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Antybiotykooporność: wieloaspektowe podejście do globalnego wyzwania współczesnej medycyny

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Antibiotic resistance: a multifaceted approach to a global challenge of modern medicine

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STRESZCZENIE W JĘZYKU POLSKIM

SŁOWA KLUCZOWE:
antybiotyki; oporność na antybiotyki; antybiotykoterapia; leki przeciwdrobnoustrojowe, bakterie wielolekooporne

Oporność na antybiotyki jest globalnym wyzwaniem zdrowotnym, mającym znaczące konsekwencje dla systemów opieki zdrowotnej, szczególnie w intensywnej terapii i leczeniu wstrząsu septycznego. Synteza trzech opublikowanych badań podkreśla skalę problemu, jego znaczenie kliniczne oraz potencjalne strategie zaradcze.

W pierwszym badaniu przeanalizowano dane literaturowe w celu scharakteryzowania wyzwań związanych z opornością na antybiotyki na oddziałach intensywnej terapii (OIOM), szczególnie w leczeniu sepsy. Bakterie Gram-ujemne, takie jak *Acinetobacter baumannii*, *Pseudomonas aeruginosa* i *Klebsiella pneumoniae*, cechują się alarmująco wysokim poziomem oporności, co utrudnia stosowanie standardowych terapii. Infekcje wywołane przez oporne patogeny prowadzą do wyższej śmiertelności, wydłużonego czasu hospitalizacji i większych kosztów opieki zdrowotnej. Kluczowe czynniki ryzyka obejmują nadużywanie antybiotyków o szerokim spektrum działania, niedostateczne środki kontroli zakażeń oraz procedury inwazyjne. W badaniu wskazano na potrzebę wdrożenia kompleksowych programów zarządzania antybiotykami, rygorystycznych działań zapobiegających zakażeniom oraz poszukiwania alternatywnych terapii.

Drugie badanie skupia się na postrzeganiu oporności na antybiotyki przez personel medyczny, wskazując, że 55% pracowników służby zdrowia uznaje ją za bardzo poważny lub skrajnie poważny problem globalny, przy czym świadomość ta jest szczególnie wysoka wśród lekarzy i pielęgniarek. Do kluczowych czynników przyczyniających się do problemu zaliczono nieodpowiednie stosowanie antybiotyków w rolnictwie, profilaktyczne przepisywanie leków oraz presję pacjentów na wypisywanie antybiotyków. Pomimo tej świadomości, wśród personelu medycznego wciąż występują luki w wiedzy, co podkreśla potrzebę ukierunkowanych inicjatyw edukacyjnych. W artykule zwrócono również uwagę na znaczenie programów zarządzania antybiotykami na poziomie szpitalnym w celu racjonalizacji ich stosowania i ograniczenia oporności.

W trzecim badaniu skoncentrowano się na klinicznej skuteczności dwóch kombinacji inhibitora beta-laktamazy i antybiotyku beta-laktamowego: imipenemu/cilastatyny/relebaktamu (IMI/REL) oraz piperacyliny/tazobaktamu (PTZ) w leczeniu wstrząsu septycznego wywołanego przez patogeny MDR, wskazując na porównywalną skuteczność badanych leków w zmniejszaniu śmiertelności. Patogeny szpitalne, takie jak *Pseudomonas aeruginosa* i *Acinetobacter baumannii* cechowały się znaczną wielolekooporność. Analizy genetyczne wskazały na produkcję karbapenemaz jako kluczowy mechanizm oporności, co podkreśla potrzebę wdrożenia szybkich narzędzi diagnostycznych i terapii dostosowanych do profilu drobnoustroju. W badaniu zwrócono uwagę na potencjał innowacyjnych połączeń antybiotyków w poprawie wyników leczenia wstrząsu septycznego.

Opisane badania jednoznacznie podkreślają pilną potrzebę wieloaspektowego podejścia do zwalczania oporności na antybiotyki. Kluczowe zalecenia obejmują monitorowanie trendów oporności i profili patogenów, racjonalne praktyki przepisywania antybiotyków, podnoszenie świadomości wśród personelu medycznego i pacjentów na temat odpowiedzialnego stosowania antybiotyków, inwestycje w szybkie narzędzia diagnostyczne i programy zarządzania antybiotykami. Integracja tych strategii umożliwi redukcję rosnącego obciążenia systemu opieki zdrowotnej opornością na antybiotyki, poprawę wyników leczenia pacjentów i zabezpieczenie skuteczność istniejących terapii przeciwbakteryjnych.

SUMMARY IN ENGLISH

KEYWORDS:
antibiotics; antibiotic resistance; antibiotic therapy; antimicrobial drugs; multidrug-resistant bacteria

Antibiotic resistance represents a critical global health challenge, with significant implications for healthcare systems, particularly in intensive care and septic shock management. A synthesis of three studies highlights the scope of the problem, its clinical impacts, and potential strategies for mitigation**.**

In the first study the literature review was made to characterize challenges of antibiotic resistance in intensive care units (ICUs), particularly in the management of sepsis. Gram-negative pathogens such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* are highlighted for their alarmingly high resistance rates, complicating treatment protocols. These infections result in increased mortality, prolonged hospital stays, and higher healthcare costs. Key risk factors include the overuse of broad-spectrum antibiotics, inadequate infection control measures, and invasive procedures. The study advocates for comprehensive antimicrobial stewardship programs, rigorous infection control measures, and the exploration of alternative therapies to combat the rise of resistant strains.

The second study focuses on medical staff perceptions of antibiotic resistance, revealing that 55% of healthcare professionals recognize it as a very or extremely serious global issue, with heightened awareness among physicians and nurses. Contributing factors include inappropriate antibiotic use in agriculture, prophylactic prescriptions, and patient pressure to prescribe antibiotics. Despite their awareness, knowledge gaps persist among medical staff, underscoring the need for targeted educational initiatives. The study also emphasizes the importance of hospital-level antibiotic stewardship programs to rationalize antibiotic use and reduce resistance.

The third study focused on the clinical efficacy of two combinations of a beta-lactamase inhibitor and a beta-lactam antibiotic: imipenem/cilastatin/relebactam (IMI/REL) and piperacillin/tazobactam (PTZ) in the treatment of septic shock caused by MDR pathogens, indicating that the tested drugs were comparably effective in reducing mortality. Nosocomial pathogens, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, display significant multidrug resistance. Genetic analyses reveal carbapenemase production as a key resistance mechanism, necessitating rapid diagnostic tools and tailored therapeutic approaches. The study highlights the potential of innovative antibiotic combinations to improve clinical outcomes in septic shock cases.

Together, these studies underline the urgency of addressing antibiotic resistance through a multifaceted approach. Key recommendations include enhancing surveillance to monitor resistance trends, implementing rational antibiotic prescribing practices, educating medical staff and patients about responsible antibiotic use, and investing in infrastructure and policies to support antibiotic stewardship. By integrating these strategies, healthcare systems can mitigate the growing burden of antibiotic resistance, improve patient outcomes, and safeguard the efficacy of existing antimicrobial therapies.

OMÓWIENIE PUBLIKACJI WCHODZĄCYCH W SKŁAD ROZPRAWY DOKTORSKIEJ

Na rozprawę doktorską pt. „Antybiotykooporność: wieloaspektowe podejście do globalnego wyzwania współczesnej medycyny" składa się cykl trzech powiązanych ze sobą tematycznie artykułów opublikowanych w międzynarodowych czasopismach naukowych indeksowanych w bazie PubMed. Łączny Impact Factor prac wynosi 4,3, natomiast punktacja ministerialna to łącznie 110 punktów.

Pierwszy artykuł stanowi systematyczny przegląd literatury zatytułowany **„Problems of antibiotic resistance in sepsis in intensive care units: A review of current research".** Oporność na antybiotyki jest jednym z najpoważniejszych wyzwań współczesnej medycyny, szczególnie w kontekście leczenia sepsy na oddziałach intensywnej terapii (OIOM). Rozprzestrzenianie się wielolekoopornych patogenów, takich jak *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* i *Escherichia coli*, prowadzi do znacznego pogorszenia wyników leczenia, zwiększając śmiertelność, długość hospitalizacji oraz koszty. Dlatego też w niniejszym artykule przeanalizowano i podsumowano wyniki badań dotyczących czynników ryzyka, klinicznych skutków oraz strategii przeciwdziałania oporności na antybiotyki w leczeniu sepsy.

Przegląd oparto na systematycznej analizie literatury z lat 2018–2023, obejmującej artykuły oryginalne i przeglądy systematyczne dotyczące oporności na antybiotyki u pacjentów z sepsą hospitalizowanych na oddziałach OIOM. Kryteria włączenia uwzględniały ponadto publikacje w języku angielskim, oparte na danych z badań klinicznych prowadzonych na ludziach. Wykluczono badania ograniczone do modeli zwierzęcych oraz przeglądy bez analizy dowodów. Analizowano trendy w rozpowszechnieniu opornych patogenów, czynniki ryzyka ich rozwoju, konsekwencje kliniczne infekcji wywołanych przez oporne szczepy oraz skuteczność różnych strategii terapeutycznych

Przegląd ujawnił alarmujące poziomy oporności wśród patogenów Gram-ujemnych, takich jak *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* i *Escherichia coli*. Odnotowano także wysoką oporność na karbapenemy, wynoszącą w przypadku *A. baumannii* ponad 70%, a na polimyksyny 30–40%. Jako główne czynniki ryzyka rozwoju oporności na antybiotyki wymieniono nadmierne i nieracjonalne stosowanie antybiotyków, niewystarczające środki kontroli zakażeń oraz wysoką intensywność inwazyjnych procedur medycznych oraz transfer pacjentów między oddziałami. Do konsekwencji klinicznych infekcji spowodowanych patogenami opornymi zaliczono zwiększenie ryzyka śmiertelności, wydłużenie hospitalizacji (średnio o 12 dni), wzrost kosztów leczenia oraz podwyższenie ryzyka powikłań, takich jak wstrząs septyczny i niewydolność wielonarządowa.

Podjęto także próbę określenia strategii przeciwdziałania oporności na antybiotyki na oddziałach OIOM. Za ważne aspekty tej strategii uznano rozwój badań nad nowymi antybiotykami, racjonalne stosowanie antybiotyków zgodne z polityką zarządzania antybiotykami (uznawaną za jedną z najskuteczniejszych strategii) oraz stosowanie środków kontroli zakażeń jak higiena rąk, izolacja pacjentów i stosowanie odpowiednich środków ochrony osobistej. Duże nadzieje pokładane są także w alternatywnych terapiach, takich jak bakteriofagi, peptydy przeciwdrobnoustrojowe czy terapie monoklonalne, które mogą stanowić uzupełnienie standardowego leczenia.

Przeprowadzony przegląd systematyczny wskazuje zatem, że oporność na antybiotyki w leczeniu sepsy na OIOM wymaga kompleksowego podejścia, łączącego rozwój nowych leków, racjonalne stosowanie obecnie dostępnych antybiotyków, wzmacnianie systemów kontroli zakażeń oraz rozwijanie innowacyjnych terapii. Jedynie dzięki wspólnym wysiłkom społeczności medycznej, naukowców, przemysłu farmaceutycznego, agencji rządowych i społeczeństwa można osiągnąć znaczący postęp w zwalczaniu antybiotykooporności poprawiając wyniki leczenia i efektywność systemów ochrony zdrowia.

Celem **drugiego** artykułu wchodzącego w skład pracy doktorskiej zatytułowanego „**Opinions of Medical Staff Regarding Antibiotic Resistance”** było zweryfikowanie opinii personelu medycznego na temat zagrożeń związanych z opornością na antybiotyki. Antybiotykooporność stanowi poważne zagrożenie dla zdrowia publicznego, które może prowadzić do zmniejszenia skuteczności wielu terapii, zwiększenia zachorowalności, wydłużenia czasu hospitalizacji, zwiększenia liczby zgonów i dodatkowych kosztów dla systemów opieki zdrowotnej. Nierozsądne stosowanie antybiotyków może wynikać z braku odpowiedniej wiedzy na temat antybiotykoterapii oraz braku wiedzy na temat zagrożeń związanych z antybiotykoopornością, zarówno wśród personelu medycznego, jak i pacjentów. Dlatego też badanie to było ukierunkowane na zrozumienie, jak personel medyczny postrzega problem oporności na antybiotyki, co według nich jest głównymi przyczynami tego zjawiska oraz jakie działania uważają za konieczne w walce z tym problemem. Badanie zostało przeprowadzone w 2023 r. wśród 605 polskich pracowników sanitarnych. Wykorzystano w nim anonimową ankietę zaprojektowaną specjalnie na potrzeby badania. Ankieta została udostępniona w Internecie za pośrednictwem Związków Zawodowych Pracowników Farmacji oraz bezpośrednio w szpitalach przy wsparciu władz lokalnych.

Większość respondentów stanowiły kobiety (77,36%). Największą grupę stanowiły osoby powyżej 40 roku życia (55,04%). Ponad połowę respondentów stanowiły pielęgniarki (56,20%), a co czwarty badany był lekarzem (23,64%).

Wyniki badania pokazują, że większość respondentów uważa oporność na antybiotyki za bardzo poważny (24,13%) lub bardzo poważny (30,75%) problem zdrowotny. Jest to zgodne z globalnymi trendami, które wskazują na rosnące zagrożenie związane z opornością bakterii na dostępne leki. Szczególną uwagę na ten problem zwracają lekarze oraz osoby posiadające specjalizację lub będące w trakcie jej zdobywania.

Respondenci wskazali kilka głównych przyczyn narastania problemu oporności. Głównymi problemami związanymi z antybiotykoopornością było stosowanie antybiotyków u zwierząt hodowlanych (36,69%), wywieranie presji pacjentów na przyjmowanie antybiotyków (38,84%) oraz profilaktyczne stosowanie antybiotyków (43,15%).

Większość respondentów zgodziła się ze stwierdzeniami, że "niewłaściwe stosowanie antybiotyków może pogorszyć stan zdrowia pacjenta" oraz "przepisywanie antybiotyków bez wskazań jest uważane za nieprofesjonalne postępowanie". Zgadzają się również, że "racjonalne stosowanie antybiotyków zmniejszy problem związany z antybiotykoopornością" oraz "ograniczenie przepisywania antybiotyków wyłącznie do leczenia szpitalnego pomoże zmniejszyć problem antybiotykooporności". Zgoda jest jednak bardziej wyraźna w przypadku dwóch pierwszych stwierdzeń. Podobny odsetek pacjentów zgadza się i nie zgadza ze stwierdzeniem, że "kwestia antybiotykooporności wpływa na pacjentów znajdujących się pod moją opieką" (41,2% vs. 43,74%).

Jednym z najważniejszych wniosków z badania jest potrzeba rozszerzenia edukacji na temat oporności na antybiotyki wśród personelu medycznego. Wiedza na temat prawidłowego stosowania antybiotyków i skutków ich nadużywania powinna być szeroko propagowana. Odpowiednie szkolenia mogą pomóc lekarzom i pielęgniarkom lepiej zrozumieć problem i wprowadzać odpowiednie praktyki w swojej pracy.

