropriate dose in patients being monitored in the ICU.[32] Antibiotics from the β-lactam group, which are often used in ICUs, have a time-dependent efficacy and require dose modification. A loading dose is needed for both time- and concentration-dependent antibiotics to reach an effective plasma concentration.[32,56] The presence of pleural effusion, ascites, high fluid therapy, edema, post-surgical drains, hypoalbuminemia, and extracorporeal membrane oxygenation treatments require high-dose antibiotics as there may be limitations in fluid volume or the binding of antibiotics. Antibiotic dose adjustments are necessary as antibiotic clearance will increase in patients using certain drugs or those with burns or sepsis.[21] Lipophilic antibiotics are more likely to reach less vascularized and/or injured tissues, have a greater volume of distribution (Vd), can penetrate cells and be more effective against sensitive intracellular infections, and are metabolized in the liver. Conversely, hydrophilic agents are typically excreted unchanged through renal clearance, have a smaller Vd and more limited cell penetration, are less active against intracellular pathogens, and may not reach effective concentrations in less irrigated tissues.[32] When determining dosage, liver and renal function must be taken into account.

Appropriate dosage adjustments are important to limit side effects and drug interactions. Even if the appropriate therapy is started in the ICU, there is a risk that antimicrobial resistance will develop because of patient-related factors, other treatment-related factors, and difficulties in modifying the optimal dose. When carbapenems or β-lactam/β-lactamase inhibitor combinations were separately evaluated in a recent meta-analysis of randomized controlled trials comparing prolonged and intermittent infusions of antipseudomonal β-lactams in patients with sepsis, the prolonged infusion was associated with better survival.[57] In some patients, those who underdose on β-lactams using intermittent administration or those with infections caused by isolates with high minimum inhibitory concentrations may require prolonged infusions. Because these features cannot be anticipated, it seems reasonable to consider the use of prolonged infusions of sufficiently stable antipseudomonal β-lactams in all patients with sepsis.[58] Table 4 summarizes the antibiotics that are frequently used in ICUs, along with their pharmacokinetics, pharmacodynamics, and typical dose amounts.

Provide source control

Drainage, debridement, device removal, compartment decompression, and frequently delayed definitive restoration of anatomy and function are the concepts of source control to eradicate infectious foci.[2] Source control, if required, improves outcomes more so than early, effective antimicrobial therapy[59] and should never be considered "covered" by broad-spectrum agents. Because the effectiveness of source control is time-dependent, appropriate procedures should be carried out as soon as possible for patients who are experiencing a septic shock.[2,60] When organ failure persists or occurs despite resuscitation and the provision of appropriate antimicrobial therapy, the failure of source control should be taken into consideration. This requires urgent (re)imaging as well as repeated or alternative interventions. In the surgical site infection and intra-abdominal infection guidelines, it is stated that source control is absolutely necessary to prevent infection.[61] Making source control a priority will help clinicians decide how long the patient needs to take antibiotics.[61] Bloodstream infections associated with central catheters are another type of nosocomial infection frequently observed in ICUs, and the most crucial recommendation in the guidelines for managing these infections is the removal of the infected catheter.[62,63]

Daily assessment of clinical symptoms and culture results

Patients in ICUs are engaged in a highly dynamic process. Even during the day, daily clinical changes, the introduction of foreign bodies, re-infections, and new colonizations can occur. For this reason, the evaluation of patients' clinical and laboratory data should be completed daily, and treatment plans should be created in accordance with these evaluations.[32] In a pediatric ICU, after rates of the initiation of new antibiotics and positive blood culture results were examined, 49% of the 174 blood culture cases with positive results showed antibiotic changes. The time taken to learn the culture result and start a new antibiotic treatment was 6 h 35 min on average.[64] Appropriate antibiotic use and mortality in bacteremic patients were investigated in a prospective study in which the clinical, laboratory,

Table 4
Pharmacodynamic and pharmacokinetic characteristics and dosing of antibiotics commonly used in the ICU.

Antibiotic	Pharmacodynamic	Pharmacokinetics	Dosing (with normal hepatic and renal function)
Piperacillin/tazobactam	T > MIC	Hydrophilic, renal clearance	4.5 g every 6 h
Ceftazidime	T > MIC	Hydrophilic, renal clearance	6 g every 24 h
Cefepime	T > MIC	Hydrophilic, renal clearance	2 g every 8 h
Aztreonam	T > MIC	Hydrophilic, renal clearance	1 g (2 g) every 8 h
Meropenem	T > MIC	Renal clearance	1 g (2 g) every 8 h
Tigecycline	AUC/MIC	Hepatic and renal clearance	100–200 mg loading dose, then 50–100 mg every 12 h
entamicin	C_{max}/MIC	Hydrophilic, renal clearance	7 mg/kg/day every 24 h
Amikacin	C_{max}/MIC	Hydrophilic, renal clearance	25–30 mg/kg/day every 24 h
Colistin	AUC/MIC	Hydrophilic, renal clearance	9 MU loading dose, then 4.5 MU every 8–12 h
Fosfomycin	AU/MIC for Gram negatives, T > MIC for Gram Positives	Hydrophilic, hepatic clearance	4–6 g every 6 h CI
Vancomycin	AUC/MIC	Renal clearance	15–30 mg/kg loading dose, then 30–60 mg/kg every 12 h
Linezolid	AUC/MIC	Lipophilic, hepatic clearance	600 mg every 12 h
eftaroline	T > MIC	Hydrophilic, renal clearance	600 mg q12 h, IV
Ceftobiprole	T > MIC	Hydrophilic, renal clearance	500 mg q8 h IV
Ceftazidime/avibactam	T > MIC	Hydrophilic, renal clearance	2.5 g q8 h IV
Ceftolozane/tazobactam	T > MIC	Hydrophilic, renal clearance	1.5 g q8 h/3 g q8 h
Meropenem/vaborbactam	T > MIC	Hydrophilic, renal clearance	2 g/2 g q8 h

