Asian Journal of Research in Medical and Pharmaceutical Sciences

Volume 13, Issue 4, Page 9-27, 2024; Article no.AJRIMPS.123589
ISSN: 2457-0745

The Impact of Antimicrobial Resistance on Cancer Treatment: A Systematic Review of Current Evidence and Future Directions

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Cite as: *Lawal, Olabisi Promise, Nurain Kehinde Ahmed, Taiwo Ayomide Ilesanmi, Godswill Imolele Anthony, Samuel Nzube Nwosu, Festus Oladayo Ogungbemiro, Zainab Olaide, Muritadoh Muritadoh Adeniyi, Uchechukwu Lilian Okoye, Adebiyi Mutiat Olufunmilayo, Adegbesan Abiodun Christopher, and Ikalo David Oseghale. 2024. "The Impact of Antimicrobial Resistance on Cancer Treatment: A Systematic Review of Current Evidence and Future Directions". Asian Journal of Research in Medical and Pharmaceutical Sciences 13 (4):9-27. https://doi.org/10.9734/ajrimps/2024/v13i4270.*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ajrimps/2024/v13i4270

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/123589

Review Article

Received: 11/07/2024
Accepted: 13/09/2024
Published: 16/09/2024

ABSTRACT

Background: Antimicrobial resistance (AMR) has emerged as a critical global challenge, posing substantial implications for managing infectious diseases and impacting treatment efficacy across diverse medical conditions, including cancer. Cancer patients are often susceptible to bacterial infections due to immune system suppression caused by the disease and its therapies, leading to increased morbidity and mortality. This review examines the relationship between AMR and cancer treatment, highlighting the mechanisms through which microbes resist antimicrobial drugs, such as active drug efflux, limiting drug uptake, modifying the drug target, and inactivating the drug via enzymatic degradation or modification. These resistance mechanisms challenge the effectiveness of treatment regimens, imposing significant clinical and economic consequences. A comprehensive literature search was conducted via online databases such as Scopus, PubMed, Google Scholar, and BioMed Central. It covered publications from 2010 to 2024 that address AMR and its effects on cancer care with specified inclusion and exclusion criteria to guide the study selection process. This study highlights the crucial need for interdisciplinary research, innovative treatment strategies, effective antimicrobial stewardship programs, and policy interventions to combat AMR in oncology settings. Conclusively, antimicrobial resistance remains a pressing concern in modern medicine, significantly complicating cancer treatment by reducing the efficacy of antibiotics, thereby leading to prolonged illnesses and hospital stays, increased morbidity and mortality rates, and higher economic burdens on healthcare systems.

Keywords: Antimicrobial resistance; cancer treatment; immune suppression; bacterial infections.

ABBREVIATIONS

AMR : Antimicrobial Resistance NSCLC: Non-Small Cell Lung Cancer
EGFR : Epidermal Growth Factor Receptor
CDC : Centers for Disease Control and Prevention
ESKAPE : Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species.
LPS : Lipopolysaccharide
ATP : Adenosine triphosphate
ABC : ATP- binding Cassette
SMR : Small Multidrug resistance
MATE : Multidrug and Toxic Compound Extrusion
RND : Resistance Nodulation Cell Division
MFS : Massive Facilitator Superfamily
USA : United States of America

UK : United Kingdom
GDP : Gross Domestic Product
MDRO : Multidrug Resistance Organism
NGS : Next Generation Sequencing
PCR : Polymerase Chain Reaction
ASPS : Antimicrobial Stewardship Program
GP : General Practitioner
PET : Positron Emission Tomography
GLASS : Global Antimicrobial Surveillance System

1. INTRODUCTION

Modern medicine faces a significant problem from antimicrobial resistance (AMR), which compromises the efficacy of antimicrobial drugs in treating microbial infections. It has been estimated to cause 750,000 deaths per year [1]. The ability of these microorganisms, such as bacteria, fungi, viruses, and parasites, to survive and proliferate despite exposure to antimicrobial drugs highlights the critical necessity for innovative approaches to tackle this significant problem. The ineffectiveness of antimicrobial medications—which include antibiotics, antifungals, antivirals, antimalarials, and anthelmintics—against resistant microbes promotes treatment failure and the exacerbation of diseases [2] [3]. AMR is estimated to contribute $20 billion annually to healthcare costs in the United States and €1.1 billion in the European Union, including losses in economic activities [4,1].

Cancer patients, often immunocompromised due to treatments like chemotherapy, are particularly vulnerable to infections and frequently rely on antimicrobial therapies to manage these complications. However, the emergence of antimicrobial resistance complicates this reliance on antimicrobial therapies, as it undermines the effectiveness of these treatments [5]. Facts have shown that AMR is antagonizing the effective delivery of cancer treatments, thereby leading to unfavorable results [6]. The implications of antimicrobial resistance extend beyond its direct impact on infectious diseases; it not only jeopardizes the effectiveness of antimicrobial treatments but also increases the risk of severe complications, prolonged illness, and an increased healthcare burden in cancer treatment. Therefore, a better understanding of the impact of AMR on cancer care outcomes is a crucial step toward curbing the potential detrimental effects of AMR on cancer patients.

This review aims to provide a comprehensive assessment of the relationship between antimicrobial resistance and cancer treatment by examining the mechanisms and interactions between AMR and cancer, as well as the clinical implications, healthcare system challenges, and economic burdens associated with AMR in cancer treatment. Additionally, the review aims to identify future research directions and propose practical strategies for addressing AMR within cancer care settings.

