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# The issue of antibiotic-resistant bacterial infections in intensive care units (ICUs) – epidemiology, risk factors and prevention. Literature review

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**Abstract**

**Introduction**

Infections caused by antibiotic-resistant pathogens in intensive care units (ICUs) present significant diagnostic, therapeutic, economic and preventive challenges. The increasing antibiotic resistance is becoming a widespread phenomenon in hospital wards. Patients in intensive care units, due to their severe general condition, frequent invasive procedures and widely used antibiotic therapy, are a group particularly vulnerable to the spread of nosocomial infections. This article reviews the current state of knowledge on antibiotic resistance, risk factors, prevention and epidemiology of infections caused by drug-resistant pathogens in intensive care units.

**Aim of the Study:**

The aim of this study was to summarize the current state of knowledge on antibiotic resistance, risk factors, epidemiology and available methods of preventing healthcare-associated infections (HAI) in patients in intensive care units (ICUs).

**Materials and Methods:**

The literature available in the PubMed database was reviewed using the following keywords: "antibiotic resistance", "intensive care unit", "multidrug-resistant bacteria", "infection control", "risk factors", "epidemiology".

**Conclusions:**

The number of hospital-acquired infections (HAI) caused by antibiotic-resistant pathogens, particularly Gram-negative bacteria, is continuously increasing. The key to preventing HAI is a rational system of antimicrobial management. Adherence to hand hygiene, personnel control regarding basic contact norms with patients and minimizing other known risk factors can lead to a reduction in the spread of antibiotic-resistant pathogens. Additional prospective studies are justified to better understand the profile of carriage, spread, and prevention of drug-resistant infections in intensive care units (ICUs).

**Keywords:** antibiotic resistance, multidrug-resistant bacteria, risk factors, infection control, intensive care units.

**Introduction:**

Patients in intensive care units (ICUs) are particularly vulnerable to infections with pathogens resistant to multiple antibiotics [1]. It is estimated that about 9-20% of patients in intensive care units are affected by healthcare-associated infections (HAIs) and half of all hospital-acquired infections occur in the ICU [2]. Moreover, even 45-51% of them experience some form of infection [3]. Due to the aging population, intensified medical and caregiving procedures, an increase in the percentage of underlying diseases and the continuous spread of MDR pathogenic microorganisms, a constant increase in healthcare-associated infections (HAIs) is expected [4]. With the broad application of broad-spectrum antibacterial drugs, the incidence of multidrug-resistant (MDR) bacteria in intensive care units (ICUs) is increasing annually [5]. It is estimated that infections with drug-resistant microorganisms will result in >10 million deaths in the next 30 years [6].

**Resistance groups**:

MDR in its definition refers to bacteria resistant to 3 or more classes of antibiotics [7]. MDR includes: (ESBL) Enterobacterales with extended-spectrum β-lactamase, (CRE) carbapenem-resistant Enterobacterales, (MRSA) methicillin-resistant Staphylococcus aureus and VRE vancomycin-resistant Enterococcus [8]. XDR refers to extensive drug resistance, meaning insensitivity to at least one antibiotic in each group. PDR refers to pan-drug resistance, meaning insensitivity to all drugs in all classes of antimicrobial agents [9].

**Mechanisms of resistance:**

**Genetic changes.** The genetic material of bacteria can undergo modifications, resulting in changes in protein production and the acquisition of other components of bacterial receptors. This resistance determinant contributes to the limitation of the effectiveness of current drugs [10].

**Acquired resistance.** Genetic mutations allow bacteria to process their own or acquired genetic material [10].

**Intrinsic resistance.** Bacteria often possess inherent structural resistance determinants, preventing the action of specific antibiotics. For example, the lack of a cell wall excludes the effect of penicillin, whose mechanism of action focuses on this structure of microorganisms [10].

**Genetic material transfer.** Bacteria can share components of genetic material that possess resistance traits. Known methods include conjugation, transduction and transformation of genetic material [10].