AUC: Area under the receiver operating characteristic curve; ICUs: Intensive care units; IV: Intravenousinjection; MIC: Minimum inhibitor concentration; T: Time.

and culture results of patients using antibiotics were monitored daily by the AMS team. Accordingly, it was determined that access to the appropriate antibiotic for bloodstream infections was faster and the de-escalation rate was higher in patients when they were evaluated compared to those not being evaluated by the team. Additionally, the implementation group was found to have lower 30-day mortality rates from bloodstream infections and antibiotic adverse effects.[65] Both the AMS team and the ICU staff should regularly examine patients being monitored in the ICU because they are at risk for various infections.

Discontinue antibiotics at the appropriate time and de-escalation

One of the basic steps in AMS practice is the de-escalation of empirically initiated broad-spectrum antibiotics according to daily patient evaluation and culture results.[21] Overly broad-spectrum treatment with longer antibiotic courses (7–14 days) may increase the incidence of adverse events such as *Clostridium difficile* infections and the cost of healthcare without necessarily improving patient outcomes.[66,67] In a study evaluating 26,598 patients followed in the surgical ICU with lung, abdominal, and urinary tract infections, patients with and without antibiotic de-escalation were compared, and no increase in mortality was observed in the de-escalated patient group.[68] To reduce adverse events and healthcare-associated infections, antibiotic therapy should be de-escalated and its duration should be limited. Recent clinical research and meta-analyses on prevalent infectious diseases have demonstrated that shorter treatment periods are just as effective as longer treatment periods.[69,70] In the DURAPOP randomized controlled trial, which evaluated 410 patients with intra-abdominal sepsis followed in the ICU, it was found that short-term antibiotic therapy (8 days) more significantly decreased antibiotic exposure compared to long-term antibiotic therapy (15 days); however, it was also reported that no increase in mortality was observed.[71]

Biomarkers such as procalcitonin can also be used to determine the duration of treatment. In a randomized controlled prospective study of 1575 patients treated in the ICU in which the duration of treatment was determined by serum procalcitonin level, short- and long-term treatment periods were compared; as a result, the average length of procalcitonin-assisted therapy decreased from 7 days to 5 days, and the usage of antibiotics also decreased concurrently.[72]

In a randomized controlled multicenter study evaluating PCT-guided antibiotic therapy in patients with sepsis, the duration of treatment with the PCT-based treatment plan was 4 days less than that achieved with the standard treatment. Despite this, the 28-day clinical cure rate, hospital mortality rate, and ICU and hospital stay lengths were not different between the two groups.[73]

In many randomized controlled studies comparing long- and short-term treatments in the context of pneumonia, intra-abdominal infection, or bacteremia and urinary system infections, no difference was observed in terms of outcomes.[71–73] For this reason, in the current sepsis guideline, it is recommended to determine the duration of treatment and to terminate the treatment early by using biomarkers such as procalcitonin after the source control is ensured and the patient is stabilized.[74] De-escalation and early termination of treatment recommendations

have, as their primary objective, the immediate termination of patient exposure to broad-spectrum antibiotics. In this way, collateral damage attributed to antibiotics can be minimized.

After Treatment

Use automatic early warning systems

One of the important AMS policies in ICUs is automated early warning systems. Antibiotic stop-orders in ICUs promote re-evaluation of the clinical state and the therapeutic response. A review of laboratory, microbiological, and diagnostic imaging reports is provided in a certain context. Re-evaluating the need to continue, change, or discontinue helps to promote safe and rational drug use by preventing unreasonable and long-term drug use.[75] A significant decrease in antibiotic use rates was attributed to an AMS program focused on neonatal sepsis, where a warning is given to terminate the empirical treatment after 36 h.[76] A significant decrease in neonatal antibiotic exposure was also reported after automatic antibiotic stop-order administration in very-low-birth-weight infants.[77] In a pediatric ICU, a 48–72-h antibiotic time-out was observed for vancomycin, meropenem, and piperacillin/tazobactam, with a significant reduction in the use of these antibiotics.[78] With these warning systems, the antibiotic exposure is reduced as a result of evaluating the suitability of antibiotics, discontinuing unnecessary antibiotics, or replacing them with narrow-spectrum antibiotics.