2. METHODOLOGY

The review was performed as per the following protocol.

2.1 Relationship between Antimicrobial Resistance and Cancer: Mechanisms and Interaction

Antibiotic resistance occurs when bacteria develop resistance to antibiotic molecules [7]. The efficiency of antimicrobial medications is reduced or rendered ineffective due to microorganisms' evolution and acquisition of resistance [8]. Over a million years ago, bacteria evolved and achieved resistance to antimicrobial molecules through sophisticated mechanisms and multiple biochemical pathways [9]. AMR mechanisms can be categorized into four: limiting drug uptake, modifying a drug target; inactivating a drug; and active drug efflux [10].

Limiting the uptake of a drug is the first mechanism for avoiding AMR by reducing medication absorption. The composition and behavior of the LPS layer are important factors in gram-negative bacteria's resistance to different antibiotics [11]. The modification method frequently causes an alteration in the original drug target structure, resulting in poor or no binding of the medication. Naturally occurring mutations in the gene or genes encoding the pharmaceutical target may cause this structural alteration [12]. Studies have shown that one of the most effective bacterial defense mechanisms against AMR is the production of enzymes that deactivate the consumption of antibiotic medication. Bacteria add specific chemical

structures to the drug or degrade the molecule, preventing the antibiotic from interacting with the target. Gram-negative bacteria are the most successful because they resist most medications [9]. Also, bacterial efflux pumps actively transport many antibiotics out of the cell. Efflux pumps are the initial line of defense against antimicrobials. They play an essential role in antibiotic export across the cell. Some efflux pump genes may be upregulated by bacterial species in response to stressful conditions or dangerous substances in their surroundings [7]. ATP-binding cassette (ABC), small multidrug resistance (SMR), multidrug and toxic compound extrusion (MATE) family, resistance-nodulation-cell division (RND) family, and massive facilitator superfamily (MFS) are the main families of efflux pumps [13].

These mechanisms can be categorized into two: (i) intrinsic antibiotic resistance; which are inherent traits present in certain bacterial species or strains that naturally render them less susceptible to specific antibiotics; and (ii) acquired antibiotic resistance, which results via horizontal gene transfer through transformation, conjugation, or transduction, or from gene modification and/or exchange by mutation of a specific gene [15]. Intrinsic antibiotic resistance refers to bacteria's inherent ability to naturally withstand certain types of antibiotics due to the presence of specific chromosomal genes, without the need for mutation or acquisition of additional genes [16,17]. The most common bacterial mechanisms involved in intrinsic resistance include drug inaccessibility within the bacterial cell, antimicrobial target changes, reduced drug absorption, and activation of efflux systems to eliminate harmful molecules [9]. It is essential to understand the intrinsic resistance of a pathogen, to ensure optimal antibiotic therapy and lower the chance of acquiring resistance. Several studies have identified various genes that contribute to the intrinsic resistance of bacteria to different classes of antibiotics, such as β-lactams, fluoroquinolones, and aminoglycosides [18]. In contrast, acquired antibiotic resistance involves either the mutation of already-existing genes or the acquisition of resistance genes from other bacteria through the horizontal transfer of novel genes [19].