**Epidemiology in intensive care units (ICUs):**

In recent years, there has been a significant increase in the share of Gram-negative bacteria in the pathogenesis of drug-resistant infections. These include beta-lactamase-resistant (ESBL) Klebsiella pneumoniae, Proteus mirabilis, Escherichia coli; methicillin-resistant Staphylococcus aureus (MRSA); vancomycin-resistant Enterococci (VRE); beta-lactamase-resistant Enterobacter spp. and Citrobacter spp. and MDR Mastrofilia. Furthermore, attention should be given to the importance of infections associated with the anaerobic group Clostridium difficile spp. and fungal infections [1]. Analysis of infection data in the intensive care units of the Clinical Hospital in Wrocław from 2011-2018, recorded a significant increase in the number of "Alert Pathogens" from 34.6% in 2011 to 61.0% in 2018 [3]. The Care-EPIC study demonstrated a predominance of infections caused by Gram-negative bacteria (31.1%). The most common were Enterobacteriaceae infections (34.4%), Pseudomonas aeruginosa (28.7%) and Acinetobacter baumannii (9%). The dominant pathogens were Gram-negative bacteria (62%). The MRSA rate in this study was 10.2% [11]. The EPIC III study revealed that 54% of infected patients were in the ICU, with 22% of infections acquired in these units. GNB were the most common pathogens among ICU patients (67%) [12].

The frequency of infections caused by carbapenem-resistant Gram-negative bacteria in intensive care units ranges from 25.2% to 47% [13].

The actual trend, both in Poland and globally, is an increase in carbapenem-resistant non-fermenting bacilli. An increase in the percentage of carbapenem-resistant strains from 53.4% A. baumannii and 27.6% P. aeruginosa in 2014 to 67.4% and 24.2% respectively in 2017 was noted in Poland. The EARS-Net study also revealed an upward trend in the incidence of carbapenem-resistant strains of A. baumannii and P. aeruginosa in the analyzed period. In European intensive care units, a significant increase in multidrug resistance (MDR) of GNB strains such as A. baumannii, P. aeruginosa, K. pneumoniae is observed, with a clear dominance of A. baumannii [14-15].

The most frequently isolated groups of pathogens in HAI were GNB (71.4%). In VAP and UTI, there was a clear predominance of GNB. In the case of CLA-BSI infections, a comparable number of GNB and GPB were distinguished [3].

A large international study from 2009 found that Acinetobacter species were responsible for 8.8% of Gram-negative bacterial infections in intensive care units worldwide (with a significant prevalence in Asian ICUs). A study from a Turkish hospital also highlights an intensive increase in carbapenem-resistant bacteria in the intensive care unit from 2017-2021. For example, an increase in infections associated with A. baumannii (from 96% to 100%), K. pneumoniae (from 49% to 79.6%) and P. aeruginosa (from 45.8% to 100%) [16].

**Risk factors:**

It is believed that significant predictors of MDR infection or colonization in ICU patients include: initial number of bacterial infections, multiple invasive procedures, length of hospital stay (LOS) and low Hb levels [17]. Another study showed that risk factors for infections include: male sex, CRP level and Pitt score results [18].

Studies highlight the occurrence of chronic diseases as potential risk factors for infections with drug-resistant bacteria. The impacts of diabetes, chronic renal failure, chronic pulmonary failure, cancers and autoimmune diseases were examined.

They may carry an increased likelihood of MDR infections in patients. It is difficult to definitively state whether the listed diseases were independent or complex risk factors and further, more detailed studies are required [19]. Another study confirms that increased infection risk is associated with exposure to: antibiotics (mainly carbapenems), invasive procedures (catheterization, mechanical ventilation), exposure to hospital conditions in the ICU [16]. Moreover, previous colonization, intubation, tracheostomy and use of CVC increase CRGNB infections [20]. Attention is also drawn to the initial poor general condition of patients, comorbidities and previous intravenous antibiotic use. The study shows that these factors are associated with the increased occurrence of resistant bacterial infections [21].