Aby skutecznie walczyć z problemem oporności na antybiotyki, konieczne jest podjęcie kilku kluczowych działań, takich jak kontrola przepisywania antybiotyków, monitorowanie stosowania antybiotyków w hodowli zwierząt czy prowadzenie kampanii edukacyjnych. Badanie pokazało, że problem oporności na antybiotyki jest szeroko rozpoznawany przez personel medyczny jako poważne zagrożenie zdrowia publicznego. Istnieje pilna potrzeba wprowadzenia skutecznych strategii edukacyjnych i regulacyjnych, aby zapobiec dalszemu rozwojowi opornych szczepów bakterii. Współpraca między różnymi grupami zawodowymi oraz zwiększenie świadomości wśród pacjentów są kluczowe dla osiągnięcia tego celu.

Trzeci z artykułów zatytułowany „**Protected beta-lactam prescription for patients with septic shock**" jest pracą oryginalną. Celem badania była ocena skuteczności leczenia wstrząsu septycznego za pomocą imipenemu/cylastatyny/relebaktamu (IMI/REL) w porównaniu z preparatem złożonym zawierającym piperacylinę/tazobaktam (PTZ). Połączenie inhibitora beta-laktamaz z antybiotykiem β-laktamowym o szerokim spektrum działania przeciwbakteryjnego jest szeroko stosowane we współczesnej praktyce klinicznej. Jest to zgodne z wytycznymi Europejskiego Towarzystwa Mikrobiologii Klinicznej dotyczącymi leczenia zakażeń szpitalnych zalecającymi stosowanie kombinacji leków imipenem/cylastyna/relebaktam lub piperacylina/tazobaktam [1]. Skuteczność leków przeciwko bakteriom Gram-ujemnym stanowiącym główną przyczynę zakażeń szpitalnych została wykazana *in vitro* [2], jednakże brakuje danych dotyczących efektywności takiego postępowania terapeutycznego u pacjentów z posocznicą i wstrząsem septycznym. Niniejsza praca stanowi próbę zapełnienia tej luki.

Przedstawione retrospektywne, niekontrolowane, nierandomizowane badanie obserwacyjne objęło 17 pacjentów z wstrząsem septycznym leczonych w latach 2021-2022 na Oddziale Intensywnej Terapii (OIT) Szpitala Uniwersyteckiego w Krakowie. Włączeni do badania pacjenci zostali podzieleni losowo na dwie grupy: grupa 1 otrzymywała dożylnie 500 mg imipenemu/cylastatyny i 250 mg relebaktamu co 6 godzin (IMI/REL) (w przypadku pacjentów z prawidłowym klirensem kreatyniny) (n=9), natomiast grupa 2 leczona była za pomocą dożylnego preparatu zawierającego 4,5 g piperacyliny i 0,5 g tazobaktamu (PTZ) podawanego co 6 godzin, w długich infuzjach, przez okres 3-4 godzin (n=8). Ponadto u wszystkich chorych zastosowano odpowiednią terapię przeciwwstrząsową, obejmującą preparaty noradrenaliny oraz wlewy roztworów krystaloidów i albumin. U 5 chorych rozpoznano zespół ostrej niewydolności oddechowej (ARDS), w związku z czym zastosowano sztuczną wentylację płuc. U 7 chorych stwierdzono objawy ostrej niewydolności nerek (ARF), w związku z czym poddani oni zostali terapii nerkozastępczej. U wszystkich pacjentów przeprowadzono ogólne badanie krwi, badanie poziomu mleczanów, prokalcytoniny, klirensu kreatyniny oraz oznaczono MIC, wrażliwość i oporność patogenów zakaźnych na antybiotyki (za pomocą metody dyfuzyjno-krążkowej), a także przy użyciu testów E w świeżych kulturach izolatów. Do fenotypowania stosowano zmodyfikowany test CarbaNP, natomiast genotypowanie izolatów opornych wielolekowo przeprowadzono za pomocą metody multiplex real-time PCR.

Badanie bakteriologiczne wykazało obecność czterech patogenów Gram-ujemnych w materiale biologicznym pacjentów, w tym wielolekoopornego szczepu *Acinetobacter* *baumanii* charakteryzującego się wysoką opornością zarówno na badane antybiotyki, oraz *Pseudomonas aeruginosae*. Wyniki fenotypowania i genotypowania potwierdziły wytwarzanie metalo-β-laktamaz przez oba drobnoustroje oraz oksacylinazy hydrolizującej karbapenemy klasy D przez *Acinetobacter baumanii*. Leczenie pacjentów ze wstrząsem septycznym wywołanym przez wspomniane szczepy było równie mało skuteczne w przypadku stosowania IMI/REL (45% pozytywnych odpowiedzi klinicznych i mikrobiologicznych), jak i PTZ (50% pozytywnych odpowiedzi) i zakończyło się w śmiercią 50% pacjentów.

Wyniki te nie potwierdzają korzyści ze stosowania imipenemu, cylastatyny, relebaktamu lub piperacyliny i tazobaktamu u pacjentów ze wstrząsem septycznym przebywających na OIT. Zastosowane terapie okazały się wysoce skuteczne w leczeniu pacjentów, u których stwierdzono bakterie z rodzaju *Escherichia coli, Staphylococcus aureus, Klebsiella pneumonia* i *Streptococcus pneumonia*. Wyraźna oporność *P. aeruginosae* na leki IMI/REL wynika z wytwarzania przez bakterie metalo-β-laktamaz, których relbaktam nie hamuje. Tazobaktam podawany w grupie 2 jest skuteczny przeciwko tym enzymom, jednakże u części pacjentów z tej grupy wykryto również typ MDR *A. baumannii* wytwarzający oksacylinazy hydrolizujące karbapenemy klasy D. Tazobaktam nie jest inhibitorem tego typu enzymów bakteryjnych i z tego powodu u pacjentów z potwierdzonym zakażeniem *A. baumannii* podawanie PTZ nie przyniosło pożądanych rezultatów.

Wielooporne szczepy wywołujące zakażenia szpitalne stanowią nadal główne wyzwanie w antybiotykoterapii wstrząsu septycznego i są jedną z głównych przyczyn zgonów w przebiegu sepsy. Mutacje w genomie prowadzące do zmniejszonej lub zwiększonej ekspresji genów, a także zdolność do horyzontalnego transferu genów, zapewniają bakteriom *A. baumannii* zdolność do syntezy β-laktamaz, metalo-β-laktamaz i beta-laktamaz o rozszerzonym spektrum (ESBL), beta-laktamazy AmpC oraz oksacylinazy hydrolizującej karbapenemy klasy D. Z tego powodu zastosowanie antybiotyków beta-laktamowych jedynie częściowo rozwiązuje problem. Liczba opornych szczepów mikroorganizmów wytwarzających karbapenemazy wzrasta na całym świecie. Przyczyną tego zjawiska może być rosnąca popularność turystyki medycznej, a także niekontrolowane stosowanie antybiotyków w niektórych krajach.

PUBLIKACJE WCHODZACE W SKŁAD ROZPRAWY DOKTORSKIEJ

PUBLICATIONS INCLUDED IN THE DOCTORAL DISSERTATION

Problems of antibiotic resistance in sepsis in intensive care units: A review of current research

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Abstract. The relevance of antibiotic resistance in intensive care units is of great concern because of the growing threat to patient and health care system health. The aim of the study is to comprehensively analyse the prevalence, risk factors, clinical implications and strategies to combat antibiotic resistance in sepsis. Methods include a systematic literature review and evaluation of the effectiveness of different approaches based on empirical evidence. Alarming levels of resistance to reserve-line antibiotics have been observed among Gram-negative pathogens in intensive care units, particularly *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli*. Irrational use of antibiotics, lack of adherence to infection control measures and limited implementation of antimicrobial stewardship programmes are key factors contributing to the development and spread of resistance. Infections caused by resistant pathogens are associated with increased mortality, risk of complications, longer hospitalization and higher treatment costs. This creates a situation where opportunities for effective antibiotic therapy become exhausted. Sepsis caused by resistant pathogens significantly complicates treatment and worsens prognosis, increasing the risk of complications and mortality. Overcoming the problem of antibiotic resistance requires a comprehensive approach that includes the development of new antibiotics, rational use of existing drugs, strengthening infection control measures, improving epidemiological surveillance and exploring alternative therapeutic strategies. Antibiotic stewardship programmes, infection control measures and combined strategies have demonstrated the greatest effectiveness in combating the spread of resistance in intensive care units. This study contributes to the understanding of the magnitude of the antibiotic resistance problem and offers specific recommendations for improving clinical practice and health policy.

Keywords: systemic inflammatory response, medications, antibacterial drugs, prolonged hospitalization, *Staphylococcus aureus*, *Pseudomonas bacillus*.

1. Introduction

The problem of antibiotic resistance in sepsis in intensive care units is a serious threat to public health and requires close attention of researchers. In conformity with the data provided by A. Baran et al. [1], the excessive and inappropriate use of antibiotics in medicine and industry has contributed to the development of resistance, leading to the emergence of multidrug-resistant pathogens such as the "ESKAPE" group: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. According to other data provided by B. Mlynarczyk-Bonikowska et al. [2], the first MRSA strains resistant to beta-lactams appeared in 1960-1961. Ceftobiprole and ceftaroline were introduced in 2010 but strains resistant to them soon emerged. MRSA spread to hospitals in the 1970s and 1980s, and CA-MRSA and LA-MRSA strains appeared in the 1990s. MRSA resistance is due to genomic islands of SCCmec with mecA and mecC genes. In 2002, VRSA strains with the vanA operon were discovered. In 2006, class I integrons with genes for resistance to streptomycin, chloramphenicol and trimethoprim were found in Staphylococcus aureus. In this regard, L. Korczak et al. [3] also emphasized that the main mechanisms of resistance include efflux pumps, gene mutations and outer membrane porins. The spread of resistance to tigecycline and other drugs of last resort poses a serious public health threat. According to a study by N. Jendrzejewska and E. Karwowska [4], although an increase in the number of strains with β-lactamase activity was not recorded, these enzymes were found in 97% of multidrug-resistant bacteria. Significant numbers of antibiotic-resistant bacteria entered treated wastewater, with more than 50% of the bacteria in the final effluent being penicillin resistant. Especially, according to A. Aleksandrowicz et al. [5], this problem is relevant in patients from low social circles, as antibiotic resistance significantly increases mortality from food and wound infections.

The urgency of studying this problem is due to the rapid growth of antimicrobial resistance, which outpaces the development of new antibiotics. In conformity with M. Wojciechowska et al. [6], this jeopardizes the effectiveness of treatment of severe infections and increases the risk of adverse outcomes. According to the World Health Organization, antibiotic resistance is a major threat to global health, food security and development. Each year, about 700,000 people worldwide die due to infections caused by resistant bacteria [6]. However, despite numerous studies, the problem of antibiotic resistance in sepsis in the intensive care unit (ICU) remains unresolved. The lack of a unified coordinated approach, limited implementation of antibiotic stewardship programmes and inadequate infection control measures contribute to the further spread of resistant pathogens. In addition, existing studies are often limited to localized data or address only selected aspects of the problem without offering comprehensive solutions.

The aim of this study is to comprehensively analyse current trends in antibiotic resistance in sepsis in the ICU setting, identify the main drivers and evaluate the effectiveness of different strategies to combat this problem. Special attention will be paid to the study of local epidemiological data, risk factors for resistance development and practices of rational antibiotic use in Russian ICUs. Based on the results obtained, recommendations will be formulated to optimize antibiotic therapy, reduce the spread of resistant pathogens and improve the outcomes of treatment of patients with sepsis.

2. Materials and Methods

To achieve the aim of this study, a systematic review of the current scientific literature on the problem of antibiotic resistance in sepsis in intensive care units was conducted. Relevant publications were searched in the following electronic databases: PubMed, Scopus, Web of Science. Search queries included combinations of keywords in English such as: "antibiotic resistance", "sepsis", "intensive care unit", "antibiotic resistance", "sepsis", "intensive care unit" and others.

Criteria for inclusion of publications in the review include original research articles, systematic reviews published in peer-reviewed scientific journals in the last five years, from 2018 to 2023. The review includes papers that address antibiotic resistance in the management of sepsis in intensive care units. In addition, only studies that were conducted in humans are accepted and publications must be written in English.

The exclusion criteria for this review cover several key aspects. Firstly, all publications that do not address the specific topic of antibiotic resistance in sepsis in the ICU setting are excluded. This means that any studies or reviews that do not focus on this narrow issue will not be considered. The second criterion relates to animal studies; such papers are excluded as the focus is on results obtained directly in human clinical settings. The third criterion is the lack of systematic analysis of evidence in literature reviews. Such reviews do not meaningfully contribute to a systematized understanding of the topic under study and are therefore not suitable for inclusion in this review. Finally, the criteria exclude publications in languages other than English to ensure that the information is uniform and accessible to an international scientific audience and that high standards of scientific communication are maintained.

The selected publications were carefully analysed to extract relevant information on key aspects related to the problem of antibiotic resistance among sepsis patients in intensive care units. Firstly, current trends in the prevalence of antibiotic-resistant pathogens were investigated. Second, risk factors that contribute to the development of antibiotic resistance in these settings were explored. The third area of analysis was the clinical consequences of infections caused by resistant strains, including mortality, length of hospital stays and associated economic costs. Strategies to combat antibiotic resistance were also considered, including the development of new drugs, optimization of the use of existing antibiotics and alternative therapeutic approaches. Finally, the effectiveness of different strategies in reducing the spread of resistant pathogens and improving sepsis treatment outcomes was evaluated. These comprehensive analyses are helping to form the evidence base for the development of new recommendations for clinical practice and health policy.

Systematic review methods, including qualitative content analysis, data extraction and synthesis, were used to analyse the selected publications. The findings were structured and presented in the relevant sections of the review. In addition, relevant epidemiological data from different regions of the world were analysed to study the local situation of antibiotic resistance in sepsis. These data included information on the prevalence of resistant strains, resistance profiles of the most clinically important pathogens, and antibiotic use practices in the ICU.

The results of the analysis of literature data and epidemiological information were integrated to formulate comprehensive recommendations to optimize antibiotic therapy and reduce the spread of resistant pathogens in sepsis in the ICU setting.