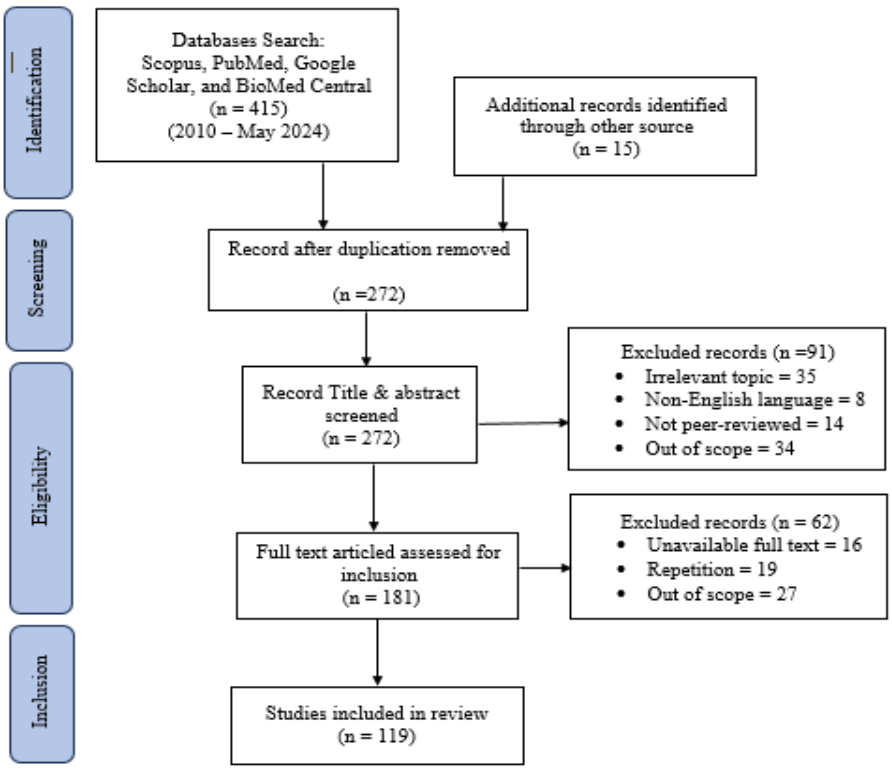

Chart 1. Flow chart showing protocol

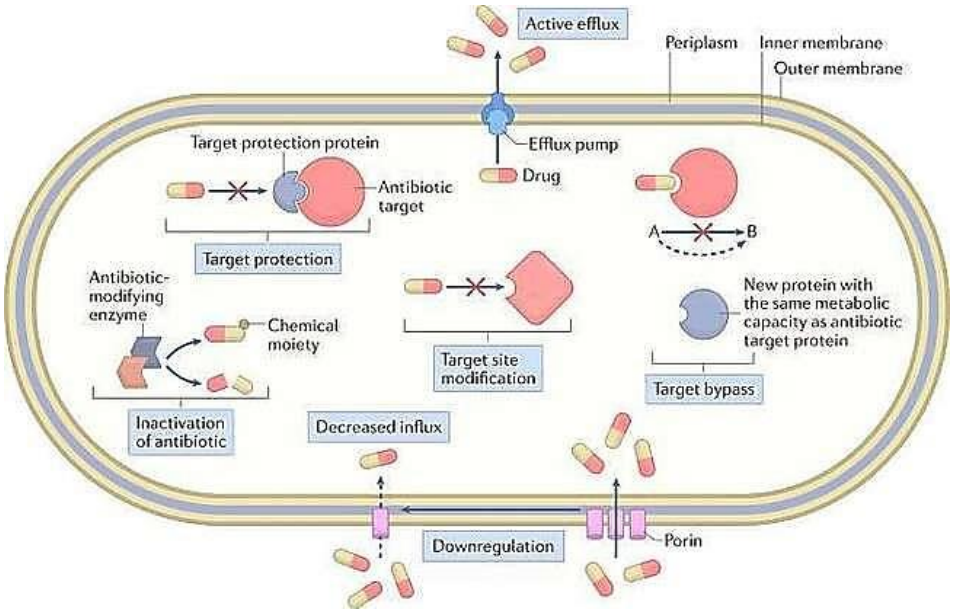

Fig. 1. This illustration shows different mechanisms by which bacteria develop resistance to antibiotics [14]

Globally, cancer is a leading cause of illness and mortality, contributing to around 20% of all deaths in affluent nations. The most common cancer therapies for patients include chemotherapy, radiation, and surgical procedures. Cancer can be effectively removed from the body through surgery, but combined chemotherapy and radiotherapy can provide superior outcomes [20]. Several studies have reported the effect of antimicrobial resistance on cancer treatment and prognoses. Patients with cancer frequently experience bacterial infections as a complication due to immunosuppression caused by both the disease itself and its treatments. Consequently, cancer patients have a threefold higher risk of a severe infection compared to those without cancer [21]. Therapies like chemotherapy, radiotherapy, hematopoietic transplantation, and surgeries further weaken their immune defenses, making them susceptible to drug-resistant bacterial infections. These drug-resistant bacteria can induce persistent infections, leading oncologists to be concerned about the effectiveness of chemotherapy in these patients [22, 23]. Effective antibiotic treatment is crucial for preventing and managing infections in cancer patients. However, the extended and extensive use of broad-spectrum antibiotics to combat infections in this population contributes to the emergence of resistance [24]. Urinary catheters, previous antibiotic therapy, pre-existing medical problems, and other urinary infection-related sources are the most common causes of antibiotic-resistant infections [25]. A study [26] reported the alarming rates of antibiotic resistance among pathogens causing surgical site infections and infections post-chemotherapy in the USA. The results of the study demonstrated that 26.8% of pathogens causing infections after chemotherapy and between 38.7% and 50.9% of pathogens causing surgical site infections were resistant to standard prophylactic antibiotics, emphasizing the urgent need for improved antimicrobial stewardship efforts, infection prevention measures, and the development of alternative strategies to address AMR in cancer care.

2.2 Clinical Implications of Antimicrobial Resistance in Cancer Care

2.2.1 Increased morbidity and mortality associated with AMR infections in cancer patients

Autopsies have revealed that infections may play a role in more than half of cancer patient deaths [27]. According to estimates from the Global Antimicrobial Surveillance System (GLASS), 500,000 individuals in 22 countries have infections caused by AMR organisms [28]. Furthermore, 2016 data showed that about 490,000 individuals globally had multi-drug resistance to tuberculosis; the continuation of medication resistance can worsen the ailment

[114]. AMR is associated with potential effects on mortality, morbidity, attributable healthcare costs, including insurance, and the burden on providers, such as hospitals and primary care centers, from the perspectives of the patient, provider, and government. On the other hand, from an economic perspective, AMR is linked to lost productivity, patient out-of-pocket costs, such as the excess cost of hospital treatment due to prolonged treatment protocols, and GDP losses for the country. The severity of antimicrobial resistance (AMR) is most apparent in low- and middle-income countries due to limited laboratory capacity, restricted drug access, and inadequate surveillance [29].

An AMR infection affects two million people in the U.S. and results in at least 23,000 deaths annually. Still, concerted attempts have been launched to obtain adequate data on this issue. Studies show that this occurs most frequently in the Southern and Appalachian regions of the United States.

In a similar vein, sepsis kills more than 44,000 people in the U.K. annually. This is more than the 35,000 lung cancer-related deaths that occur each year when antibiotic resistance is the main contributing factor [30]. Zembower (2014) states that the following are the main clinical implications of antimicrobial resistance (AMR): Antimicrobial resistance makes treatment efficacious for many bacterial, fungal, and viral disorders less effective. Novel resistance mechanisms in bacteria threaten our ability to treat common illnesses like flu and typhoid, which could result in treatment-resistant strains, protracted illness, irreversible disability, or even death. The novel medications have the potential to undermine the efficacy of cancer chemotherapy, organ transplants, and minor dental procedures. People resistant to antibiotics need more expensive and prolonged treatments, which raises the overall cost of healthcare [27].