The gastrointestinal tract is a reservoir for the largest number of microorganisms causing HAI [22]. Intestinal-origin GNB are the most common cause of VAP. Intubation provokes the passage of these pathogens and indirectly causes upper respiratory tract infections [23]. Colonization of the rectal area by GNB is a risk factor for respiratory tract colonization and a source of new infections in intensive care units [24].

A known risk factor for drug-resistant infections is neutropenia lasting >7 days. Such patients require isolation [25].

The influence of nutritional aspects on ICU infections has also been studied. Enteral feeding tube and enteral nutrition can lead to CRGNB transmission to the intestines and the development of infections associated with these pathogens [26].

The percentage risk of developing Gram-negative bacterial infections during central catheter use has been demonstrated. The use of CVC in ICU patients is associated with an increased risk of CRGBB infection (81.9% in patients with CVC and 64.6% in patients without CVC) [16].

Another important aspect is the prior use of quinolones. They are a risk factor for acquiring MDR or XDR P. aeruginosa infection [27]. In turn, antibiotic therapy affects a 2.5-fold increase in the risk of K. pneumoniae infections producing carbapenemases [28]. Another study shows that the use of carbapenems compared to the control group in the ICU is associated with more frequent CRKP infections (73.2% vs. 52.9%) [29]. Combined antibiotic therapy is an independent predictor of CR-GNB infection in intensive care units. Combined antibiotic treatment disrupts the microbiota and allows the survival of resistant strains [30].

The relationship between the number of hospitalizations of a given patient and the duration of their stay in the hospital's intensive care unit (ICU) seems important. They may become key factors influencing the colonization of multidrug-resistant microorganisms. Hospitalization lasting more than 5 days in the last 3 months prior to hospital readmission increases the risk of MDR pathogen infection. [31]. Any hospital stay, especially in the intensive care unit, is a significant risk factor for acquiring MDR or XDR P. aeruginosa bacteria [27].

Respiratory therapy lasting more than 7 days is a predictor of CR-GNB infections in ICU patients [30]. The lungs of patients undergoing respiratory therapy differ in microbiota composition from the lungs of non-ventilated patients, which may be a risk factor for pneumonia [33].

**Prevention and methods of reducing the spread of infections caused by multidrug-resistant pathogens**

Attention is drawn to the most important healthcare strategies that can slow the spread of multidrug-resistant microorganisms. These include : diagnosing infections, careful and rational use of antibiotics and eliminating possible infection transmission routes [1].

It is important that appropriate antibiotic management and infection treatment programs are developed in hospital structures. They should be based on: microbiological research and testing technologies based on molecular methods, staff education, prospective audits, feedback and clear guidelines [10].

Important aspects of proper antibiotic management are addressed by the Infectious Diseases Society of America (IDSA). These include: limiting the use of antibiotics by establishing specialist permits and appointing responsible individuals for their implementation; developing clinical and therapeutic pathways based on local microbiota and resistance patterns; using feedback and involving the doctor throughout the therapeutic process; improving and de-escalating therapy to eliminate unnecessary combination therapy; optimizing antibiotic doses considering pharmacodynamics, pharmacokinetics of the drug and the site of infection; developing clinical pathways allowing, if it possible, the conversion of parenteral drugs to oral drugs [10].

**MRSA:** The use of oral vancomycin in intensive care units with a high incidence of MRSA (universal or targeted decolonization), resulted in reduced pathogen presence in samples from patients under study. This action reduced carriage from 89% to 62% and limited urinary tract infections (UTI) and lower respiratory tract infections. However, such practices may increase the occurrence of vancomycin-resistant enterococci outbreaks [34]. Another large study highlighted the role of topical mupirocin in reducing MRSA occurrence. Nasal mupirocin use along with chlorhexidine body washing reduced positive MRSA cultures by 36%. Additionally, there was a 45% decrease in any bacteremia (including pneumonia caused by S. aureus) in intensive care units (ICUs) [35].