3. Results and Discussion

3.1. Prevalence and trends in antibiotic resistance

A systematic review has shown very alarming levels of resistance to back-up line antibiotics among Gram-negative pathogens in intensive care units. Microorganisms such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa* have particularly high rates of resistance (Table 1). In *A. baumannii*, the average level of resistance to carbapenems in different regions of the world exceeds 70%, and resistance to polymyxins reaches 30-40% [7]. In *P. aeruginosa*, the level of resistance to carbapenems varies from 30 to 50% depending on the region [8]. A.M. Kabrah et al. [9] report that maximum resistance was observed to aztreonam (96.4%) and ampicillin (87.3%) among isolated pathogens in ICUs in Saudi Arabia, emphasizing the need for strict adherence to infection prevention practices and judicious use of antibiotics to slow down the spread of antibiotic resistance. Further, M.T. Mustapha et al. [10] find that the prevalence of antibiotic resistance was 22.3% and mortality among antibiotic-resistant patients reached 68.4%. These data emphasize the need for careful management of antibiotic use and monitoring of resistant infections. The most frequent antibiotic-resistant pathogens included *Klebsiella pneumoniae (K. pneumoniae)* (59.4%), coagulase-negative staphylococci (CoNS) (11.5%), *Escherichia coli* (*E. coli*) (8.4%), *Acinetobacter baumannii (A. baumannii)* (7.3%) and *Staphylococcus aureus* (*S. aureus*) (6.2%). It was observed to aztreonam (96.4%), ampicillin (87.3%), followed by coamoxiclav (83.9%), cotrimoxazole (79.5%) and antibiotics of cephalosporin group [10]. F.A. Wani et al. [11] estimated that 85.1% of Gram-negative bacteria were multiresistant and recommends increased monitoring and strengthening of antibiotic stewardship programmes. The study recorded 570 cases of bacterial growth, of which 437 (76.7%) belonged to the Gram-negative bacteria (GNB) group. Among ICU patients, bacteria such as *Klebsiella pneumoniae* (21%), *Pseudomonas aeruginosa* (11.8%) *and Staphylococcus aureus* (13.2%) were the most commonly encountered bacteria. There was a high rate of resistance to third and fourth generation cephalosporins, 73.2% and 70.1%, respectively. The rate of resistance to carbapenems was 48.2% and to fluoroquinolones was more than 65% [11]. A study by D. Chaudhari [12] was conducted in the ICU of a hospital in Ahmedabad to study the prevalence and antibiotic resistance of microorganisms from August 2019 to August 2020. Out of 941 samples submitted for analysis, 322 were positive. The most commonly isolated bacteria included *Klebsiella* (37.26%), *Escherichia coli* (16.45%) and *Pseudomonas* (12.42%). Gram-negative bacteria showed high sensitivity to colistin (96.26%) and tigecycline (83.40%), while Gram-positive organisms were most sensitive to linezolid (100%). Finally, H. Meriyani et al. [13] investigates in his study dated 2021 the relationship between antibiotic use and resistance in the ICU, showing that widespread antibiotic use correlates with high rates of resistance, highlighting the need for more controlled antibiotic use and programme planning to manage resistance.

Table 1. Prevalence of antibiotic resistance in different pathogens

Pathogen	**Sustainability level**
Acinetobacter baumannii	>70% to carbapenems, 30-40% to polymyxins
Pseudomonas aeruginosa	30-50% to carbapenems (regional variations)
Klebsiella pneumoniae	>50% to carbapenems (in some regions)
Staphylococcus aureus (MRSA)	50-60% methicillin-resistant strains, some with vancomycin resistance
Enterococci	Vancomycin-resistant strains are widespread
Candida auris	Up to 90% of azole-resistant strains (in some regions), increasing resistance to echinocandins

Source: compiled by the authors.

The rapidly increasing prevalence of carbapenem-resistant Enterobacteriaceae, such as *Klebsiella pneumoniae* and *Escherichia coli*, is also of concern. In some countries in Southern Europe, South Asia and Latin America, the rate of carbapenem resistance in *K. pneumoniae* may exceed 50%, posing a serious threat to the treatment of serious infections. The study by C. Aurilio et al. [14] examines the mechanisms of resistance to carbapenems due to the widespread use of these antibiotics worldwide. The authors categorize resistance mechanisms into three groups: poor penetration or excretion of the drug, modification of the target by bacteria, and inactivation of the drug by enzymes such as carbapenemases. The study emphasizes the need to improve antibiotic stewardship and develop new treatments to combat growing resistance. A study conducted by A.J. Gondal et al. [15] analysed the prevalence of carbapenem resistance among 2170 clinical strains collected from a hospital in Pakistan. The study revealed a significant level of carbapenem resistance of 42.1%. A high prevalence of carbapenemase genes such as blaNDM-1 and blaOXA-48 was also observed, highlighting the critical need for continuous monitoring and development of innovative strategies to stop the spread of resistance.

Studies by H. Lade and J.S. Kim [16] have shown that methicillin-resistant *Staphylococcus aureus*, one of the major causative agents of sepsis, reaches 50-60% in most countries of the world, exceeding 60% in regions such as the USA, Southern Europe and East Asia. Vancomycin-resistant enterococci are also common, especially in intensive care units of countries with high levels of resistance. W.T. Liu et al. [17] conducted an extensive analysis of MRSA resistance to major classes of antibiotics such as vancomycin, daptomycin, ceftaroline and linezolid. The study revealed increasing resistance to vancomycin, the first-line treatment for MRSA, where intermediate vancomycin-resistant (VISA) and vancomycin-resistant strains (VRSA) have already been observed.

The increasing incidence of invasive fungal infections in intensive care units is accompanied by a rise in antifungal drug resistance. The prevalence of azole-resistant *Candida auris* strains is rapidly increasing in many countries, reaching 90% in some regions. Resistance to echinocandins, a new class of antifungal agents, is also becoming increasingly common among *Candida* species [**Error! Reference source not found.**]. N.P. Wiederhold [19] emphasizes the growing problem of antifungal drug resistance, especially in *Candida auris* species, which poses a significant threat due to its ability to resist major classes of antifungal agents, including azoles and echinocandins. This infection is difficult to diagnose and treat, leading to poorer treatment outcomes due to inappropriate therapeutic approach or development of resistance. The study highlights the importance of raising awareness and training clinical professionals to effectively recognize and manage such cases. Genomically, *Candida auris* is divided into five geographical clades: clades I (South Asian), II (East Asian), III (African), IV (South American) and V (Iranian). Given the sequencing results, each clade differs by more than 10,000 SNPs, and the differences within clades do not exceed 70 SNPs. This indicates multiple occurrences of the species rather than clonal spread. In the USA, about 90% of isolates are resistant to fluconazole, 30% to amphotericin B, and 5% to echinocandins. Up to 4% of isolates are resistant to all available classes of antifungal drugs.

An overall analysis of data over the past decades has revealed a clear trend towards an increase in the prevalence of resistant pathogens in intensive care units. This is due to several factors, including excessive and irrational use of antibiotics, lack of adherence to infection control measures and limited implementation of antimicrobial stewardship programmes. The spread of emerging threats such as carbapenem-resistant Enterobacteriaceae and *Candida auris* poses serious challenges to clinical practice and emphasizes the need for urgent action to combat antibiotic resistance. These actions include developing new antibiotics, implementing strict infection control measures and optimizing the use of existing antimicrobials to ensure effective treatment of infections and improve patient outcomes.

3.2. Risk factors for the development of antibiotic resistance

Irrational use of antibiotics is one of the main factors contributing to the development and spread of antibiotic resistance. Studies show that on average 70% of patients in intensive care units receive antibiotics, with the prescription of these drugs found to be inappropriate in 42% of cases. The widespread use of broad-spectrum antibiotics creates a selective pressure that favours the selection and multiplication of resistant strains, making them particularly dangerous and difficult to treat. Failure to adhere to infection control measures such as proper hand hygiene of nursing staff, effective isolation of infected patients, and proper use of personal protective equipment also contributes significantly to the spread of resistant pathogens. Prior use of antibiotics, especially broad-spectrum drugs, is a risk factor for colonization and infection by resistant strains. This is associated with the disruption of the normal microbiota of the body, which creates conditions for the selection and spread of resistant pathogens.

The movement of patients between different wards and healthcare facilities can be a channel for the transmission of resistant strains, increasing the risk of their spread over large areas. G. Eric et al. [20] found that antibiotic use, prolonged hospital stays, male gender and infections caused by methicillin-resistant *Staphylococcus aureus* served as risk factors for resistance, and 45.7% of patients with chronic renal failure were infected with resistant bacteria. Further, M. Opatowski et al. [21] pointed out that the risk of antibiotic resistance was highest in the first three months after treatment initiation, especially when broad-spectrum antibiotics were used, with broad-spectrum antibiotics increasing the risk of resistance 3.6-fold. Finally, Y.Q. Chan et al. [22] investigated risk factors for antibiotic resistance among children in the Asia-Pacific region, finding that antibiotic use in the last three months, daycare attendance and hospitalization were significant risk factors, while breastfeeding and concomitant Streptococcus pneumoniae colonization served as protective factors.

Patients in intensive care units often suffer from severe co-morbidities, are immunocompromised and undergo various invasive procedures such as intubation or catheterization. These factors significantly increase the risk of developing infections caused by resistant pathogens. Prolonged ICU stays increase the likelihood that patients will become colonized with resistant bacteria and develop healthcare-associated infections. In ICUs, empirical antibiotic regimens are often used until microbiological results are available, which may contribute to further development of resistance. Horizontal transfer of resistance genes between different bacterial species and strains plays a significant role in the spread of resistance and can occur rapidly in settings with high patient densities and frequent antibiotic use. O. Rodríguez-Núñez et al. [23] found that independent predictors of antibiotic resistance among patients with bacteraemia due to intra-abdominal infections were cirrhosis, immunosuppression, previous exposure to ceftazidime, and shock, the main causative agents were methicillin-resistant *Staphylococcus aureus* and cephalosporin-resistant *Enterobacteriaceae,* which may be related to the treatment of these pathologies, which most often contains broad-spectrum antibiotics. Q. Chen et al. [24] systematically analysed the risk factors for antibiotic resistance in the Chinese population, revealing that socio-demographic factors, length of hospitalization and performance of invasive procedures significantly influenced the risk of developing resistance, highlighting the need to strengthen primary health care and surveillance systems for antimicrobial resistance (AMR). These studies highlight the many factors that may influence the development of antibiotic resistance, confirming the complexity of the problem and the need for an integrated approach to antibiotic therapy management to minimize risks.

Thus, combating antibiotic resistance requires an integrated approach that includes rational use of antimicrobials, strengthening infection control measures, optimizing antibiotic therapy and improving epidemiological surveillance strategies. Only integrated efforts can reduce the risk of the development and spread of antibiotic resistance, improve therapeutic outcomes, and provide safer treatment for patients.

3.3. Clinical consequences of antibiotic resistance

Infections caused by antibiotic-resistant pathogens result in a multitude of adverse clinical outcomes and cause significant economic consequences for the health care system (Table 2). Meta-analyses have shown that infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) are associated with a significantly higher risk of death in patients with sepsis in intensive care units compared to infections caused by carbapenem-sensitive strains. Similar results have been observed for other resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). The first study by C. Elvionita et al. [25] looked at the rational use of antibiotics in children with pneumonia. They found that 40% of children who received targeted antibiotic therapy showed improvement in clinical outcomes. The main pathogens were *Klebsiella pneumoniae* and *Acinetobacter baumannii*, showing resistance to broad-spectrum antibiotics in 60% of patients. A study by W, Ling et al. [26] focused on infections caused by carbapenem-resistant *Acinetobacter*. The results showed that mortality in such patients was 45% higher than in patients with infections caused by sensitive strains. A further study by L. Chelkeba et al. [27] found that more than 70% of wound infections in Ethiopia were caused by resistant Gram-negative bacteria, which significantly worsened clinical outcomes. The major pathogens included resistant strains of *Escherichia coli* and *Pseudomonas aeruginosa*.

Table 2. Impact of antibiotic resistance on treatment outcomes

Consequence	Description
Increased mortality	Significantly higher risk of death from sepsis caused by resistant pathogens
Increased risk of complications	Higher risk of septic shock and multi-organ failure
Increased length of hospitalization	On average, 12 days longer for infections caused by resistant pathogens
Increased treatment costs	Need for more expensive reserve antibiotics, additional tests
Limited therapeutic options	Exhaustion of effective antibiotic therapy for highly resistant strains

Source: compiled by the authors.

Treatment of infections caused by resistant pathogens requires the use of more expensive and often less effective back-up antibiotics. In addition to increased costs, there is a need for additional diagnostic tests and longer hospital stays, which significantly increase the economic cost to the health system. Estimates suggest that the annual additional costs associated with treating such infections are in the billions of dollars globally. Another study by S.A. Upula et al. [28] found significant antibiotic resistance among bacteria causing postoperative wound infections, resulting in a 50% increase in length of hospitalization compared to patients whose infections were treated with effective antibiotics. The predominant pathogens were *Staphylococcus aureus* and *Enterococcus faecalis*. The spread of resistance to back-up antibiotics, such as carbapenems and polymyxins, creates a situation, in which the possibilities for effective antibiotic therapy become exhausted, significantly worsening the prognosis of patients with severe infections. This is particularly relevant in light of the fact that new antimicrobial agents are not being developed as rapidly as pathogen resistance is increasing. Sepsis caused by resistant bacteria is often associated with longer hospital stays. Systematic reviews have reported that infections caused by CREs result in an average of 12 days longer hospitalization compared to infections caused by susceptible strains. This prolongation of hospitalization not only impairs the quality of life of patients, but also significantly increases the burden on healthcare facilities. A study by G. Samsarga et al. [29] analysed clinical outcomes in patients with burns infected with multiple resistant organisms. It was observed that these patients had a 3-fold higher risk of sepsis and pneumonia, and overall mortality reached 60% in cases infected with resistant bacteria.

These serious clinical and economic consequences of antibiotic resistance highlight the urgent need to strengthen infection control measures, optimize the use of existing antibiotics, develop new effective antimicrobials, and develop and implement alternative therapeutic strategies. This will improve treatment outcomes, reduce the economic burden on the health system and improve public health.

3.4. Sepsis caused by antibiotic-resistant pathogens

Sepsis caused by antibiotic-resistant pathogens is a serious clinical problem that significantly complicates treatment and worsens the prognosis of patients. Antibiotic resistance significantly increases the risk of complications such as septic shock and multiple organ failure, and increases mortality. C. Gudiol et al. [30] discusses the problems of sepsis in patients with cancer in the setting of antimicrobial resistance, emphasizing that delay in initiating adequate empirical antibiotic therapy can lead to poor outcomes, with high morbidity and mortality rates in this patient group. B. Tessema et al. [31] conducted a meta-analysis on antibiotic resistance of bacterial isolates from patients with neonatal sepsis at the University Hospital of Leipzig, Germany. The study found that 74% of 134 isolates were Gram-positive bacteria. *S. epidermidis* showed the highest resistance to penicillin G and roxithromycin (90% each), followed by cefotaxime, cefuroxime, imipenem, oxacillin and piperacillin-tazobactam (88% each), ampicillin-sulbactam (87%), meropenem (86%) and gentamicin (59%). *E. coli* showed the highest resistance to ampicillin (74%), followed by ampicillin-sulbactam (52%) and piperacillin (48%). S. Jannah et al. [32] found that Gram-positive bacteria detected in septic patients were resistant to piperacillin-tazobactam in 100% of cases, and to daptomycin and clindamycin in 99.2% of cases, which significantly complicated the administration of adequate antibiotic therapy. K. Sands et al. [33] reveal that out of 36,285 neonates in the study, 2,483 were diagnosed with culture-confirmed sepsis. *Klebsiella pneumoniae* with multiple antibiotic resistance was the leading cause of neonatal sepsis, emphasizing the need for research to develop more effective treatments.

Early identification of pathogens and their resistance to antibiotics is critical for timely initiation of adequate therapy. This requires the use of advanced molecular and microbiological diagnostic methods. In settings where antibiotic resistance is highly likely, it is important to initiate treatment with empirical use of antibiotics that are active against suspected resistant strains. This approach helps to control the infection until the results of sensitivity tests become available. W.K. Oliveira et al. [34] performed a meta-analysis on 3872 bacterial genomes isolated from blood and identified 71,745 antibiotic resistance genes (ARGs). Taxonomy analysis showed that *Proteobacteria* and *Firmicutes* phyla, and *Klebsiella pneumoniae* and *Staphylococcus aureus* species were the most represented. A comparison of the ARG with the Resfams database showed that the main mechanism of antibiotic resistance was the action of excretion pumps.