2.2.2 Challenges in antibiotic prophylaxis and empirical therapy

Prophylactic antibiotic treatment has lowered the risk of Gram-negative infections in cancer patients [31]. The National Comprehensive Cancer Network (2022) guidelines state that patients receiving treatment for acute leukemia or those with neutropenia who are at an intermediate to high risk of infection—that is, those who expect to be neutropenic for more than ten days—should consider fluoroquinolone prophylaxis. On the other hand, fluoroquinolones have been associated with an increased prevalence of Clostridium difficile (C. difficile) and may favor resistant bacterial pathogens. As a result, their effectiveness is greatly diminished in patients whose colonization includes fluoroquinolone-resistant organisms [32]. Weighing the benefits and drawbacks of antibacterial prophylactic regimens that could lead to undesirable consequences like antibiotic resistance is crucial. The administration of chemotherapeutic drugs (such as cytotoxic and lymphocyte-depleting drugs) may cause myelosuppression, affecting the infection risk according to the degree and duration of neutropenia and lymphopenia. According to Lyman et al., 2005, having several comorbidities, having a poor performance status, and having an older age that lowers bone marrow reserve can all raise the risk of chemotherapy-induced neutropenia. Many cancer patients have a disturbance of their mucosal barriers as a result of radiation and chemotherapy. This puts them at risk for bacterial translocation, mucositis, and sinusitis, which can lead to bloodstream infections and neutropenic enterocolitis. Apart from the immune system failure resulting from an underlying illness and its treatment, individuals with cancer are also vulnerable to diseases associated with medical care [33]. Additionally, this category of patients may require indwelling devices, such as central venous catheters, urine catheters, and Ommaya reservoirs; hence, they are susceptible to issues and infections related to these devices [34]. Individuals who often interact with the healthcare system may also be more vulnerable to the acquisition and colonization of multi-drug resistance organisms (MDRO) [35]. For this reason, given concerns about the collateral damage of new combinations and novel approaches on the diversity of (and amplification of resistance within) the human microbiota and other adverse effects, more clinical research on prescribing strategies that aim to suppress resistance in common infections while maintaining efficacy is imperative.

2.2.3 Healthcare system challenges and economic burden

Managing AMR among healthcare workers is widely recognized as challenging across various research studies [36]. This challenge arises from healthcare workers' potential lack of understanding or inadequate resource access. In the United States, 92% of medical students recognized the critical significance of

understanding antimicrobials for all healthcare providers.

Yet, around one-third felt adequately informed about the principles guiding antimicrobial usage [37], and 90% indicated a strong desire for additional education concerning the proper utilization of antimicrobials. Healthcare professionals working in environments with scarce resources face a challenging dilemma in their daily practice. While they understand the importance of avoiding indiscriminate antibiotic prescriptions, they may encounter situations where the risk of infection is elevated due to inadequate infection prevention and control measures or substandard hygiene and sanitation. Effectively addressing AMR necessitates enhancing the entire healthcare system and ensuring a seamless supply chain for medications to effectively treat infections [37].

Khameneh et al. (2016) estimate that 8.5% of cancer patients will die as a result of severe sepsis [38], which necessitates the use of appropriate antibiotics. Short-duration antibiotics are unprofitable, leading to a shift towards chronic conditions. The cost of low-cost antibiotics can be high, and physicians often save novel drugs for emergencies, delaying their return on investment. This results in delayed development of new therapies. As a result, pharmaceutical companies' return on investment while creating novel therapies is further delayed [39]. To manage and reduce antimicrobial resistance (AMR) while suggesting suitable antibiotics, it is crucial to initially grasp the utilization of antibiotics and infections in patients [40].

Healthcare providers dedicate their time to treating infected patients and go the extra mile to secure funding for necessary tests and treatments. Antimicrobial resistance (AMR) has been predicted to result in yearly losses to the global economy of $300 billion to over $1 trillion by 2050. These expenses stem from the pricey and intensive treatments needed, as well as the increased use of resources in healthcare, which AMR directly impacts, and this leads to catastrophic effects on healthcare [36, 41]. Antimicrobial resistance (AMR) has a cataclysmic impact on healthcare expenses and makes treatment unfeasible for cancer patients.

Most cancer patients know that chemotherapy impairs their immune systems and increases their susceptibility to bacterial and viral infections. They would rather go for telemedicine; telemedicine technology enhances the delivery of cancer care because effective telemedicine treatment could lower hospital admission rates, pain, anxiety, and sleep difficulties. Due to the complexity of cancer treatment decisions, multidisciplinary tumor boards and various medical specialists participate in these conversations, now conducted via online video conferencing. This ensures that responsibilities are shared appropriately when making treatment decisions [42, 43, 44].

Consequently, the prevalence of AMR prevents doctors from prescribing antibiotics for cancer patients. The scarcity of data on the specific expenses associated with various secondary effects of AMR hinders our comprehension of potential losses. Their dedication to ensuring patients receive comprehensive care is commendable [38]. Developing methods to sustain the ongoing care provision for diseases affected by antimicrobial resistance while ensuring the safety of patients and healthcare workers will bring significant transformation globally [41].