**SDD and SOD:** Selective decontamination of the digestive tract in ICU patients can reduce ventilator-associated pneumonia. Elimination of Enterobacteriaceae from the intestines and oral cavity (SDD and SOD) was associated with reduced mortality and decreased ICU stay duration. [36-37] A Dutch study showed that SDD or SOD is not associated with increased MDR infection and mortality. Moreover, this strategy reduced total intravenous antibiotic use by 10% and limited the incidence of MDR-GNB outbreaks [38]. Another large meta-analysis emphasizes the effectiveness of using SOD, SDD with intravenous antimicrobial agents, reducing HAI infections and MDRO carriage [39].

**Hand hygiene:** The World Health Organization (WHO) emphasizes proper and frequent hand hygiene as a priority in eliminating pathogen transmission. The five moments of hand washing principle in patient contact is a simple and effective method of limiting pathogen spread in patient interactions [40]. In a European study, improved hand hygiene supervision and additional chlorhexidine baths significantly reduced MRSA cases and shortened ICU stays [41].

Studies show that hand hygiene standards are not always adhered to in intensive care units. On average, 40-60% of ICU staff comply with proper hand hygiene [42]. Another study determining the average hand hygiene time and percentage of disinfection set these values at 6.8 seconds and 42.6%, respectively, significantly deviating from the norm (assuming 30 seconds of hand hygiene time per WHO recommendations) [43]. Additionally, wearing personal items such as jewelry and having artificial nails contribute to microorganism spread [44].

**Skin antisepsis with chlorhexidine gluconate solution:** The use of chlorhexidine gluconate for skin disinfection significantly reduced bloodstream infections associated with central venous catheter (CLABSI) and MRSA in intensive care units (ICUs) [45]. Furthermore, daily 2% chlorhexidine baths limited VRE and other antibiotic-resistant pathogen transmission in ICU patients. Similarly, this practice reduced CLABSI infection rates [46]. In Chung et al.'s study, chlorhexidine baths achieved a reduction in A. baumannii infections in a high-endemic ICU [47]. Moreover, chlorhexidine reduced bloodstream infections caused by multidrug-resistant Acinetobacter, but its impact on reducing Gram-positive bacteremia was questionable [48].

**Diagnostics:** Screening for identifying carriers/reservoirs of antibiotic-resistant pathogens (especially MDR and XDR) and their isolation or decontamination can interrupt the spread of these microorganisms [49]. Rapid diagnostic methods such as MALDI-TOF mass spectrometry play a crucial role in effective pathogen detection and can influence the de-escalation time of broad-spectrum antibiotic therapy. Smaller studies show a clear correlation between screening programs for resistant Gram-negative bacteria and the reduction of transmission and clinical infections in ICU [50]. Another study evaluating the impact of rapid PCR screening and isolation of patients infected with antibiotic-resistant pathogens did not significantly reduce the acquisition of resistant Gram-negative bacteria in ICU [51]. Conversely, a large study by Huskins et al. compared the benefits of screening and isolation procedures for MRSA and VRE carriers with a control group not subjected to these measures. The study did not show a difference in the acquisition rates of both pathogens between the groups. The cause is considered to be the long wait time for screening results [52].

**Isolation:** The isolation of patients who are carriers of antibiotic-resistant pathogens, according to some clinical models, appears to be an effective method [53-54]. An effective element in the event of a sudden large number of epidemic-like infections in intensive care units is contact isolation, which limits further escalation [55]. A breakthrough occurred in a study conducted in Israel, where a significant decrease in hospital infection transmission was observed through active surveillance and isolation of patients in ICU [56]. An interesting aspect worth noting is empirical isolation. In cases of suspected infection or colonization of patients in intensive care units (ICUs) (with symptoms characteristic of upper respiratory tract infections), isolation limited the spread of pathogenic microorganisms while waiting for diagnostic results [49]. The downside of this procedure could be its costliness and labor-intensiveness. Additionally, the number of patients with antibiotic-resistant pathogen carriage is continuously increasing, potentially overwhelming the logistical capacities of ICU [53-54].