The use of antibiotic combinations can be effective in combating resistance and preventing the development of new resistant forms. However, the choice of drugs must be careful to minimize the risk of further development of resistance. Maintenance of vital organ function and prevention of additional infections also play a key role in the management of sepsis. Regular monitoring of treatment response and adaptation of antibiotic therapy according to the patient's clinical condition and laboratory results are integral to the management of sepsis in the setting of antibiotic resistance.

3.5. Strategies to counter antibiotic resistance

To overcome the problem of antibiotic resistance in sepsis in ICU, a comprehensive approach involving several key strategies is needed. An important area of focus is the development of new antibiotics. Pharmaceutical companies are actively working to develop new classes of antibiotics with novel mechanisms of action. For example, agents such as ceftazidime-avibactam, ceftolozan-tazobactam and plazomicin have already demonstrated efficacy against resistant Gram-negative pathogens and represent an important addition to the armoury of drugs for the treatment of sepsis in the ICU [**Error! Reference source not found.**].

The rational use of antibiotics also plays a key role in combating resistance. Antibiotic Stewardship Programmes (ASPs) in ICUs aim to improve the quality of antibiotic prescribing, reduce inappropriate use and slow the development of resistance. Systematic reviews have shown that the introduction of ASPs leads to a significant reduction in the use of broad-spectrum antibiotics, lower rates of inappropriate therapy and fewer infections caused by resistant pathogens. In addition, ASPs contribute to reduced mortality and lower treatment costs. M. Stracy et al. [36] present a methodology based on machine learning to personalize antibiotic selection to minimize the risk of resistance. The study is based on the analysis of 140,349 cases of urinary tract infections and 7,365 wound infections, showing that it is possible to predict the emergence of resistance and manage it effectively. J. Ye and X. Chen [37], F. Alqahtani et al. [38] discussed the development of alternative strategies against antibiotic-resistant bacteria. The study suggests several approaches, including bacteriophages, antibiofilm drugs, probiotics, and nanomaterials. It is indicated that clinical and pre-clinical trials show the significant potential of these methods against resistant bacteria. G.B. Nair and M.S. Niederman [39] indicate that the key principle in the treatment of infections caused by antibiotic-resistant microorganisms is the correct identification of the pathogen, adequate timing of therapy, use of 2 or 3-component regimens to reduce the risk of resistance development.

With the growing threat of antibiotic resistance, researchers are exploring alternative approaches such as phage therapy, antimicrobial peptides and monoclonal antibody therapy. Phage therapy, which uses phage viruses to fight bacterial infections, has shown promising results, but its widespread adoption has been hampered by the lack of a clear regulatory framework. Antimicrobial peptides, such as cationic antimicrobial peptides (cAMPs), represent a promising class of antibacterial agents with novel mechanisms of action, but they require further research to be fully utilized in clinical practice. Additionally, strengthening infection control measures, improving epidemiological surveillance for resistance, and developing vaccines and immunotherapeutic agents for the prevention and treatment of infections play an important role in reducing the spread of resistant pathogens. Intersectoral collaboration and raising awareness of antibiotic resistance among health-care workers and the public are also important. Thus, an integrated approach combining different strategies is the key to overcoming the threat of antibiotic resistance in sepsis in the ICU setting and improving clinical outcomes for patients. These measures not only help to reduce the negative consequences of antibiotic resistance, but also improve the overall quality of care.

3.6. Effectiveness of strategies for managing the spread of resistance

Different strategies to combat antibiotic resistance in sepsis in the ICU have shown varying degrees of effectiveness. The most promising results are seen with an integrated approach, combining several complementary measures. Antimicrobial stewardship programmes (ASP) are recognized as one of the most effective strategies [40]. A systematic review conducted by D. Donà et al. [41] showed that the implementation of ASPs in the ICU resulted in a significant reduction in the use of broad-spectrum antibiotics (by 19.1%), a reduction in inappropriate antibiotic therapy (by 19.6%) and a reduction in the number of infections caused by resistant pathogens (by 23.4%). In addition, ASPs contributed to a 17.5% reduction in mortality and an average cost savings of USD 621 per patient.

Strengthening infection control measures, such as hand hygiene, isolation of infected patients and appropriate use of personal protective equipment, also plays an important role in containing the spread of resistant strains. A meta-analysis by J. Ma et al. [42] showed that strict adherence to infection control measures leads to a 51% reduction in the incidence of infections caused by resistant pathogens. Combination strategies that combine ASP, infection control measures and other approaches, such as epidemiological surveillance and training of health care personnel, have been shown to be most effective. According to H.A. El-Mahallawy et al. [43], implementation of an integrated programme resulted in a 54% reduction in carbapenem resistance among Enterobacteriaceae, as well as a significant reduction in mortality from infections caused by these pathogens. However, it should be noted that the effectiveness of resistance management strategies may vary depending on local epidemiological conditions, resources, and the commitment of health care personnel to adhere to recommendations. Therefore, it is important to tailor and implement strategies to the specific needs and capacities of each ICU [44, 45]. The accumulated evidence suggests that an integrated, multicomponent approach combining different strategies is the most effective way to overcome the threat of antibiotic resistance in sepsis in the ICU setting and improve clinical outcomes in patients [46, 47].

This review article plays a critical role by providing a wealth of data and analyses that can serve as a valuable resource for clinicians, medical researchers, and health policymakers. The data collected and analysed aims to inform these groups of the latest trends and scientific advances in the field of antibiotic resistance, which in turn can contribute to the development of new, more effective strategies to control and combat antibiotic resistance. The need for an integrated approach that includes strengthened research, innovations in clinical practice and changes in antibiotic stewardship policies is emphasized. Thus, based on this review, strategic courses of action can be developed to minimize the spread of antibiotic resistance, improve the diagnosis and treatment of infections, and increase awareness and responsibility among health care providers and the public. As a result of these efforts, we can expect to see significant improvements in the outcomes of patients with infectious diseases and significant improvements in the efficiency of the public health system.

4. Conclusions

The problem of antibiotic resistance in intensive care units, especially in the context of sepsis, remains one of the most pressing challenges of modern medicine. This problem requires urgent attention and coordinated action at all levels of the medical and pharmaceutical community. The development of new antibiotics remains critical to overcome resistance to existing drugs. New drugs such as ceftazidime-avibactam, ceftolozan-tazobactam and plazomicin have already shown encouraging results against resistant Gram-negative pathogens and may play a key role in the treatment of severe infections in the ICU. However, given the length and cost of the process of developing new antibiotics, it is also important to focus on the rational use of existing antibacterials.

Antibiotic Stewardship Programmes (ASPs) demonstrate the importance of antibiotic stewardship efforts to reduce unnecessary antibiotic use, which, in turn, reduces the risk of resistance development. These programmes have helped to achieve significant improvements in the quality of care, reducing the incidence of infections with resistant pathogens, reducing mortality and the economic costs of treatment. Research into alternative therapeutic strategies such as phage therapy, antimicrobial peptides, and monoclonal antibody therapy offer new opportunities to combat resistant infections. These approaches may offer complementary therapies that can be integrated into existing protocols for the management of severe bacterial infections. In addition, strengthening infection control measures, improving epidemiological surveillance, and developing vaccines and immunotherapeutics are vital strategies to prevent and manage the spread of infections. Intersectoral collaboration and active public participation are also needed to raise awareness of the seriousness of the threat of antibiotic resistance and to support sustainable health practices.

In conclusion, a comprehensive approach to the problem of antibiotic resistance, including the development of new drugs, optimization of the use of current drugs, introduction of innovative therapies and improved infection control measures, is the key to overcoming this threat. Only through the collaborative efforts of the medical community, researchers, the pharmaceutical industry, government agencies and the public can significant progress be made in combating antibiotic resistance and improving clinical outcomes for patients worldwide.

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Opinions of Medical Staff Regarding Antibiotic Resistance

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Abstract: Introduction: Antibiotic resistance poses a significant threat to public health, that can lead to reduced effectiveness of many therapies, increased morbidity, longer hospitalization times, increased deaths, and additional costs for health care systems. Unreasonable use of antibiotics may result from a lack of adequate knowledge about antibiotic therapy and a lack of knowledge of the risks associated with antibiotic resistance, both among medical personnel and patients. Aim. The primary objective of the study was to verify the opinion of medical personnel on the risks associated with antibiotic resistance. Material and Methods: The study was conducted in 2023 among 605 Polish sanitary workers. An anonymous survey designed specifically for the purpose of the study was used. The survey was made available on the Internet through the Trade Unions of Pharmacy Workers and directly to hospitals with the support of local authorities. Results: The majority of respondents were women (77.36%). The largest group consisted of individuals over 40 years of age (55.04%). More than half of the respondents were nurses (56.20%), and every fourth of the respondents was a physician (23.64%). Most respondents consider antibiotic resistance to be a very serious (24.13%) or extremely serious (30.75%) problem. The problem of antibiotic resistance on a global scale was mentioned, especially in the opinions of physicians and nurses ($p < 0.01$), people working in the profession for over a year ($p < 0.01$), and people with a specialization or undergoing specialist training ($p = 0.00$). Similarly, these groups most often indicated that antibiotic resistance poses a problem in their workplace. The main problems of antibiotic resistance were the use of antibiotics in farm animals (36.69%), the pressure on patients to take antibiotics (38.84%), and the prophylactic use of antibiotics (43.15%). Conclusions: Medical personnel consider antibiotic resistance a somewhat serious problem, although not all agree in this regard. The risk of antibiotic resistance is much more seriously assessed by physicians and nurses, as well as by people with specializations or undergoing specialization training. Knowledge about antibiotic resistance should be further spread among all groups of medical personnel.

Keywords: opinions; attitudes; knowledge; antibiotics; antibiotic resistance; medical staff

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1. Introduction

Antibiotic resistance is one of the most significant threats to public health [1]. Antibiotics are a class of antimicrobials used to combat bacterial infections and antibiotic resistance, which is the most commonly used class of antimicrobials. Therefore, in order to resist forced environmental selection, bacteria tend to develop drug resistance, which leads to the ineffectiveness of previous therapies [2]. This situation in turn contributes to higher morbidity, longer hospitalizations, and higher mortality and generates many additional costs for healthcare systems [3–5]. It is estimated that in 2019, antibiotic resistance was the direct cause of 1.27 million deaths worldwide and contributed to another 4.95 million deaths [1]. In the European Union (EU) and the European Economic Area, 33,000 people die each year from infection with a resistant strain of bacteria, with no sign of change in the years to come. World Bank data indicate that AMR will contribute to the increase in healthcare costs by 1 trillion USD by 2050 and additional costs of lost productivity many times higher, translating into losses in GDP of up to 3.4 trillion USD per year [6]. The costs include, among others: patients' stay in hospitals, which, in the case of hospitalization due to infections with a resistant strain of bacteria, lasts on average 13 days. Given the number of patients infected with drug-resistant bacteria, the annual hospitalization time amounts to 8 million days and costs up to 29,000 USD per patient [7]. Increased mass use of antibiotics during the COVID-19 pandemic will increase bacterial resistance and ultimately lead to more deaths [7].

The unreasonable use of antibiotics, which causes antibiotic resistance, is contributed by, among others, inadequate knowledge in the use of antibiotic therapy, unconsciousness of the risks associated with antibiotic resistance, lack of rapid and sufficient diagnostic tests, but also advertising of drugs and the pressure of patients to prescribe this group of drugs [8–11].

The optimal use of existing antimicrobials, the use of alternative treatment options, education of health care professionals and patients, the implementation of antibiotic policies, and effective measures to control infections are examples of strategies to prevent the development and spread of antibiotic resistance [2,12]. Due to their global scope, these issues have been recognized as priorities in the area of public health by a number of organizations and agencies around the world, including: the World Health Organization, the European Parliament, the European Center for Disease Prevention and Control (ECDC) for Disease Prevention and Control), the US Centers for Disease Control and Prevention (CDC), or the US Food and Drug Administration (FDA). In Poland, these types of activities are undertaken as part of the National Antibiotic Protection Program.

Awareness among medical personnel and patients of the dangers of antibiotic resistance is extremely important in the prevention of antibiotic resistance. Studies show that medical personnel are not always fully aware of the risks of the improper use of antibiotics [13,14]. The problem is also the lack of awareness of how medical personnel can contribute to reducing antibiotic resistance [15].

Due to the above, the main aim of our research was to explore the opinion of medical staff on the threats related to antibiotic resistance. In addition, the study sought a relationship between work experience and specialized training in antibiotic therapy and the awareness of respondents.

2. Material and Methods

2.1. Study Design

The study was conducted between September and December 2023 among 605 medical workers using an anonymous survey. It was an online survey where the link was provided to the pharmacists through Trade Unions of Pharmacy Workers (ZZPF—https://www.zzpf.org.pl (accessed on 1 April 2024)) and directly to hospitals through the Central Office of Marshal in Warsaw (https://mazovia.pl/en/ (accessed on 1 April 2024)) with the support of local governments. The questionnaire was sent with government support to all hospitals in the Masovian Voivodeship at the request of the management and sent to all medical employees.

The survey was created specifically for the purposes of the study and included 4 basic questions (containing specific questions) regarding the purpose of the study and the demographics (gender, age, profession, work experience, specialization, voivodeship, workplace, place of work: public/private hospital, nursery, individual practice, public/hospital pharmacy, and pharmaceutical company).

A questionnaire was created based on a literature review and our local needs due to the high impact of AMR in Poland.

The questionnaire consisted of four main questions as well as extension questions:

1. Rate on a scale of 1 (no problem) to 7 (very serious problem) how serious antibiotic resistance is in the following locations: worldwide/hospital in your city/in your province/your workplace.
2. Rate on a scale of 1 (no problem) to 7 (very serious problem) how strongly you think the following factors influence the increase in antibiotic resistance in Poland: antibiotic use inbred animals/antibiotic use in humans in your region/antibiotic use in patients in hospitals/patient pressure for a physician to prescribe antibiotics/prophylactic antibiotic use/antibiotic use in children.
3. Rate on a scale of 1 (no problem) to 7 (very serious problem) health care workers' perception of the problem of drug resistance in the context of patient care and strategies to combat antibiotic resistance (questions only for respondents working in hospitals): the problem of antibiotic resistance affects patients under my care/rational use of antibiotics will reduce the problem of antibiotic resistance/antibiotics used incorrectly may worsen the patient's health/prescribing antibiotics without indications is professionally unethical/limiting the prescription of antibiotics only in hospital treatment will help reduce the problem of antibiotic resistance/a policy of rational use of antibiotics should be introduced in my hospital/a computer application should be launched that would advise on the selection and duration of antibiotic therapy for patients in my hospital/a team should be established consisting of a physician specialist, clinical pharmacist and nurse providing personalized advice on antibiotic prescribing in my hospital/I will be happy to take part in any initiatives related to the use of antimicrobials in my hospital.
4. Rate on a scale of 1 (no problem) to 7 (very serious problem) the attitude of healthcare professionals towards strategies to combat antibiotic resistance: strategies to combat antibiotic resistance/regular hospital antibiotic audits and follow-up recommendations/limiting the prescribing of all antibiotics/limiting the prescribing of some antibiotics/easily accessible advice from microbiologists/regular educational training on the rational use of antibiotics.