Cooperate and communicate

Reducing the unnecessary use of antibiotics in ICUs cannot be achieved by any single person. From the beginning to the end of the treatment course, everyone involved in treating the patient should adopt a collective consciousness. Ideally, the AMS team consists of a physician and clinical pharmacist with infectious diseases expertise as well as key stakeholders in clinical care, infection control, and patient safety and quality. While the infectious diseases doctor is responsible for the initiation and follow-up of treatment in the ICU, the intensive care specialist is responsible for removing invasive instruments, ensuring source control, determining the clinical pharmacist antibiotic doses and drug interactions, overseeing nurse drug administration, determining the causative microorganism by clinical microbiology, and integrating data processing personnel with the early warning system. An infection control physician or epidemiologist should also be part of the team to inform on the local epidemiology using hospital surveillance at the beginning of empirical antibiotics administration. The typical members of the AMS team in an ICU include infectious diseases physician, clinical pharmacist, infection control professional, clinical microbiologist, hospital epidemiologist, intensive care unit physician, information system specialist and nurse. These team members can also perform collaborative work, such as providing training on infection control measures, giving feedback on the results, and preparing treatment guides.[79]

Infection Control and Feedback

The basis of AMS in the ICU is infection control given that the majority of bacteria we detect as nosocomial infectious agents in ICUs are transmitted by contact.[80] The basis of the success of AMS is the reduction of antibiotic resistance. The importance of infection control is increased by the fact that ICUs are where resistant microorganisms are most frequently encountered. For this reason, routine surveillance is carried out in ICUs, and compliance with infection control measures is observed 24/7. An evaluation of compliance with hand hygiene, employing bundle applications in infection control, and providing feedback on these results are important for the control of resistant microorganisms and the success of AMS.[7,81] According to the ICU design, staff compliance, and sustainability, a bundle can be applied to prevent VAP, central catheter-associated bloodstream infections (CLABSIs), and catheter-related urinary system infections.[7] The rate of VAP occurring in the late period after bundle application decreased from 31% to 13.5% in an adult ICU when the bundle was administered for the prevention of VAP.[81] The

Table 5
Some AMS protocols used in ICUs and their outcomes.

Study	ICU	AMS protocols	Outcomes
Johansson et al., 2011[87]	General ICU	Antimicrobial consumption Hygiene precautions	Improvement in antibiotic use
Hou et al., 2014[88]	General ICU	Antimicrobial consumption Antibiotic stop-order	Reduced antibiotic consumption Significantly improved antibiotic resistance
Ruiz et al., 2017[89]	Medical ICU	Antimicrobial consumption Feedback	Reduced antimicrobial use
Kitano et al., 2019[90]	Neonatal	Daily antimicrobial management Antibiotic stop-order Weekend report of blood culture result	Significantly reduced antimicrobial prescriptions
Jones et al., 2019[91]	Pediatric ICU	Piperacillin–tazobactam consumption AMS team Positive feedback	Broad-spectrum antimicrobial consumption
Devchand et al., 2019[92]	Mixed medico-surgical ICU	Electronic medical records 5 “moments” of antimicrobial prescribing (escalation, de-escalation, discontinuation, switch, and optimization)	High clinician compliance with recommendations Improved rates of choosing the right antibiotic
Quirós et al., 2022[93]	Multicenter, medical ICU	Antimicrobial consumption, appropriateness of antimicrobial treatments, crude mortality, and MDR-resistant microorganisms in healthcare-associated infections	Significant improvement in antimicrobial utilization

AMS: Antimicrobial stewardship; ICUs: Intensive care units; MDR: multidrug-resistant.

CLABSI rate decreased from 4.7 to 1.4 per 1000 catheter days in 2 years in an adult ICU following treatment with a bundle designed for the prevention of CLABSI.[82]

The epidemic emergence of resistant microorganisms in ICUs can be rapidly identified and controlled through education, source identification, and source control due to infection control and surveillance procedures. An MDR *P. aeruginosa* outbreak from an infected sink,[83] an MDR *A. baumannii* outbreak[84] with an environmental origin, and an *A. baumannii* outbreak[85] caused by bronchofiberoscopy ended in the ICU after infection control procedures were introduced. The design of ICUs is also an important parameter to curb the spread of resistant microorganisms. The number of nosocomial infections due to resistant microorganisms decreased after patients were treated in single rooms and positioned in such a way that hand-washing units were easily accessible.[86] Some AMS protocols used in ICUs and their outcomes are shown in Table 5.

Conclusions

In ICUs, where resistant microorganism colonization and infection rates are high, the usage of antibiotics is concomitantly high. To decrease resistance rates, fewer broad-spectrum antibiotics should be used. The use of AMS during antibiotic treatment has a significant impact on decreasing inappropriate antibiotic use and antibiotic resistance rates when initiating antibiotics in the ICU.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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