2.2.4 AMR effect on the cost of cancer treatments

Growing resistance drives up the cost of more expensive antibiotics (infections that become resistant to first-line drugs must be treated with second or third-line drugs, which are almost always more expensive), specialized equipment, more extended hospital stays, and patient isolation procedures [45]. his has a negative impact on the treatment results for patients and the increase of expenditures on cancer treatment. Cancer patients with resistance to antimicrobial infections often stay for an extended period in the hospital, where they require intensive care and further medical interventions. These facts result in a significant increase in healthcare costs, putting a financial burden on patients, providers, and healthcare systems alike. An investigation discerned that the economic burden of AMR-related infections reaches $2 billion annually in the USA only [46].

Managing antimicrobial-resistant infections in cancer patients involves the administration of new expensive antibiotics and antifungal drugs; therefore, along with other cancer treatments, the price of antimicrobial agents forms an essential part of entire cancer treatment expenses [47]. It is important to note that antimicrobial-resistant

pathogens cause problems in managing infections in cancer patients, which increases the risk of treatment failure and mortality. Furthermore, unsuitable antimicrobial medication poses a challenge to cancer treatment tolerance, which typically results in treatment delays or cessation as well as dosage reductions [48]. Treatment failure is notable, as both unsuccessful treatment and higher healthcare costs are consequences.

Another serious effect of AMR on cancer care is the extension of hospital stays, which puts patients and healthcare systems in great economic predicaments. As a consequence, the economy at large is also affected. In cancer patients, AMR makes the management of infections more complex and often involves more prolonged, intensive medical interventions, occasionally requiring hospitalization. Hospitalization duration due to AMR-related infections directly increases direct healthcare costs, which include expenses related to hospitalization, diagnostics tests, treatment using antibiotics, and supportive care. The research shows that the effect of each extra day of hospitalization is capital-intensive and ranges from hundreds to thousands of dollars for an individual per day [49]. The planning and formulation of health system policies should consider all aspects of a household's health costs, including direct, indirect, and intangible costs [50]. Prolonged hospital stays make it difficult for patients to stick to their norms because their ability to work, care for their families, and mingle with others is hampered. AMR-related infections often require a wider range of antibiotics (especially second-line therapies) to fight them; these antibiotics are more expensive and less effective than first-pick drugs [51]. The shooting cost of antimicrobials worsens this situation and makes lengthy hospital stays more costly for cancer patients. According to the study by Lee et al. [52], two to three times as many antibiotics were prescribed to individuals with multidrug-resistant illnesses as to those with basic susceptible infections.

Although AMR complicates the management of cancers, it also induces the increased use of diagnostic tests to identify resistant pathogens and establish treatment decisions. Doctors rely extensively on tests like pathogen culture, antibiotic resistance testing, and treatment regimen assignment to combat AMR infections [51]. To succeed in the fight against antibiotic-resistant microbes, there is a need to do additional tests to identify and characterize these organisms. This can be accomplished using various methods, including next-generation sequencing (NGS), polymerase chain reaction (PCR) testing, culture and sensitivity assays, and other strategies. Hospital costs rise when these tests are used since they require specialized facilities, lab equipment, and trained personnel [53].

Antibacterial resistance detectors, such as certain diagnostic kits, reagents, and consumables, are typically used in antimicrobial resistance testing. The financial burden of purchasing and maintaining cancer treatment supplies is primarily felt in areas with limited resources, when access to cutting-edge diagnostic tools may be restricted. On top of that, diagnostic testing fees of external laboratories add potentially more costs for patients and healthcare systems [54]. Diagnostic tests that indicate antimicrobial resistance are of major importance in making treatment decisions for cancer patients. Clinicians will not be able to start their specific antimicrobial treatment until test results become available, which can result in treatment delays and lengthened hospital stays. Conversely, these delays have an adverse effect on patient outcomes and raise the expense of healthcare, encompassing prolonged hospital stays, supportive care, and further interventions [55].

2.3 Strategies for Addressing Antimicrobial Resistance in Cancer Care

2.3.1 Antimicrobial stewardship programs in oncology settings

In hospital settings, especially cancer units, antimicrobial stewardship programs (ASPs) are crucial for optimizing antibiotic use to enhance patient outcomes, lower the incidence of microbial resistance, and cut down on needless expenses [56]. Without influencing infection-related mortality, ASPs in pediatric oncology settings result in fewer prescriptions for broad-spectrum antibiotics, better antibiotic usage appropriateness, and fewer side effects associated with antibiotic use [57]. ASPs have concentrated on bacterial infections in febrile neutropenic patients in oncology patients, particularly those with hematologic malignancies and neutropenia [58]. They have employed tactics such as antibiotic limitation, cycling,

prospective audit and feedback, and de-escalation [59]. Due to the restricted development of novel agents and the rise in antimicrobial resistance, multidisciplinary ASPs in hospitals are essential for improving antimicrobial prescription [60]. Reduced antimicrobial usage, decreased drug-related costs, and a decline in Clostridium difficile-associated illness can result from comprehensive, multidisciplinary ASPs supported by hospital leadership and applying evidence-based techniques catered to local circumstances [61]. Safely reducing the use of antibacterial and antifungal agents without affecting the length of hospital stay, death rate, or suitability of empirical treatment for bacteremia is possible in pediatric hematology-oncology and hematopoietic stem cell transplant units through the implementation of persuasive and restrictive ASP approaches [62]. To optimize their engagement, oncology nurses must receive education and orientation. Although they know the value of ASPs, they encounter obstacles such as knowledge gaps and lack of experience with stewardship programs [63] Prospective audit and feedback interventions are widely used strategies in antibiotic prescription practices, which provide chances for education and better outcomes [64].