Each of the questions respondents could rate on a scale of 1–7 (where 1—strongly disagree, 7—strongly agree).

2.2. Ethical-Legal Aspects

The study was approved by the Bioethics Commission of the Karol Marcinkowski Medical University in Poznań (Decision No. EC 988/23).

2.3. Statistical Analysis

The statistical analyses were performed using the STATISTICA data analysis software system version 13.0, StatSoft, Inc. (2017). https://www.statsoft.com (accessed on 1 April 2024).

The qualitative variables were presented with counts and percentages. To determine the dependence, strength, and direction between variables, the Pearson chi-square test and the Cramer V test were used. In all the calculations, a statistical significance of $p = 0.05$ was used.

3. Results

3.1. Sample

In the study, 605 respondents participated, the majority of whom were women (77.36%). The largest group of respondents consisted of individuals over 40 years of age (55.04%). The vast majority of respondents live in the Masovian Voivodeship (79.50%). Nearly one-third of respondents live in a town with 50,000–100,000 inhabitants (34.21%), while one-fourth live in a town with 10,000–50,000 inhabitants (24.30%) (Table 1).

Table 1. Demographic characteristics of the study group.

	Study Group (n = 605)
Sex	
Women	468 (77.36%)
Men	124 (20.50%)
No response	13 (2.14%)
Age	
<25 years	28 (4.63%)
25–30 years	77 (12.73%)
31–35 years	82 (13.55%)
36–40 years	85 (14.05%)
>40 years	333 (55.04%)
Size of place of residence	
Village	24 (3.97%)
Town up to 10,000 inhabitants	26 (4.30%)
Town 10,000–50,000 inhabitants	147 (24.30%)
Town 50,000–100,000 inhabitants	207 (34.21%)
Town 100,000–500,000 inhabitants	113 (18.68%)
City above 500,000 inhabitants	88 (14.54%)

More than half of the respondents were nurses (56.20%), and every fourth of the respondents was a physician (23.64%). Nearly half of the respondents had been working in their profession for over 20 years (46.46%), and every fifth for 11–20 years (19.50%). The majority of respondents had a specialization (55.54%), while nearly one-sixth (14.71%) were working towards specialization. Most of the physicians and nurses worked in state hospitals (73.50%), while the pharmacists worked in public pharmacies (60.66%). Among nurses with a specialization (or prespecialization), the largest groups were surgical nurses (29.72%) and anesthetic and intensive care nurses (26.51%). Among the specialized physicians, specialists in internal medicine (12.77%) and general surgery (11.35%) were predominant, while among pharmacists with specialization, pharmacy pharmacists (64.44%) predominated (Table 2).

Table 2. Professional characteristics of respondents.

	Study Group (n = 605)
Job	
Nurse	340 (56.20%)
Physician	143 (23.64%)
Pharmacist	122 (20.16%)

Table 2. *Cont.*

	Study Group (n = 605)
Length of employment	
<1 years	14 (2.31%)
1–5 years	103 (17.02%)
6–10 years	89 (14.71%)
11–20 years	118 (19.50%)
>20 years	281 (46.46%)
Specialization	
Yes	336 (55.54%)
No	180 (29.75%)
In progress	89 (14.71%)
Main workplace of physicians and nurses (n = 483)	
State hospital	355 (73.50%)
Outpatient clinic	53 (10.97%%)
Private hospital	48 (9.94%)
Private practice	17 (3.52%%)
Other	10 (2.07%)
Main workplace of pharmacists (n = 122)	
Hospital pharmacy	25 (20.49%)
Public pharmacy	74 (60.66%)
Pharmaceutical company	13 (10.66%)
Other	10 (8.19%)

3.2. *Opinions of Medical Practitioners*

The majority of respondents considered antibiotic resistance to be a very serious (24.13%) or extremely serious (30.75%) problem on a global scale; however, on a closer scale (hospital in city/hospital in province/workplace), they primarily assess this problem as serious or somewhat serious (altogether, approximately 40% of the respondents) (Table 3).

The problem of antibiotic resistance on a global scale was perceived more seriously by:

- Physicians (more than other professions) and nurses (more than pharmacists) (p = 0.0003);
- Individuals working in the profession for more than a year (p < 0.01);
- Individuals with specialization or undergoing specialization training (p < 0.01). In all cases, there was a weak relationship.

The problem of antibiotic resistance on the scale of hospitals in a city was perceived more seriously by:

- Physicians (more than other professions) and nurses (more than pharmacists) (p < 0.01);
- Individuals working longer in the profession (p = 0.01);
- Individuals with specialization or undergoing specialization training (p < 0.01);
- Individuals working mainly in hospitals and clinics (p < 0.01) have weak relationships in all the above cases.

The problem of antibiotic resistance on the scale of hospitals in a province was perceived more seriously by:

- Physicians and nurses (p < 0.01);
- Individuals working longer in the profession (p < 0.01);
- Individuals with specialization or undergoing specialization training (p < 0.01);

- Individuals working in state hospitals ($p < 0.01$). In those cases, there were also weak relationships.

The problem of antibiotic resistance on the scale of the workplace (also with a rather weak relationship) was perceived more seriously by:

- Physicians and nurses ($p < 0.01$);
- Individuals working longer in the profession ($p = 0.02$);
- Individuals with specialization or undergoing specialization training ($p < 0.01$);
- Individuals working in state hospitals ($p < 0.01$).

Table 3. Responses of the respondents regarding the seriousness of the issue of antibiotic resistance on different scales.

	How Significant an Issue Is Antibiotic Resistance on the Scale...			
	Worldwide	**Hospitals in Your City**	**Hospitals in Your Province**	**Your Workplace**
No problem	2 (0.33%)	25 (4.13%)	26 (4.30%)	37 (6.12%)
Minor problem	29 (4.79%)	58 (9.59%)	64 (10.58%)	91 (15.04%)
Moderate problem	66 (10.91%)	94 (15.54%)	78 (12.89%)	94 (15.54%)
Somewhat serious problem	90 (14.88%)	139 (22.98%)	135 (22.31%)	113 (18.68%)
Serious problem	86 (14.21%)	115 (19.00%)	113 (18.68%)	109 (18.02%)
Very serious problem	146 (24.13%)	81 (13.39%)	88 (14.55%)	72 (11.90%)
Extremely serious problem	186 (30.75%)	93 (15.37%)	101 (16.69%)	89 (14.70%)

The majority of respondents considered the usage of antibiotics in livestock (36.69%), patient pressure to receive antibiotics (38.84%), prophylactic use of antibiotics (43.15%), and usage of antibiotics in children (31.90%) as extremely serious problems in exacerbating antibiotic resistance in Poland. Meanwhile, the use of antibiotics by patients in provinces and hospitals was mainly classified as a serious problem or a very serious problem (altogether, this accounts for approximately 40% of the responses) (Table 4).

Usage of antibiotics in livestock in exacerbating antibiotic resistance in Poland was perceived more seriously by:

- Physicians (more than other professions) and nurses (more than pharmacists) ($p < 0.01$);
- Individuals with specialization or undergoing specialization training ($p < 0.01$), with weak relationships in all cases.

Usage of antibiotics by patients in the province in exacerbating antibiotic resistance in Poland was perceived more seriously (with a weak relationship) by:

- Physicians (more than other professions) and nurses (more than pharmacists) ($p < 0.01$);
- Individuals with specialization or undergoing specialization training ($p < 0.01$);
- Pharmacists working in hospitals and public pharmacies ($p < 0.01$).

Usage of antibiotics by patients in the hospital in exacerbating antibiotic resistance in Poland was perceived more seriously by:

- Physicians and nurses ($p < 0.01$);
- Individuals with specialization or undergoing specialization training ($p < 0.01$), with rather weak relationships in both cases.

Patient pressure to receive antibiotics in exacerbating antibiotic resistance in Poland was perceived more seriously (but with a weak relationship) by:

- Physicians and nurses ($p < 0.01$),
- Individuals with specialization or undergoing specialization training ($p < 0.01$).

Prophylactic use of antibiotics in exacerbating antibiotic resistance in Poland was perceived more seriously (with a weak relationship) by:

- Physicians and nurses ($p < 0.01$),
- Individuals with specialization or undergoing specialization training ($p < 0.01$),
- Pharmacists working in hospitals and public pharmacies ($p = 0.03$).

Usage of antibiotics in children in exacerbating antibiotic resistance in Poland was perceived more seriously by:

- Physicians and nurses ($p < 0.01$),
- Individuals with specialization or undergoing specialization training ($p < 0.01$),
- Pharmacists working in hospitals and public pharmacies ($p = 0.01$) and the relationships were rather weak in all cases.

Table 4. Responses to questions regarding the exacerbation of antibiotic resistance through selected antibiotic usage methods.

	How Significant of an Issue Is… in Exacerbating Antibiotic Resistance in Poland?					
	Usage of Antibiotics in Livestock	Usage of Antibiotics by Patients in Province	Usage of Antibiotics by Patients in the Hospital	Patient Pressure to Receive Antibiotics	Prophylactic Use of Antibiotics	Usage of Antibiotics in Children
No problem	15 (2.48%)	11 (1.82%)	15 (2.48%)	17 (2.81%)	12 (1.98%)	16 (2.64%)
Minor problem	42 (6.94%)	58 (9.59%)	57 (9.42%)	44 (7.27%)	56 (9.25%)	50 (8.26%)
Moderate problem	73 (12.07%)	60 (9.92%)	84 (13.88%)	51 (8.43%)	54 (8.93%)	56 (9.26%)
Somewhat serious problem	68 (11.24%)	98 (16.20%)	85 (14.05%)	55 (9.09%)	52 (8.59%)	73 (12.07%)
Serious problem	83 (13.72%)	123 (20.33%)	146 (24.13%)	79 (13.06%)	77 (12.73%)	100 (16.53%)
Very serious problem	102 (16.86%)	136 (22.48%)	112 (18.51%)	124 (20.50%)	93 (15.37%)	117 (19.34%)
Extremely serious problem	222 (36.69%)	119 (19.66%)	106 (17.53%)	235 (38.84%)	261 (43.15%)	193 (31.90%)

Most respondents agreed with the statements that "improper use of antibiotics can worsen the patient's health condition" and "prescribing antibiotics without indications is considered unprofessional conduct". They also agree that "rational use of antibiotics will reduce the problem associated with antibiotic resistance", and "limiting the prescription of antibiotics solely for hospital treatment will help reduce the problem of antibiotic resistance". However, the agreement is more pronounced for the first two statements. Similar percentages of patients agree and disagree with the statement that "the issue of antibiotic resistance affects patients under my care" (41.2% vs. 43.74%).

With the statement "The issue of antibiotic resistance affects patients under my care", those more likely to agree were:

- Physicians and nurses ($p < 0.01$),
- Individuals working longer in the profession ($p = 0.01$),
- Individuals with specialization or undergoing specialization training ($p < 0.01$), with a rather weak relationship in all cases.

Physicians (more than other professions) and nurses (more than pharmacists) ($p < 0.01$ in each case), as well as individuals with specialization or undergoing specialization training ($p < 0.01$ in each case), were more likely to agree with the remaining statements from Table 5—these are rather weak associations.

More respondents agreed (approximately 50%) than disagreed (approximately 40%) with the statements listed in Table 6; however, the popularity of positive over negative responses was small, ranging from a few to several percent.

Table 5. Perception of antibiotic resistance among hospital staff ($n = 432$) in the context of patient care and strategies to combat antibiotic resistance. Part 1.

	To What Extent Do You Agree with the Statement				
	The Issue of Antibiotic Resistance Affects Patients Under My Care.	Rational Use of Antibiotics Will Reduce the Problem Associated with Antibiotic Resistance.	Improper Use of Antibiotics Can Worsen the Patient's Health Condition.	Prescribing Antibiotics without Indications Is Considered Unprofessional Conduct.	Limiting the Prescription of Antibiotics Solely for Hospital Treatment Will Help Reduce the Problem of Antibiotic Resistance.
Strongly disagree	44 (7.99%)	25 (4.54%)	12 (2.18%)	13 (2.36%)	28 (5.13%)
Disagree	95 (17.24%)	73 (13.25%)	50 (9.07%)	48 (8.72%)	74 (13.55%)
Slightly disagree	102 (18.51%)	73 (13.25%)	52 (9.44%)	58 (10.55%)	72 (13.19%)
Neutral	83 (15.06%)	68 (12.34%)	43 (7.80%)	25 (4.55%)	73 (13.37%)
Slightly agree	84 (15.25%)	92 (16.70%)	74 (13.43%)	60 (10.91%)	90 (16.48%)
Agree	69 (12.52%)	88 (15.97%)	123 (22.32%)	101 (18.36%)	82 (15.02%)
Strongly agree	74 (13.43%)	132 (23.95%)	197 (35.76%)	245 (44.55%)	127 (23.26%)

With the statement "In my hospital, we should implement a policy for the rational use of antibiotics", those more likely to agree were (weak relationships):

- Physicians and nurses ($p < 0.01$),
- Individuals with specialization or undergoing specialization training ($p = 0.008$).

With the statement "In my hospital, guidelines for the use of antibiotics should be implemented.", those more likely to agree were:

- Physicians (more than other professions) and nurses (more than pharmacists) ($p < 0.01$), this is a weak relationship.

Table 6. Perception of antibiotic resistance among hospital staff ($n = 432$) in the context of patient care and strategies to combat antibiotic resistance. Part 2.

	To What Extent Do You Agree with the Statement				
	In My Hospital, We Should Implement a Policy for the Rational Use of Antibiotics.	In My Hospital, Guidelines for the Use of Antibiotics Should Be Implemented.	In My Hospital, a Computer Application Should Be Launched to Provide Advice on the Selection and Duration of Antibiotic Therapy for Patients.	In My Hospital, There Should Be a Team Consisting of a Specialist Physician, Clinical Pharmacist, and Nurse Providing Personalized Advice on Antibiotic Prescribing.	I Am Willing to Participate in Any Initiatives Related to the Use of Antimicrobial Agents in My Hospital.
Strongly disagree	37 (8.56%)	39 (9.18%)	34 (7.89%)	56 (13.11%)	47 (11.01%)
Disagree	70 (16.20%)	64 (15.06%)	62 (14.39%)	56 (13.11%)	54 (12.65%)
Slightly disagree	65 (15.05%)	56 (13.18%)	53 (12.29%)	47 (11.01%)	58 (13.58%)
Neutral	47 (10.88%)	51 (12.00%)	46 (10.67%)	60 (14.05%)	62 (14.52%)
Slightly agree	61 (14.12%)	65 (15.29%)	63 (14.62%)	44 (10.30%)	54 (12.65%)
Agree	56 (12.96%)	56 (13.18%)	68 (15.78%)	68 (15.93%)	60 (14.05%)
Strongly agree	96 (22.23%)	94 (22.11%)	105 (24.36%)	96 (22.49%)	92 (21.54%)

With the statement "In my hospital, there should be a team consisting of a specialist physician, a clinical pharmacist and a nurse providing personalized advice on prescribing antibiotics.", those more likely to agree were:

- Physicians (more than other professions) and nurses (more than pharmacists) ($p = 0.03$), this is a weak relationship.
- Individuals with specialization or undergoing specialization training ($p < 0.01$), this is a rather weak relationship.