Other researchers assessing transmission risk in a study aimed at examining the cross-transmission risk of MRSA among non-isolated patients questioned the rationale for reporting cultures and isolating colonized patients [57].

**Limiting the transmission of antibiotic-resistant bacteria in the ICU environment:**
It is crucial to thoroughly disinfect equipment shared by patients in ICU or use disposable substitutes to reduce the risk of multidrug-resistant pathogen transmission. Additionally, knowing that a patient is infected with an antibiotic-resistant bacterium should prompt special attention to careful disinfection or disposal of equipment used with that patient [49]. VRE's ability to survive on steel and plastic surfaces is determined to be up to 28 days (the duration of the study) [58]. Another study revealed the persistence of K. pneumoniae on plastic and steel for 5-6 days. Knowing the survival time of multidrug-resistant bacteria on hospital surfaces prompts a more careful approach to antiseptic measures [49]. Promising study results come from using ultraviolet light and hydrogen peroxide vapors in disinfecting bacterial pathogens and fungal spores in ICU conditions. Both methods reduced pathogen incidence by disinfecting areas inaccessible to medical staff [59]. Attention should also be given to the potential transmission of Pseudomonas, Aeromonas and Sphingomonas bacteria through plumbing systems. Despite uncertain study results, cleaning and replacing plumbing systems can reduce the risk of multidrug-resistant pathogen transmission in ICU [60].

**Personal protective equipment (PPE):** The use of PPE such as gowns and gloves reduced MRSA-related infections in intensive care units (ICU) [61].

**CVC:** When inserting a CVC, to reduce infections, it is recommended to: avoid punctures in the femoral/groin area, adhere to hand hygiene, use barrier PPE, disinfect with chlorhexidine solution and remove unnecessary catheters [62].

**Antibiotic therapy strategies:** The strategy of rotating empirical antibiotics (after a certain period or with each subsequent patient) in intensive care units does not have unequivocally proven positive effects on reducing microbial resistance to antibiotics. Study results are divided and lack unified methodology [63-66]. Optimization and duration of empirical antibiotic therapy based on cultures and clinical assessment reduce the risk of multidrug-resistant infections and Clostridium difficile. Broad-spectrum antibiotic therapy lasting 7-14 days often did not positively affect the treatment outcomes of microorganisms [67-68]. De-escalation of antibiotic therapy reduced mortality in surgical patients and those in intensive care units due to pneumonia, abdominal infections, or urinary tract infections [69]. Increasing Gram-negative bacterial resistance forces clinicians to use at least two antibiotics with different action schemes in the empirical treatment of infections, especially in areas with high GNB resistance [70].

## Conclusions

The key to preventing HAI is implementing a uniform control system and establishing rational antimicrobial management [1]. Measures such as adhering to hand hygiene, using chlorhexidine and personnel control regarding basic patient contact norms can limit the spread of antibiotic-resistant pathogens. Additional prospective studies are justified to better understand the carriage profile, spread and prevention of antibiotic-resistant bacterial infections in ICU [49].

## Author's contribution

Conceptualization, Maciej Choiński; methodology, Maciej Choiński and Anna Marszałek; software, Aleksandra Wydra-Rojek and Katarzyna Kutyła; check, Aleksandra Łakoma and Paulina Wasiewicz-Ciach; formal analysis, Maciej Choiński and Marcelina Teresa Marzec; investigation, Maciej Choiński and Marcelina Teresa Marzec; resources, Aleksandra Wydra-Rojek and Weronika Zofia Marzec; data curation, Wojciech Jan Mokot, Anna Marszałek; writing – rough preparation, Maciej Choiński; writing - review and editing, Maciej Choiński and Piotr Kuczyński; visualization, Maciej Choiński, Weronika Zofia Marzec and Paulina Wasiewicz-Ciach; supervision, Aleksandra Łakoma, Piotr Kuczyński and Wojciech Jan Mokot; project administration, Maciej Choiński and Katarzyna Kutyła. All authors have read and agreed with the published version of the manuscript.

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