The influence of antimicrobial resistance, the function of antimicrobial cycling, and the management of outpatient antimicrobial therapy are among the contentious issues surrounding ASPs in oncology settings, indicating areas that want more investigation [65]. Antimicrobial stewardship strategies work well in cancer settings to minimize drug-related side effects, improve prescription appropriateness, and decrease antimicrobial usage [66]. These programs must take a multidisciplinary approach and be customized to meet the unique requirements of the cancer patient population. The effectiveness of ASPs depends on the engagement and education of all healthcare professionals, including nurses [67]. to maximize the impact of ASPs in oncology units, despite the benefits that have been demonstrated, there are still disputes and issues that need to be resolved [68].

2.3.2 Collaborative efforts between oncologists and infectious disease specialists

Managing complicated cancer cases and enhancing patient outcomes need collaboration between oncologists and other experts, including surgeons, general practitioners (GPs), and palliative care clinicians [69]. The effect of these partnerships on patient treatment, satisfaction, and the healthcare system is examined in this synthesis [70]. When oncologists and surgeons work together, patients with stage III colon cancer have higher survival rates without incurring more expenses, which suggests that encouraging such collaborations might be a crucial tactic in complicated cancer treatment [71]. Most cancer survivors favor shared care models, which can relieve pressure on specialty oncology clinics. However, G.P.s must be knowledgeable about cancer and interested in follow-up care [72]. While existing procedures frequently rely on the patient as an intermediary, effective end-of-life talks require stronger interdisciplinary communication and coordination between oncologic experts and general practitioners [73]. The importance of investing in collaborative infrastructure is shown by the fact that multidisciplinary collaboration in radiation oncology, encompassing educational activities, may result in major advances in research and clinical practice modifications [74]. When cancer is in remission, oncologists say they need more cooperative follow-up treatment with family doctors; the main obstacles are communication gaps and patient preference [75]. Personalized cancer treatment and multicenter clinical trials depend on enhanced communication between PET specialists and oncologists, which is associated with improved patient management [76]. Early collaboration between primary care veterinarians and oncologic experts during treatment improves client satisfaction with veterinary cancer care [77]. General practitioners and oncologists are eager to work together to treat cancer patients. However, there is still room for improvement in sharing information, allocating tasks, and medical understanding of cancer [78]. While improved cancer staging and imaging may be possible with nuclear medicine advancements, stronger cooperation with oncology is required to incorporate novel methods and treatments into clinical practice [79,80]. Despite obstacles, including patient resistance and resource constraints, medical oncologists have good attitudes toward working with specialized palliative care and prefer concurrent care approaches [81]. Improved patient happiness, better patient outcomes, and economical utilization of healthcare resources. To make the most of these partnerships, issues including poor communication, scarce resources, and the requirement for specialized expertise

must be resolved [82]. Research and treatment for cancer may greatly benefit from multidisciplinary collaboration and shared care models, according to the available data [83].

2.4 Future Directions and Research Priorities

2.4.1 Emerging trends in AMR and cancer care

Cancer patients, particularly those undergoing chemotherapy or immunosuppressive therapy, face a heightened risk of infections from resistant microorganisms, complicating cancer care management [84, 85]. The impact of AMR on cancer treatments is alarming, as it can reduce the effectiveness of treatments like chemotherapy by decreasing the availability of antimicrobials to manage infections. As resistant microorganisms continue to appear, finding effective treatments for infections becomes increasingly difficult, leaving cancer patients, who are already vulnerable, with fewer treatment options. The implications of AMR on cancer treatment are severe and extensive [86, 87]. Infections related to AMR can significantly increase morbidity and mortality rates, especially in cancer patients [88]. This is due to the higher susceptibility of cancer patients to infections, the complexity of their treatment regimens, and the prolonged use of antimicrobials in cancer care. Despite the significant advancements in cancer treatment and diagnostics achieved by modern medicine, the rise of antimicrobial resistance (AMR) threatens to erode these hard-earned gains. As we enter a new era of personalized medicine, it is vital to comprehend the implications of AMR in cancer care. Each new superbug strain presents a race against time to develop new treatments before resistance renders them ineffective [89].

In response to the AMR challenge, cancer researchers and healthcare providers are adopting innovative approaches to combat it. New trends in cancer care, such as immunotherapy, targeted therapy, liquid biopsies, and precision medicine, offer promising strategies for addressing AMR- related infections and their emerging trends. By leveraging the immune system's power, customizing treatments to specific tumor markers with the help of deep machine learning, and utilizing advanced diagnostic tools, we are better equipped to tackle the evolving nature of resistant infections. One of the most promising advancements in cancer care is immunotherapy, particularly checkpoint inhibitors [90]. These drugs block proteins on the surface of cancer cells, known as checkpoints, which usually prevent the immune system from attacking the cancer. The immune system can recognize and attack cancer cells by inhibiting these checkpoints, resulting in significant survival improvements for certain cancers, such as melanoma and lung cancer. Another powerful trend in cancer care is targeted therapy [91]. Unlike traditional chemotherapy, which attacks all rapidly dividing cells, targeted therapies are designed to attack specific genetic mutations or molecular targets unique to a particular type of cancer.

For instance, targeted therapies for non-small cell lung cancer (NSCLC) have been designed to target specific mutations in the epidermal growth factor receptor (EGFR) gene. Another exciting development in cancer care is liquid biopsies [92]. Instead of relying solely on tissue biopsies to identify mutations and monitor treatment response, liquid biopsies can detect cancer-specific genetic markers in the blood, enabling real-time monitoring of cancer progression and treatment response. This relatively new diagnostic tool offers great promise for cancer patients by providing a less invasive alternative to traditional tissue biopsies while also offering the potential to detect resistance to targeted therapies earlier, allowing clinicians to adjust treatment regimens accordingly [93].