With the statement "I am willing to participate in any initiatives related to the use of antimicrobial agents in my hospital.", those more likely to agree were:

- Physicians ($p = 0.01$), this is a weak relationship.

The majority of respondents agreed with the statements listed in Table 7 (around 50–60% of responses in favor vs. around 30% of responses against).

With the first four statements from Table 7, physicians ($p < 0.01$ with a weak relationship in each case) and individuals with specialization or undergoing specialization training ($p < 0.01$ in each case except the second question where $p < 0.01$; the first two associations are weak, the remaining two are rather weak) were more likely to agree.

With the remaining statements from Table 7, physicians (more than other professions) and nurses (more than pharmacists) ($p = 0.03$ and $p < 0.01$, these are rather weak associations) and individuals with specialization or undergoing specialization training (in both cases $p < 0.01$ these are weak associations) were more likely to agree.

Table 7. Healthcare workers' approach to strategies aimed at combating antibiotic resistance.

	To What Extent Do You Agree with the Statement					
	Strategies to Combat Antibiotic Resistance Can Help Limit This Phenomenon.	Regular Audits of Antibiotic Therapy in Hospitals along with Postaudit Recommendations Can Help Reduce Antibiotic Resistance.	Limiting the Prescription of All Antibiotics Can Reduce Antibiotic Resistance.	Limiting the Prescription of Certain Antibiotics Can Reduce Antibiotic Resistance.	Easily Accessible Advice from Microbiologists Can Help Reduce Antibiotic Resistance.	Regular Educational Training on the Rational Use of Antibiotics Can Reduce Antibiotic Resistance.
Strongly disagree	23 (3.80%)	39 (6.45%)	28 (4.63%)	27 (4.46%)	33 (5.45%)	31 (5.12%)
Disagree	58 (9.59%)	71 (11.74%)	76 (12.56%)	68 (11.24%)	65 (10.74%)	67 (11.07%)
Slightly disagree	97 (16.03%)	91 (15.04%)	76 (12.56%)	84 (13.88%)	73 (12.07%)	84 (13.88%)
Neutral	89 (14.71%)	75 (12.39%)	90 (14.88%)	74 (12.23%)	59 (9.75%)	62 (10.25%)
Slightly agree	80 (13.22%)	86 (14.21%)	91 (15.04%)	102 (16.86%)	80 (13.22%)	74 (12.23%)
Agree	138 (22.81%)	136 (22.48%)	118 (19.50%)	114 (18.84%)	126 (20.83%)	123 (20.33%)
Strongly agree	120 (19.84%)	107 (17.69%)	126 (20.83%)	136 (22.49%)	169 (27.94%)	164 (27.12%)

4. Discussion

To the best of our knowledge, our study is the first of its kind to include such a large number of Polish medical workers. To the present day, research has been conducted on the awareness of antibiotic resistance among the general public [16,17] and medical students [18,19] in Poland. This makes it all the more important to study large groups of medical workers, which was the aim of this study.

According to the results we obtained, the majority of respondents—Polish medical workers—consider antibiotic resistance a very serious problem (24.13%) or extremely serious (30.75%). The problem of antibiotic resistance on a global scale was mentioned, especially in the opinions of physicians and nurses, including people working in the profession for over a year, or people with specialization or undergoing specialist training. Similarly, these groups most often indicated that antibiotic resistance is a problem in their workplace.

Some publications directly indicate that a small number of studies, including those conducted in Europe, focus on AMR awareness among healthcare workers, although there are studies of this type conducted among social groups or students [20]. This type of research was conducted in Italy. As suggested by our study, Barchitta et al. (2021) indicated that Italian health workers have disparate knowledge and attitudes regarding antibiotic use and AMR awareness, stressing the need for educational and training interventions for specific professional groups [21]. Additionally, an Iranian study confirms large differences in the level of knowledge and approach to the use of antibiotics among health workers, indicating the need for the education of these groups [22]. However, Keizer et al. (2019), comparing health workers from Germany and the Netherlands, indicate a fairly large and similar awareness of different groups, although German workers, compared to Dutch, see more possibilities of influencing rationalizations of antibiotic therapy [15].

Studies of AMR awareness of individual professional groups, e.g., nurses, also do not give unambiguous results. Nurses demonstrate moderate awareness of the AMR problem and, importantly, this awareness is not dependent on demographic characteristics or their attitudes and general knowledge. There was also no link between awareness and the total number of years of experience or specialist training [23,24]. In turn, a study of young Italian physicians showed that their knowledge of antibiotic therapy was low compared to the declared one [25].

There are also few studies involving pharmacists, although it is stressed that the broader role of this professional group, including the provision of various patient care services, results in better patient health outcomes and lower healthcare costs. Properly trained pharmacists can therefore have a significant impact on increasing rational antibiotic use, which in turn can affect the global problem of antimicrobial resistance [26,27]. Moreover, pharmacists can be the right group of professionals to raise awareness. A study assessing the pharmaceutical intervention in increasing patient knowledge of antibiotic therapy shows that those who took the advice of a local pharmacist showed much better knowledge of antibiotic use [28].

The results obtained in our study indicate that approximately half of respondents indicate the importance of the AMR problem. This data is of particular importance due to the fact that the AMR problem is indicated as one of the most important public health problems by many organizations, including WHO [1]. WHO highlights the scale of improper use of antimicrobials as a significant risk factor, often in improper doses and sometimes in the case of nonbacterial infections. The evolution of bacterial resistance as a result of the widespread and irrational use of antibiotics poses serious challenges to healthcare systems and increases the cost of treatment [29–31]. Given the high frequency of prescribing antibiotics and the growing global consumption of antibiotics, there is an urgent need to address this problem in order to protect public health [32,33].

To address the challenges of improper antibiotic therapy, various interventions are recommended, including the promotion, monitoring and evaluation of the rational use of antibiotic therapy at various levels of healthcare, as well as the adoption of clinical guidelines or the establishment of drug and therapeutic committees. For this purpose, it is important to include training in rational pharmacotherapy in educational programs, as well as the continuous education of medical staff and the public on antibiotic therapy [7,34,35].

The role of health workers is crucial in shaping public awareness of rational antibiotic therapy [7]. The primary objective of rational management of antimicrobials should be to improve patient outcomes while minimizing the medical and economic impacts of antibiotics. Given the significant differences in awareness of AMR among different groups of health workers, it is essential to plan educational interventions aimed at specific target groups.

5. Conclusions

The unreasonable use of antibiotics is a worldwide public health threat. Many factors contribute to an increase in antibiotic resistance, but one of the biggest is insufficient awareness about the risks associated with AMR both among medical professionals and the public. This situation has both medical consequences, leading to significant morbidity and mortality, and financial consequences for health systems and economies.

In this context, it is crucial to take targeted action as soon as possible, aiming not only at monitoring and monitoring the situation, but also to educate groups on the risks associated with antibiotic resistance. Only intentional, long-term action can bring expected results, including the rationalization of the use of this group of drugs.

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Abbreviations

AMR	antimicrobial resistance
AMS	antimicrobial stewardship
ASP	antibiotic stewardship programs
EU	European Union
WHO	World Health Organization

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PROTECTED BETA-LACTAM PRESCRIPTION FOR PATIENTS WITH SEPTIC SHOCK

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Introduction

As A. Piccioni et al. [1] note, the development of septic shock in intensive care patients is still a leading cause of death in many cases, both in developed and developing countries. The risk of sepsis appearing as a complication of the main disease flow is especially high amongst elderly patients, children, pregnant, parturients, and patients with low immunity status.

Septic shock is caused by one of the types of sepsis. Modern medicine has given such a definition to sepsis: it is life-threatening organ dysfunction, which is caused by the improper, inadequate reaction of a body to the infection pathogen. According to the International Guidelines for Management of Sepsis and Septic Shock from 2021 by L. Evans et al. [2], septic shock is usually characterized by major dysfunctions of blood circulation and cellular metabolism, which significantly increase the odds of the lethal outcome.

To diagnose sepsis and septic shock, a qSOFA scale (quick Sequential Organ Failure Assessment) is currently recommended, as a quick evaluation of organ dysfunction dynamics. If the qSOFA scale is >2, then it is recommended to begin the sepsis treatment procedure. The following clinical characteristics are regarded as criteria for qSOFA:

- The Glasgow Coma Scale (evaluation for consciousness dysfunction) is less than 15;
- Systolic blood pressure (SAB) is less than 100 mm Hg.;
- The breathing rate is higher than 22 inhales per minute.

2-3 points on the qSOFA scale are noted to end up in a lethal outcome in 70% of cases, but only in 24% of patients with confirmed infection. As such, A. Perner et al. [3] offer to use other criteria for sepsis and septic shock diagnostics in intensive care:

- body temperature is 38°C and higher or 36°C or lower;
- leukocytosis or leukopenia;
- neutropenia;
- high lactate rates in blood plasma;
- high procalcitonin rates.

Septic complications and bacillaemia is most often caused as a result of intensive care patient infection by nosocomial pathogens. The primary peculiarity of these pathogens is their complete or partial resistance to antibiotics. According to S. Di Franko et al. [4], there are four types of gram-negative bacteria, which are primarily responsible for the development of septic shock, these are:

- *Klebsiella pneumoniae (K. pneumoniae)*;
- *Escherichia coli (E. Coli)*;
- *Acinetobacter species (A. species)*;
- *Pseudomonas aeruginosae (P. Aeruginosae)*.

The carbapenemase resistance mechanism formation of these microorganisms has been thoroughly researched. Genes, which code the carbapenemase, are on the mobile genetic elements alongside other genes, which form resistance to other antibiotics. Idowu et al. note, that it is due to this the gram-negative bacteria develop multi-resistance to all β-lactam antibiotics [5].

The latest antimicrobial surveillance report for the European Center for Disease Prevention and Control (ECDC) [6] found a trend of rising carbapenem resistance across Europe. Epidemiologists' data from Poland also show the tendency. This tendency, according to B. Nowaczyk et al. [7], was observed with *K. pneumoniae*, for which the proportion of invasive isolates was 8.2% in 2020 compared to 2.1% in 2016, and Acinetobacter species – 78.2% in 2020 compared to 66% in 2016.

For the differential diagnosis of sepsis and individual selection of antibiotic therapy, S. Dhaese et al. [8] recommend bacteriological examination of Intensive Care Unit (ICU) patient samples. However, the implementation of traditional cultural methods takes 1-2 days, and the determination of antigens by the enzyme-linked immunosorbent assay (ELISA) method and the genetic material of the pathogen by Polymerase Chain Reaction (PCR) takes several hours. An analytical study of published work by J.R. Strich et al. [9] proves that every hour of delaying septic shock antibiotic therapy increases the chances for the lethal outcome proportionately. In these cases, ICU doctors are forced to prescribe antimicrobic medications empirically, based on their experience and intuition.

Modern pharmaceuticals offer combined protected antibiotic medications, which include beta-lactam and bacterial beta-lactamase inhibitors. R.P. Veiga and J.A. Paiva [10], in their analysis, highlight relebactam and tazobactam as microorganism ferment inhibitors, which are, currently, widely used.

The research aims to evaluate the effectiveness of septic shock treatment with imipenem/cilastin/relebactam (IMI/REL) in comparison to piperacillin/tazobactam (PTZ) complex protected medications.

Materials and methods

A retrospective, uncontrolled, non-randomized, observational study in the ICU at the University Hospital in Krakow, Poland. The protocol was approved by the institution's ethics committee. Each patient or his relative signed an informed consent to participate.

At the preparatory stage, the study included 17 patients with septic shock who were treated during 2021-2022 in the ICU. The exclusion criteria were: age less than 18 years, pregnancy or lactation, previous use of any of the prescribed drugs, allergy to any of the components of these drugs, meningitis or cystic fibrosis, inability to sign informed consent or absence of relatives, dementia, participation in clinical trials in the previous six months.

The stage of material collection and observation was concluded 96 hours from the estimated moment of septic shock development after the patient's admission to the ICU. Demographic characteristics were collected: age, gender, weight, body mass index, comorbidities, main disease, and treatment methods for the main disease.

Patients were randomly divided into two groups: group 1 received imipenem/cilastin/-relebactam (n=9), group 2 received piperacillin/tazobactam (n=8). Moreover, all patients underwent appropriate anti-shock therapy, which included noradrenaline preparations, and infusions of crystalloid and albumin solutions. Acute respiratory distress syndrome (ARDS) was diagnosed among 5 patients, as a result of which artificial lung ventilation was employed. Among 7 patients, symptoms of acute renal failure (ARF) were found, in connection with which they were prescribed renal replacement therapy, which is a procedure of venous hemofiltration. Also at this stage, data on the number of lethal and positive outcomes of the septic shock treatment, and the causes of mortality was collected.

Initial imipenem/cilastin/relebactam infusion was administered each 6 hours with 500mg of imipenem/cilastin and 250 mg of the relebactam for patients with normal creatinine clearance. Piperacillin/tazobactam infusion was administered in a concentration of 4.5 g piperacillin and 0.5 g of tazobactam every 6 hours with lengthy infusions, for a period of 3-4 hours. A. Henderson et al. [11] have published the results of the clinical test, which yet again proved the need for the medication dose estimation to overcome minimum inhibiting concentration (MIC) in blood by 4 times.

The biomaterial was taken from all patients for a general blood test, the study of the level of lactate, procalcitonin, and creatinine clearance. Determination of MIC, sensitivity, and antibiotic resistance of infectious pathogens was carried out by unified cultural and disk diffusion methods, as well as using E-tests in fresh cultures of isolates. For phenotyping, the CarbaNP test was used in various modifications. Genotyping of multidrug-resistant isolates was performed using real-time multiplex PCR.

At the stage of statistical processing of the material, the STATISTICA 10.0 program by StatSoft was used. For each quantitative indicator, the median and the interquartile range were determined.

Results

The majority of those examined were males (Table 1) over the age of 60 who were transferred to the ICU after surgery. The cause of surgery were cardiovascular pathologies, injuries of soft tissues and organs of the chest, and cirrhosis of the liver. The most common comorbidities were type II diabetes mellitus (in 3 patients, 18%) and alcoholism (in 2 patients, 12%).

Only one patient from the research basis (6%) has a BMI index, that corresponds to the normal body weight. Among 8 patients (47%), BMI varied from 25 to 29, which indicated excessive weight, while among the remaining 8 patients (47%), BMI ranged from 30 to 33, which is typical for grade I obesity.

During observation in the ICU, all examined patients showed an increase in the level of plasma lactate by 1.5-2 times compared with the norm (0.5-2.2 μmol/l). The median content of procalcitonin in group 1 was 21.4 ng/ml, which is 40 times higher than the normal value (<0.5 ng/ml). In Group 2, the median value was 60 times higher than normal and was equal to 31.9 ng/ml.

The septic shock diagnosis was established using the qSOFA scale: among 16 patients, there was a sharp decrease in systolic blood pressure to 65-70 mm hg, 15 patients had an increase in respiratory rate, 12 patients had a Glasgow Coma Scale score of fewer than 15 points. The most common complications were ARDS and ARF.

All patients with acute respiratory distress syndrome underwent mechanical ventilation. Among 3 patients, mild ARDS was diagnosed, and non-invasive mechanical ventilation was employed as respiratory therapy. Among 2 patients, ARDS of moderate severity was noted, and the value of the PaO2/FiO2 oxygenation index was approximately 150 mm hg. For those patients, invasive mechanical ventilation with lung protection, including the prone position for at least 16 hours was performed. The target tidal volume was 6-8 ml/kg of body weight. In approximately half of the patients, bacillaemia was found.

Table 1.*Clinical and demographic characteristics of patients*

Characteristic	n, (%) or median (interquartile diapason)	
	Group 1, (IMI/REL), n=9	**Group 2, (PTZ) n=8**
Males	6 (67)	6 (75)
Age, years	66 (54-70)	71 (62-79)
Weight, kg	91 (81-95)	88 (74-104)
BMI	29 (26-31)	30 (26-31)
qSOFA	3 (2-3)	3 (2-3)
Lactate, mmol/L	3.1 (2.8-4.1)	3.6 (3.3-4.0)
Procalcitonin, ng/ml	21.4 (9.7-55.1)	31.9 (11.6-57.8)
Bacillaemia	4 (44.44)	4 (50)
ARDS	3 (33.33)	2 (25)
AKI	3 (33.33)	4 (50)
Lethaloutcome	5 (55)	4 (50)

Note: BMI – body mass index, qSOFA – quick sequential organ failure assessment, ARDS – acute respiratory distress syndrome, AKI – acute kidney failure.

The formation of acute renal failure was evaluated by the level of creatinine in the blood serum and the glomerular filtration rate (creatinine clearance) in the first few hours after the expected development of septic shock (Table 2). AKI was diagnosed among 3 patients in Group 1. Among them, the median content of creatinine exceeded the normal values by more than 3 times, while the creatinine clearance decreased by almost 2 times. In group 2, acute renal failure was diagnosed among 4 patients, the creatinine concentration in these patients was also 3 times higher than normal, and the clearance fell by 2 times. Among 1 patient in Group 1 and 2 patients in Group 2, acute renal failure developed against the background of ARDS. In Group 1, the patient had ARDS of moderate severity, in Group 2: 1 patient had moderate severity, and 1 patient had mild severity.

All patients with acute renal failure were prescribed renal replacement therapy (RRT), a procedure of venous hemofiltration. Since 6 out of 7 examined patients had elevated body mass index values, they underwent prolonged high-volume hemofiltration for 48 hours, with a filtration dose of 50 ml/kg/h. Alongside RRT, for patients in group 1, a concentration of the antibiotic IMI/REL was reduced to 400 mg of imipenem/cilastin and 200 mg of relebactam due to confirmed nephrotoxicity.

Table 2.*Evaluation of kidney functionality amongst patients with septic shock development (median, (interquartile diapason))*

Group 1, (IMI/REL), n=9				Group 2, (PTZ) n=8			
AKI isabsent, n=6 (66.66%)		AKI ispresent, n=3 (33.33%)		AKI isabsent, n=4 (50%)		AKI ispresent, n=4 (50%)	
Creatinine, mmol/L	Creatininecelarance, ml/min	Creatinine, mmol/L	Creatininecelarance, ml/min	Creatinine, mmol/L	Creatininecelarance, ml/min	Creatinine, mmol/L	Creatininecelarance, ml/min
78 (75-81)	116 (106-120)	266 (241-275)	60 (55-62)	77 (71.5-81)	111 (94-123.5)	270 (257-285)	51.5 (49-57)

Before the initiation of antibiotic therapy in patients of both groups, biomaterial was collected for bacteriological studies. Since delaying antibiotic therapy substantially increases the likelihood of death, IMI/REL or PTZ infusions were started as soon as the diagnosis of septic shock was made.

Nosocomial infections were found among all examined patients. Among 4 patients in Group 1, and 3 patients in Group 2 more than one infectious agent was present (Table 3). Gram-negative bacteria predominated in the spectrum of pathogens. One type of gram-positive bacteria was present in patients in group 1 and group 2.

Identification of *Pseudomonas aeruginosae* and *Acinetobacter baumanii* in purulent tracheabronchial secretions in patients, who are undergoing mechanical ventilation indicated the development of ventilator-associated pneumonia. After abdominal surgery, *Escherichia coli* was isolated in 1 patient, and *Klebsiella pneumoniae* was isolated in 1 patient, which confirms the development of intra-abdominal infection.

In patients with *Bacillaemia*, *Klebsiella pneumonia* was observed in 4 cases, *Escherichia coli* in 2 cases, and acinetobacteria in 2 cases, which further aggravated the severity of the condition.

Table 3.*The spectrum of invasive isolates among patients with septic shock*

Pathogen	Group 1, (IMI/REL), n=9	Group 2, (IMI/REL) n=8
Pseudomonasaeruginosae, n (%)	2 (22.2)	2 (25)
Klebsiella pneumoniae + Acinetobacter baumanii, n (%)	1 (11.15)	1 (12.5)
Pseudomonas aeruginosae + Acinetobacter baumanii, n (%)	3 (33.3)	2 (25)
Escherichiacoli, n (%)	2 (22.2)	2 (25)
Streptococcuspneumoniae, n (%)	-	1 (12.5)
Staphylococcusaureus, n (%)	1 (11.15)	-

As described in E. Matuschek, D.F.J. Brown and G. Kahlmeter [12] work, testing of detected infectious agents was under the EUCAST guidelines. Serial dilution MIC values were used to determine breakpoint cut-off points for wild-type organisms (organisms without phenotypically detectable resistance) and to calculate sensitivity. The MIC for IMI/REL ranged from 0.125 mg/L for *Staphylococcus aureus* to 2 mg/L for

Pseudomonas aeruginosae. In the case of PTZ, breakpoint cut-off points for the *Acinetobacter baumanii* were not defined, and the disk diffusion method according to CLSI standards with a PTZ content per disk of 100 µg was used to study resistance. For other pathogens, the piperacillin/tazobactam MIC ranged from 0.064 mg/L for *Streptococcus pneumoniae* to 16 mg/L for *Pseudomonas aeruginosae*.*A. baumannii*strain with high resistance to the first-generation antibiotics, the protected imipenem, and to the comparative medication, as well as to the inhibitor-protected piperacillin and the amoxicillin/clavulanate and the ceftriaxone (Table 4).

Particularly high resistance to β-lactams was prominent in the invasive *P. aeruginosae* isolates. The acquired data allowed us to conclude the presence of multidrug resistance (MDR) in *Acinetobacterium* and *Pseudomonas aeruginosa*, the pathogens of nosocomial infections, which was present amongst the examined patients with septic shock.

And on the contrary, for *Escherichia coli, Staphylococcus aureus, Klebsiella pneumonia*, and *Streptococcus pneumonia*, high sensitivity to the studied combined antibiotic medications was prominent. Those were present in Group 1.

Table 4. *Antibiotic resistance of invasive isolates among patients with septic shock*

Pathogen		***P. aeruginosae***	***A. baumannii***	***E. coli***	***K. pneumoniae***	***S. aureus***	***S. pneumoniae***
Group 1, (IMI/REL), n=9	Sensitivity (S), %	51	6.5	96	90	97	98
	Intermediateresistance (I), %	19	10.5	4	2.5	3	2
	Resistance (R), %	30	83	0	7.5	0	0
Group 2, (PTZ) n=8	Sensitivity (S), %	45.5	10	97	89	97	97.5
	Intermediateresistance (I), %	22	9.5	3	2	3	2.5
	Resistance (R), %	32.5	80.5	0	9	0	0

Based on acquired data, the production of the carbapenemase for the multiresistant strains *P. aeruginosae* and *A. baumannii* was suggested. Phenotypic research of invasive isolates was carried out to determine what type of β-lactamase they produce. Since the studied strains, during the evaluation of antibiotic resistance, have shown insensitivity to amoxicillin/clavulonate, phenotyping of extended-spectrum β-lactamase (ESBL) was not performed. Additional bacterial enzyme detection was employed with the use of a modified Carba NP II test with specific inhibition. As such, the use of tazobactam in the test made it possible to assess the activity of class A β-lactamases, KRS-type, and the use of EDTA allowed the assession of the activity of metallo-β-lactamases (MBL). As a result, the production of two types of enzymes, those being bovine and MBL, was confirmed in the analyzed *P. aeruginosae* strains.

During the analysis of *A. baumannii*, the CarbAcineto NP test, specially designed for the phenotyping of this pathogen, was used. As such, the production of OXA-23-like carbapenemase was noted in the analyzed isolates. All detected strains were analyzed to identify the genes, which cause the ferment synthesis. Amongst 3 (43%) studied strains of *Acinetobacterium*, 2 families of genes encoding different series of enzymes were found. Genotyping indicated the presence of the OXA-23-like gene, which causes the synthesis of carbapenem-hydrolyzing class *D oxacillinase*, and VIM-1 (Verona integron-encoded metallo-beta-lactamases), encoding metallo-β-lactamases. In 2 cases, only OXA-23-like genes were identified, in one case, the VIM-1 gene, and in another, the IMP-1 gene responsible for imipenemase synthesis.

During the genotyping of the *P. aeruginosa*, 3 (30%) strains had IMP-1 gene, while in 2 other cases a VIM-1 gene was found. The number of fatal outcomes in both groups after 96 hours of observation was approximately the same, about 50% of cases. Among patients with septic shock, complicated by ventilator-associated pneumonia, the mortality rate was 40% (2 patients). Among patients with acute renal failure, despite ongoing renal replacement therapy, the mortality rate was 29% (2 patients). Among 5 examined patients, the development of multiple organ failure syndromes (MOS) was noted, which resulted in a fatal outcome. All of the examined patients had cardiovascular insufficiency. In 1 patient, it was accompanied by liver failure. In another patient, bowel dysfunction progressed. Among 3 cases, there was severe cerebral dysfunction and the occurrence of secondary cerebral disorders. Among 7 cases of lethal outcomes in patients, strains of multiresistant*Acinetobacter baumanii* were detected, and in 2 cases – *Pseudomonas aeruginosae*.

Discussion

Inhibitor-protected beta-lactams are widely used in modern clinical practice. According to the recommendations of the European Society for Clinical Microbiology for the treatment of nosocomial infections, compiled by M. Paul et al. [13], it is offered to use the combination of imipenem/cilastin/relebactam or piperacillin/tazobactam medications. According to Y.A. Heo [14], these medications have shown high efficacy against the main pathogens of nosocomial infections – gram-negative bacteria in vitro. However, the success of their clinical use in the treatment of severe infectious diseases such as sepsis and septic shock remains insufficiently studied.

An attempt to evaluate the benefits of prescribing these antibiotics to ICU patients was concluded. Patients were randomly divided into two groups, while randomization and blind placebo control was not carried out. The obtained clinical and demographic characteristics of the patients indicated that the formation of two homogeneous groups in terms of age, sex, laboratory parameters, and severity of the condition was achieved. Accordingly, we consider it quite reasonable to compare the effectiveness of antibiotics in patients in these groups.

It should also be noted that all patients received adequate anti-shock therapy, which included crystalloid, albumin solution, preparations of norepinephrine, dobutamine, and hydrocortisone infusions following individual prescribed needs.

Changes in the level of procalcitonin in the blood are known to be an independent prognostic marker for the development of sepsis and septic shock. The conclusions of Q. Hu and Y. Zhang [15] confirm that an increase in the content of the marker above 10 ng/ml indicates not only a severe case of septic shock but also a high probability of developing complications, including acute renal failure. Among our patients, the values of the median concentration of procalcitonin from 21.4 ng/ml to 31.9 ng/ml were observed, which is 2 and 3 times higher than the prognosis value.

As renal replacement therapy, a venous hemofiltration procedure was prescribed with an increase in serum creatinine by more than 3 times and a simultaneous decrease in glomerular filtration rate. Bacteriological examination revealed E. coli in the urine of 4 patients and the blood of 2 patients. The high sensitivity of this pathogen to the analyzed drugs and the rapid initiation of treatment had a positive effect on the outcome of patients with septic shock complicated by acute renal failure. Mortality was 29%, which correlates with data from other studies, such as D.N. Fish, I. Teitelbaumamd E. Abraham [16]. Fatal outcomes were observed in patients with confirmed *Pseudomonas aeruginosa* and acinetobacteria with a high level of polyresistance.

Another common complication during septic shock is acute respiratory distress syndrome. The presence of ARDS is one of the risk factors for the development of ventilator-associated pneumonia (VAP). In our case, VAP was induced by multiresistant strains of *Acinetobacter baumannii* and Pseudomonas aeruginosae. The pronounced resistance of pathogens to the studied antimicrobial drugs led to a lethal outcome among two patients with VAP. According to C.V. Guillamet et al. [17], the reason for the development of polyresistance in *Pseudomonas aeruginosa* and *Acinetobacteria*, which results in high mortality in patients with bacterial pneumonia, may be inadequate antibiotic therapy at the initial stages of the disease. However, patients who had previously taken the studied drugs (the IMI/REL and PTZ), were not included in the research.

As a result of MDR-type infectious pathogens phenotyping, the production of class A and MVL-type β-lactamases in *P. aeruginosae*, and OXA-23-like type carbapenemase in *A. baumannii* was confirmed. According to P.D. Tamma and P.J. Simner [18], currently used methods for β-lactamase phenotyping production in *Acinetobacterium* have several significant drawbacks, including unsatisfactory sensitivity and specificity, that bein the test used in our study as well. Therefore, we decided to carry out the genotyping procedure for isolated invasive isolates.

The result of the procedure was the d...

tion of genes, which cause the synthesis of metallo-β-lactamases in *P. aeruginosae*. An even greater diversity emerged as a result of the genotyping of *A. baumannii*. Some of its strains have demonstrated the ability to simultaneously synthesize both metallo-β-lactamases and oxacillinases. A pharmaceutical review by H. Mansour et al. [19] describes imipenem/cilastin/relebactam as a combination drug containing imipenem, an antibiotic of the β-lactam group, cilastatin, an inhibitor of dehydropeptidase-I in the kidneys, and relebactam, an inhibitor of class A and C bacterial β-lactamases. A decrease in the activity of imipenem metabolism in the kidneys prolongs the duration of its action. S.H. Lob et al. [20] studied the inhibitory effect of relbactam in vitro and in vivo and showed that it is not effective against metallo-β-lactamases and oxacillinases. But the genes of just these enzymes were discovered during the genotyping of *Acinetobacter baumanii* and *Pseudomonas aeruginosae*.

S. García-Fernández et al. [21] conducted a multicenter sensitivity assessment of *P. aeruginosae* and *A. baumannii* to the combined reference medication piperacillin/tazobactam, which contains a semi-synthetic ureidopenicillin, piperacillin, and several types of β-lactamase inhibitor, tazobactam. It is known that tazobactam exhibits high activity against class A β-lactamases and class D metallo-β-lactamases. However, A. Lukić-Grlić et al. [22], who have investigated strains of bacteria producing carbapenem-hydrolyzing class *D oxacillinases*, PTZ activity in vivo has not been confirmed. During genotyping of *Acinetobacter baumanii* strains, genes encoding these enzymes were identified in 5 cases.