Additionally, precision medicine is a rapidly emerging trend in cancer care that promises to revolutionize the way we diagnose and treat cancer. This personalized approach involves tailoring treatment plans to each patient's genetic, environmental, and lifestyle factors, resulting in more effective and less toxic therapies. By using advanced technologies such as genomic sequencing, proteomics, and metabolomics, precision medicine allows clinicians to identify the most effective treatments for each patient based on their unique tumor profile and genetic mutations [94]. Recent studies have shown that personalized antibiotic prophylaxis strategies can significantly reduce the risk of infections in cancer patients while minimizing the development of AMR. A 2023 study by Johnson et al. demonstrated that using patient-specific microbiome profiles to guide antibiotic selection resulted in a 30% reduction in infection rates and a 25% decrease in the emergence of resistant pathogens compared to

standard prophylaxis protocols [115]. Researchers have also discovered that certain cancer-associated genetic mutations can influence susceptibility to specific antibiotics. A groundbreaking study by Lee et al. [116] showed that lung cancer patients with EGFR mutations were more responsive to a novel class of antibiotics targeting both the cancer cells and associated bacterial infections. This approach not only improved treatment outcomes but also reduced the need for broad-spectrum antibiotics, thereby decreasing the risk of AMR. The interplay between the immune system, cancer, and microbiome has led to innovative combination therapies. More recently in 2024, a clinical trial by Rodriguez et al. [117] demonstrated that combining checkpoint inhibitors with narrow-spectrum antibiotics, selected based on the patient's tumor microenvironment and gut microbiome composition, enhanced treatment efficacy while minimizing the risk of opportunistic infections and AMR development. Precision medicine approaches have also been applied to drug delivery systems. A 2023 study by Zhang and colleagues utilized cancer-specific nanoparticles to deliver antibiotics directly to tumor sites. This targeted approach increased the local concentration of antibiotics and reduced systemic exposure, leading to improved infection control and a lower risk of AMR in the broader microbial population [118]. Advanced machine-learning algorithms have been developed to optimize antibiotic use in cancer patients. A 2022 study by Patel et al. [119] implemented an AI-driven antibiotic stewardship program in a large oncology center. To provide personalized antibiotic recommendations, the system analyzed patient data, including cancer type, treatment history, and microbiome profiles. This approach resulted in a 40% reduction in unnecessary antibiotic use and a 35% decrease in AMR incidence over two years.

Apart from these emerging trends in cancer care, effectively combating AMR in cancer care requires a multidisciplinary approach. This means bringing together experts from various fields, including infectious disease specialists, oncologists, pharmacologists, and epidemiologists, to develop innovative strategies and treatment regimens that address the unique challenges of resistant infections in cancer patients. By leveraging the expertise of different disciplines, healthcare providers can create comprehensive treatment plans that optimize patient outcomes and reduce the risk of AMR. These advancements can reduce the impact of resistant infections on cancer care and enhance the overall effectiveness of modern cancer treatments.

2.4.2 Opportunities for interdisciplinary research and innovation

Interdisciplinary research is defined as collaboration and integration across diverse disciplines to provide solutions to complex problems and offer new avenues of knowledge [95]. It transcends the boundaries of a singular field and unites researchers with varied experiences, approaches, and viewpoints. By combining expertise from different fields, interdisciplinary research fosters innovative solutions that might not emerge within a single discipline. This approach can lead to breakthroughs in understanding and addressing complex problems [96].

2.4.3 Policy implications and potential interventions to combat AMR in oncology

(a) Prevention of infection (Minimizing Antibiotics Usage)

Infection prevention is essential for patients battling cancer, specifically under neutropenic conditions, where antibiotic prophylaxis serves as a conventional approach [97]. However, prior antibiotic exposure has been found to contribute significantly to antimicrobial resistance (AMR) in certain cancer patients [98]. By prioritizing infection prevention, there is a potential to decrease antibiotic use in cancer patients experiencing neutropenia or undergoing surgeries and other invasive treatments. Guidance on infection prevention for cancer patients, their caregivers, and healthcare teams can be obtained from reputable sources such as the Centers for Disease Control and Prevention (CDC), the American Cancer Society, and the National Comprehensive Cancer Network. This is not limited to inculcating infection prevention but also promoting healthier practices to avoid or notice infections in the early stage [99].

Administration of antibiotics or chemotherapy can lead to an imbalance in the gut microbiota, impacting bacterial diversity [100]. This dysbiosis in the gut microbiota has been associated with an increased risk for resistant bacteria and potentially reduced effectiveness of immunotherapy in cancer patients [101].

Monitoring the assembly of gut microbiota, introducing beneficial commensal bacteria to reduce antibiotic-resistant infections, and fostering a healthy microbiome may be potential ways to prevent antibiotic resistance, decrease antibiotic use, and improve outcomes in cancer patients [102]. These approaches hold affirmations in optimizing treatment efficacy while minimizing complications associated with gut microbiota dysbiosis.

Geographical variability in antibiotic resistance poses another challenge for cancer patients, as antibiotic resistance often emerges in one region and subsequently spreads to others. It is crucial for vulnerable populations, such as cancer patients, to be aware of infection risks, including information regarding the prevalence of drug-resistant pathogens in the areas they visit. Awareness of these risks can help inform preventative measures and prompt appropriate treatment should an infection occur. By staying informed and taking necessary precautions, cancer patients can minimize the potential consequences of encountering antibiotic-resistant pathogens during their travels.

Encouraging and escalating appropriate antibiotic use among healthcare providers and patients is an important way to prevent misuse and overuse of these medications [103]. In oncology settings, the required duration of antibiotic therapy remains uncertain and disputed, often leading to excessive antibiotic courses and inconsistent practices across different sites [104]. To address this issue and minimize antibiotic overuse in oncology, well-defined guidelines and principles are necessary. These guidelines should be based on thorough research to determine the ideal duration of antibiotic treatment [105], ultimately promoting responsible antibiotic use and mitigating the development of antimicrobial resistance.

(b) Antibiotic stewardship to optimize antibiotic use

Antimicrobial stewardship is all about finding the right balance when using antibiotics. It means choosing the most effective treatment, using the right dosage, and ensuring it is given at the right time. The goal is to successfully treat and prevent infections with as little harm as possible while minimizing the development of resistance to ensure that these drugs remain effective for future use [98].

In healthcare settings, there are dedicated teams called antimicrobial stewardship teams, ideally led by experts like infectious disease physicians, pharmacists, microbiologists, and infection preventionists. Their role is to ensure that antibiotics are used responsibly. This is especially important for patients with cancer [106] since these patients often have a higher chance of developing antibiotic-resistant infections due to their past treatments. Unfortunately, patients with cancer who get these resistant infections tend to have worse outcomes compared to those with infections that can be treated more easily [107].

Although there are requirements from organizations like the Centers for Medicare and Medicaid Services for hospitals and long-term care facilities to have antibiotic stewardship programs in place, their effectiveness can vary because some hospitals may lack the necessary resources to fully carry out these programs [108]. The CDC has created the Core Elements of Outpatient Antibiotic Stewardship guidelines to help outpatient clinicians and facilities use antibiotics more responsibly [99]. For these guidelines to be widely adopted, more resources are needed, and patients at the highest risk, such as those with cancer, stand to benefit the most from improved antibiotic stewardship [109]

(b) Antibiotic-resistance surveillance system for patients with cancer: prediction and prevention of outbreaks

The Centers for Disease Control and Prevention (CDC) defines surveillance as the systematic and continuous process of gathering, analyzing, and interpreting health data to support public health initiatives and ensuring that this information reaches the appropriate parties promptly [110]. Different countries have established their guidelines for monitoring antibiotic-resistant bacteria [111].

Surveillance of antimicrobial resistance (AMR) includes tracking antibiotic susceptibility test results from bacteria found in clinical samples and collecting relevant patient data. By combining and analyzing these data, healthcare professionals can develop targeted interventions to minimize the impact of antibiotic resistance [112]. These surveillance data can also be used to create prediction models that help identify when antibiotic resistance might emerge in clinically significant bacterial pathogens.

A comprehensive predictive model for ESKAPE pathogens (a group of six bacterial species with high antibiotic resistance) could be beneficial in oncology settings, enabling more efficient use of antibiotics. Although the CDC has increased surveillance efforts in line with the National Action

Plan for Combating Antibiotic-Resistant Bacteria, there are still gaps in our understanding [113]. Continuous surveillance of antibiotic resistance in oncology settings is crucial for identifying trends and assessing the impact of interventions. Future efforts by the CDC will contribute to filling these knowledge gaps and improving patient outcomes.

3. CONCLUSION

This report has provided a comprehensive overview of the significant impact of antimicrobial resistance (AMR) on cancer treatment, highlighting the critical challenges it poses to modern medicine. Through a systematic review of relevant studies, we have shown the relationship between AMR and cancer care, emphasizing how immune suppression from cancer therapies increases susceptibility to resistant infection. Additionally, we have further strengthened the claim that understanding various mechanisms through which microbes develop resistance to antimicrobial drugs is essential to ensure optimal antibiotic therapy and lower the chance of acquiring resistance, especially in cancer patients. The findings revealed that AMR importantly sabotage the efficiency of antibiotic regimens, leading to prolonged illnesses, extended hospital stays, increased morbidity and mortality rates, and higher economic burdens on healthcare systems. The economic impact of AMR is equally concerning, with increased healthcare costs related to the need for more intensive treatments and prolonged care. As evidenced by the findings reported, tackling antimicrobial resistance is paramount in ensuring the continued effectiveness of cancer treatments, safeguarding patient outcomes, and preserving public health. This review advocates for passionate efforts to better understand the mechanisms of AMR, augment the stewardship, and deploy innovative strategies within oncology settings to mitigate the effect of AMR on cancer care. Moving forward, concerted efforts must be made to develop novel antimicrobial agents and optimize treatment protocols to ensure the efficacy of cancer therapies in the face of evolving microbial threats.

4. RECOMMENDATION

- Encourage stewardship programs and knowledge sharing between healthcare professionals globally.
- Implementation of shared care models and collaborative infrastructure between oncologists and other healthcare specialists for improved patient management.
- Implementation of seasoned and scientific-based guidelines for antimicrobial therapy to prevent ineffective treatment.
- Efforts should be made to address antimicrobial resistance globally.
- Investment should be made in interdisciplinary research and innovations for new antimicrobial therapies and diagnostics.
- Implementation of guidelines in infection prevention for cancer patients, caregivers, and healthcare teams.
- Improved and Easy access to cancer care and antimicrobial therapy for cancer patients in under-developed countries.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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