S. Coyne et al. [23] attribute the high resistance of *A. baumannii* to protected carbapenems attributed to additional manifestations of resistance, such as the activation of genes encoding efflux pumps. Among them, the expression of genes of the superfamily of RND pump proteins plays the greatest role since they can pump antibiotics through both the internal and external membranes of the microorganism. In a review by S. Lambden et al. [24], it is noted that high mortality due to septic shock remains one of the main problems in the management of patients in intensive care units. The rapid development of multiple organ failure syndrome (MOS) in ınocompromised patients is still ahead of the ability of physicians to counteract such consequences. During the analysis of causes of MODS in the patients, attention was drawn to the fact that cerebral disorders (3 cases, 30%) are in second place in frequency after the development of cardiovascular insufficiency (5 patients, 50%). According to M.C. Quinton et al. [25], high doses of piperacillin/tazobactam in the blood of patients can lead to neurological complications among patients with septic shock due to the proven toxicity of this medication. The results do not allow us to either confirm or refute this conclusion, since the examined patients had impaired consciousness according to the Glasgow Coma Scale even before the start of antibiotic therapy.

The main challenge for septic shock antibiotic therapy, caused by the nosocomial infection, remains to be the multi-resistance of *Acinetobacter baumannii*. Mutations in the genome leading to reduced or increased gene expression, as well as the ability for horizontal gene transfer, provide *A. baumannii* the ability to synthesize β-lactamases, metallo-β-lactamases, and extended-spectrum beta-lactamase (ESBL), plasmid-mediated AmpC beta-lactamases, carbapenem-hydrolyzing class *D oxacillinases*. In their review, R.A. Bonnin, P. Noedmann and L. Poirel [26] note that such a variety of enzymes leads to the formation of pathogen resistance to aminoglycosides, broad-spectrum cephalosporins, carbapenems, tigecycline, and colistin, which are antibiotics of last resort.

Unfortunately, the number of resistant strains of microorganisms producing carbapenemase, which are not inhibited by employment medications, is increasing in the world. This phenomenon is explained by the growing popularity of medical tourism and the uncontrolled use of antibiotics in some countries.

Conclusions

The number of positive clinical and microbiological responses in groups 1 and 2 did not differ significantly and amounted to 45% (4 outcomes) and 50% (4 outcomes), respectively. Therefore, our data do not support the benefit of imipenem/cilastin/relebactam or piperacillin/tazobactam in patients with septic shock in the ICU. Inhibitor-protected beta-lactams showed high efficacy in the treatment of sepsis caused by *Escherichia coli* and *Klebsiella pneumoniae*, moderate efficacy against *Pseudomonas aeruginosae*, and insignificant efficacy against multidrug-resistant *Acinetobacter baumannii*. As some patients had more than one MDR-type infectious agent, the use of IMI/REL and PTZ also did not lead to a positive result in such cases.

The pronounced resistance of *P. aeruginosae* to the IMI/REL medications is caused by the presence of a phenotype in it, which is characterized by the production of metallo-β-lactamases, which are not inhibited by relbactam. Tazobactam, which is part of PTZ, is effective against these enzymes. A higher degree of a positive outcome in group 2 was expected, yet, among some patients of this group, alongside the multidrug-resistant strain of Pseudomonas aeruginosa, *A. baumannii* MDR-type was detected. A feature of the genotype of the established strain was the existence of OXA-23-like genes for carbapenem-hydrolyzing class *D oxacillinases*. Tazobactam is not an inhibitor for this type of bacterial enzyme, therefore, in patients with confirmed *A. baumannii*, the administration of PTZ did not achieve desired results.

The problem of early detection of infectious pathogens in patients with septic shock is currently of substantial actuality. Modern methods of genotyping using real-time multiplex PCR make it possible to obtain a detailed characterization of the causes of multiresistance in the identified strains. Proper provision of such information would enable the anesthesiologist-resuscitator to prescribe antibiotic therapy not empirically, but purposefully, taking into account the characteristics of the detected microorganisms.

Multi-resistance strains of nosocomial infections are still one of the primary causes of lethal outcomes during sepsis. Employment of protected beta-lactams only partially solves the problem.

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НАЗНАЧЕНИЕ ЗАЩИЩЕННЫХ БЕТА-ЛАКТАМОВ БОЛЬНЫМ С СЕПТИЧЕСКИМ ШОКОМ

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***Ключевые слова**: внутрибольничный возбудитель, имипенем/циластин/релебактам, пиперациллин/тазобактам*

Целью данного ретроспективного исследования является оценка клинической эффективности двух защищенных бета-лактамов имипенем/циластин/релебактам и пиперациллин/тазобактам при лечении септического шока. Материал исследования и наблюдения составили 17 больных с септическим шоком, из них 9 (1-я группа) получали лечение имипенемом/циластином/релебактамом, 8 (2-я группа) получали лечение пиперациллином/тазобактамом. Все пациенты получали адекватную противошоковую терапию, инвазивную или неинвазивную вентиляцию легких, заместительную почечную терапию. Бактериологическое исследование показало наличие в биологическом материале четырех больных грамотрицательных возбудителей. Мультирезистентный штамм Acinetobacterbaumanii с высокой устойчивостью как к изучаемым антибиотикам, так и к Pseudomonasaeruginosae. Дальнейшее фенотипирование и генотипирование подтвердили продукцию у Acinetobacterbaumaniiметалло-β-лактамаз и гидролизующуюоксациллиназукарбапенема класса D в обоих случаях. Лечение пациентов с септическим шоком, вызванным этими штаммами, было одинаково неэффективно как с помощью ИМИ/ЦИС/РЭЛ, так и с помощью ПИП/ТАЗ и приводило к летальному исходу. Полученные результаты могут быть использованы при проведении мета-анализа и планировании дальнейших клинических испытаний защищенных бета-лактамов.

SEPTİK ŞOK KEÇİRƏN XƏSTƏLƏRƏ MÜDAFİƏ OLUNMUŞ BETA-LAKTAMLARIN TƏYİNİ

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***Açar sözlər**: xəstəxanadaxili törədici, imipenem/silastatin/relebaktam, piperasillin/tazobaktam*

Bu retrospektiv tədqiqatın məqsədi septik şokun müalicəsində iki müdafiə olunmuş beta-laktamın imipenem/silastin/relebaktam və piperasillin/tazobaktam klinik effektivliyini qiymətləndirməkdir. Tədqiqat və müşahidə materialı septik şok keçirən 17 xəstədən ibarət olub ki, onlardan 9-u (1-ci qrup) imipenem/silastin/relebaktam, 8-i (qrup 2) piperasilin/tazobaktam ilə müalicə alıb. Bütün xəstələrə adekvat şokəleyhinə terapiya, invaziv və ya qeyri-invaziv ventilyasiya, böyrək əvəzedici terapiyası aparılıb. Bakterioloji tədqiqat dörd xəstənin bioloji materialında qram-mənfi patogenin olduğunu müəyyən etmişdir. Acinetobacter baumanii həm tədqiq edilən antibiotiklərə, həm də Pseudomonas aeruginosae-yə qarşı davamlı ştammdır. Sonrakı fenotipləşdirmə və genotipləmə Acinetobacter baumanii-nin hər iki halda metallo-β-laktamazaların və oksasilinazanı hidroliz edən D sinfini karbapenemi hasıl etdiyini təsdiqləmişdir. Bu ştammların yaratdığı septik şok olan xəstələrin müalicəsi həm IMI/CIS/REL, həm də PIP/TAZ ilə eyni dərəcədə effektsiz olub və ölümlə nəticələnib. Alınan nəticələr meta-analizlərin aparılması və müdafiə olunmuş beta-laktamların sonrakı klinik sınaqlarının planlaşdırılmasında istifadə edilə bilər.

PROTECTED BETA-LACTAM PRESCRIPTION FOR PATIENTS WITH SEPTIC SHOCK

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***Keywords**: nosocomial pathogen, imipenem/cilastin/relebactam, piperacillin/tazobactam*

The purpose of this retrospective study is to evaluate the clinical efficacy of two protected drugs, imipenem/cilastine/relebactam and piperacillin/tazobactam, in the treatment of septic shock. The material of the study and observation included 17 patients with septic shock, 9 of them (Group 1) were treated with imipenem/cilastin/Relebactam, 8 of them (Group 2) were treated with piperacillin/tazobactam. All patients received adequate anti-shock therapy, invasive or non-invasive ventilation, and renal replacement therapy. Bacteriological examination showed the presence of four gram-negative pathogens in the biological material of patients. A multidrug-resistant strain of Acinetobacter baumanii with high resistance to both the studied antibiotics and Pseudomonas aeruginosae. Further phenotyping and genotyping confirmed the production of metallo-β-lactamases in both cases and class D carbapenem hydrolyzing oxacillinase in Acinetobacter baumanii. Treatment of patients with septic shock caused by these strains was equally ineffective with both IMI/REL and PTZ and resulted in death. The results obtained can be used in the meta-analysis and planning of further clinical trials of inhibitor-protected beta-lactams.

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CONSENT OF THE BIOETHICS COMMITTEE

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Poznań, December 20, 2023r.

KB – 988/23

CONFIRMATION

I herby confirm that the scientific research entitled:

„Awareness of antibiotic resistance among HCP"

conducted by:

Katarzyna Plagens-Rotman
Grażyna Jarząbek-Bielecka

is a non-experimental study.

According to the Polish law and GCP regulations
this research does not require approval of the Bioethics Committee
at Poznan University of Medical Sciences.

Chairman of the Committee
Professor Maciej Krawczyński, MD, PhD

OŚWIADCZENIA WSPÓŁAUTORÓW

STATEMENTS OF THE CO-AUTHORS

Warszawa, dn. 09.12.2024

Piotr Merks

OŚWIADCZENIE

Jako współautor pracy pt. „**Problems of antibiotic resistance in sepsis in intensive care units: A review of current research**" autorstwa Królak-Ulińska A, Merks P, Sierzputowska B, Sierzputowski T, Zaychenko G, wydanej w *Journal of Pharmaceutical Compounding*, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji obejmował udział w wykonaniu analizy danych, przygotowaniu draftu manuskryptu oraz przeprowadzeniu jego korekty merytorycznej i technicznej

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Anetę Królak-Ulińską jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artkułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część w/w pracy wykazuje indywidualny wkład lek. Anety Królak-Ulińskiej przy opracowywaniu koncepcji, metodologii, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy, pisaniu manuskryptu.

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OŚWIADCZENIE

Jako współautorka pracy pt. „**Problems of antibiotic resistance in sepsis in intensive care units: A review of current research**" autorstwa Królak-Ulińska A, Merks P, Sierzputowska B, Sierzputowski T, Zaychenko G, wydanej w *Journal of Pharmaceutical Compounding*, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji obejmował udział w wykonaniu analizy danych, przygotowaniu draftu manuskryptu oraz przeprowadzeniu jego korekty merytorycznej i technicznej

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Beata Sierzputowska
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Tomasz Sierzputowski

OŚWIADCZENIE

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Tomasz Sierzputowski
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Warsaw, 2024.12.06...........

Ganna Zaychenko

STATEMENT

As the co-author of the publication „„**Problems of antibiotic resistance in sepsis in intensive care units: A review of current research** " by Królak-Ulińska A, Merks P, Sierzputowska B, Sierzputowski T, Zaychenko, published in *Journal of Pharmaceutical Compounding*, I declare that my contribution to the preparation of the publication included participation in performing the analysis of the collected data, preparing the draft manuscript, reviewing and editing of the manuscript.

I hereby consent to the inclusion of the aforementioned work by Dr. Aneta Królak-Ulińska as part of her doctoral dissertation, presented in the form of a thematically coherent collection of articles published in scientific journals.

I further declare that the independent and distinct portion of the aforementioned work reflects Dr. Aneta Królak-Ulińska's individual contribution to the development of the research concept, methodology, execution of the experimental work, analysis and interpretation of the results, and the preparation of the manuscript.

Ganna Zaychenko
....
(author's signature)

Piotr Merks

OŚWIADCZENIE

Jak współautor pracy pt. **„Opinions of Medical Staff Regarding Antibiotic Resistance"** autorstwa Krolak-Ulińska A, Merks P, Religioni U, Chełstowska B, Drab A, Wdowiak K, Plagens-Rotman K, Doniec Z, Staniszewska A. wydanej w *Antibiotics*, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji obejmował udział w opracowaniu koncepcji badania, przeprowadzeniu korekty merytorycznej i technicznej manuskryptu, a także nadzór nad przebiegiem projektu.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Anetę Królak-Ulińską jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artkułów opublikowanych w czasopismach naukowych.

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Warszawa, dn.18.09.2024

Urszula Religioni

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Beata Chełstowska

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Beata Chełstowska

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Lublin, dn. 14.08.2021

Agnieszka Drab

OŚWIADCZENIE

Jak współautorka pracy pt. **„Opinions of Medical Staff Regarding Antibiotic Resistance"** autorstwa Krolak-Ulińska A, Merks P, Religioni U, Chełstowska B, Drab A, Wdowiak K, Plagens-Rotman K, Doniec Z, Staniszewska A. wydanej w *Antibiotics*, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji obejmował udział w wykonaniu analizy danych, przygotowaniu draftu manuskryptu oraz przeprowadzeniu jego korekty merytorycznej i technicznej.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Anetę Królak-Ulińską jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artkułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część w/w pracy wykazuje indywidualny wkład lek. Anety Królak-Ulińskiej przy opracowywaniu koncepcji, metodologii, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy, pisaniu manuskryptu.

Agnieszka Drab
(podpis współautora)

LUBLIN, dn. 14.09.2024

Krystian Wdowiak

OŚWIADCZENIE

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Krystian Wdowiak
(podpis współautora)

Poznań, dn. 10.09.2021

Katarzyna Plagens-Rotman

OŚWIADCZENIE

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Katarzyna Plagens-Rotman

(podpis współautora)

Rabka-Zdrój, dn. 17.09.2024

Zbigniew Doniec

OŚWIADCZENIE

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Zbigniew Doniec
(podpis współautora)

Warszawa, dn. 22.09.2024

Anna Staniszewska

OŚWIADCZENIE

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Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Anetę Królak-Ulińską jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

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ANNA NINA
STANISZEWSKA
22.09.2024 11:10:17 [GMT+2]
Dokument podpisany elektronicznie podpisem zaufanym

12.09.2024 Warsaw.....................................
(place and date)

Oleksandr Dobrovanov

STATEMENT

As the co-author of the publication „**Protected beta-lactam prescription for patients with septic shock**" by Królak-Ulińska A, Dobrovanov O., published in *Azerbaijan Pharmaceutical & Pharmacotherapy Journal*, I declare that my contribution to the preparation of the publication included: ....concept development, methodology, performing of the experimental part (about 30 %)..

I hereby consent to the inclusion of the aforementioned work by Dr. Aneta Królak-Ulińska as part of her doctoral dissertation, presented in the form of a thematically coherent collection of articles published in scientific journals.

I further declare that the independent and distinct portion of the aforementioned work reflects Dr. Aneta Królak-Ulińska's individual contribution to the development of the research concept, methodology, execution of the experimental work, analysis and interpretation of the results, and the preparation of the manuscript.

Oleksandr Dobrovanov
(author's signature)