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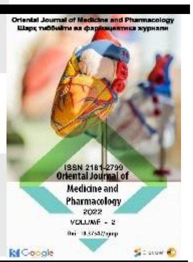

THE IMPORTANCE OF ANTIBIOTIC RESISTANCE IN MEDICAL PRACTICE AND THE RELEVANCE OF ITS PREVENTION

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ABOUT ARTICLE

Key words: Antimicrobial resistance, antibiotic stewardship initiatives, epidemiology, mechanisms, innovative treatments, the One Health concept, policy interventions.

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Abstract: A thorough understanding of the emergence, processes, advancements, and implications of antimicrobial resistance (AMR), which is often seen as a major worldwide public health problem, is necessary. The epidemiological landscape of antimicrobial resistance (AMR) is marked by its extensive prevalence and ever-changing patterns, with multidrug-resistant organisms (MDROs) posing new problems on a daily basis. The establishment and spread of novel resistance strains are facilitated by the most prevalent processes driving AMR, which include genetic alterations, horizontal gene transfer, and selective pressure. Antimicrobial stewardship programs (ASPs) and infection prevention and control strategies (IPCs) are examples of mitigation techniques that highlight the significance of responsible antimicrobial use and surveillance. The interdependence of human, animal, and environmental health is highlighted by a One Health approach, which emphasizes the need for interdisciplinary cooperation and all-encompassing tactics in the fight against AMR. Novel treatment developments (such as vaccines and other antimicrobial medicines) present intriguing ways to address AMR issues. ASPs that seek to control the use of antibiotics are also supported by national and international policy measures. Even with all of the progress that has been seen, antimicrobial resistance (AMR) is still a serious issue that requires ongoing work to address new threats and advance the sustainability of antibiotics. Future studies must focus on novel strategies and tackle the intricate socioecological factors that underlie AMR. For researchers, legislators, and medical professionals trying to understand the complicated AMR landscape and create practical mitigation methods, this book is an extensive resource.

TIBBIY AMALIYOTDA ANTIBIOTIKLARGA CHIDAMLILIKNING AHAMIYATI VA UNING OLDINI OLISHNING DOLZARBLIGI

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MAQOLA HAQIDA

Kalit so‘zlar: antimikrob rezistentlik, antibiotiklardan oqilona foydalanish tashabbuslari, epidemiologiya, mexanizmlar, innovatsion davolash usullari, One Health konsepsiyasi, siyosiy aralashuvlar.

Annotatsiya: Ko‘pincha global sog‘liqni saqlashning yirik muammosi sifatida qaraladigan antimikrob rezistentlik (AMR)ning paydo bo‘lishi, mexanizmlari, rivojlanishi va oqibatlarini chuqur tushunish zarur. Antimikrob rezistentlikning epidemiologik manzarasi keng tarqalganligi va doimiy o‘zgaruvchan xususiyati bilan ajralib turadi, bunda ko‘p dori ta’siriga chidamli mikroorganizmlar (MDRO) har kuni yangi muammolarni yuzaga keltirmoqda. AMRni kuchaytiruvchi eng asosiy jarayonlarga genetik o‘zgarishlar, gorizontal gen uzatilishi va selektiv bosim kiradi, ular yangi rezistent shtammlarning shakllanishi va tarqalishiga yordam beradi. Antimikrob vositalardan oqilona foydalanish va monitoring muhimligini ta’kidlovchi kamaytirish strategiyalariga antibiotiklardan oqilona foydalanish dasturlari (ASP) hamda infeksiyani oldini olish va nazorat qilish choralarini (IPC) misol qilib keltirish mumkin. One Health yondashuvi inson, hayvon va atrof-muhit salomatligi o‘rtasidagi o‘zaro bog‘liqlikni ta’kidlab, AMRga qarshi kurashda fanlararo hamkorlik va kompleks strategiyalar zarurligini ko‘rsatadi. Davolashning yangi yo‘nalishlari (masalan, vaksinalar va boshqa antimikrob preparatlar) AMR muammolarini hal etish uchun istiqbolli imkoniyatlarni taqdim etadi. Antibiotiklardan foydalanishni nazorat qilishga qaratilgan ASP dasturlari milliy va xalqaro siyosiy choralar bilan ham qo‘llab-quvvatlanmoqda. Erishilgan yutuqlarga qaramay, antimikrob rezistentlik hanuzgacha jiddiy muammo bo‘lib qolmoqda va yangi tahdidlarga qarshi kurashish hamda antibiotiklar barqarorligini ta’minlash uchun uzluksiz sa’y-harakatlarni talab etadi. Kelajakdagi tadqiqotlar yangi strategiyalarga e’tibor qaratishi va AMRning asosida yotuvchi murakkab ijtimoiy-ekologik omillarni o‘rganishi lozim. Ushbu maqola AMRning murakkab manzarasini tushunish va samarali kamaytirish choralarini ishlab chiqishga intilayotgan tadqiqotchilar, siyosatchilar va tibbiyot xodimlari uchun keng qamrovli manba hisoblanadi.

ЗНАЧЕНИЕ АНТИБИОТИКОРЕЗИСТЕНТНОСТИ В МЕДИЦИНСКОЙ ПРАКТИКЕ И АКТУАЛЬНОСТЬ ЕЁ ПРОФИЛАКТИКИ

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О СТАТЬЕ

Ключевые слова: антимикробная резистентность, программы рационального использования антибиотиков, эпидемиология, механизмы, инновационные методы лечения, концепция One Health, политические меры.

Аннотация: Глубокое понимание возникновения, механизмов, развития и последствий антимикробной резистентности (AMR), которая часто рассматривается как одна из крупнейших глобальных проблем общественного здравоохранения, является крайне необходимым. Эпидемиологическая картина антимикробной резистентности характеризуется широкой распространённостью и постоянно меняющимися тенденциями, при этом микроорганизмы с множественной лекарственной устойчивостью (MDRO) ежедневно создают новые вызовы. К основным процессам, способствующим развитию AMR, относятся генетические изменения, горизонтальный перенос генов и селективное давление, которые облегчают формирование и распространение новых резистентных штаммов. Стратегии снижения риска, такие как программы рационального использования антимикробных препаратов (ASP) и меры по профилактике и контролю инфекций (IPC), подчёркивают важность ответственного применения антибиотиков и эпиднадзора. Подход One Health акцентирует взаимосвязь здоровья человека, животных и окружающей среды, подчёркивая необходимость междисциплинарного сотрудничества и комплексных стратегий в борьбе с AMR. Новые направления терапии (например, вакцины и другие антимикробные средства) открывают перспективные пути решения проблем AMR. Национальные и международные политические меры также поддерживают программы ASP, направленные на контроль применения антибиотиков. Несмотря на достигнутый прогресс, антимикробная резистентность остаётся серьёзной проблемой, требующей постоянных усилий для противодействия новым угрозам и обеспечения устойчивого использования антибиотиков. Будущие исследования должны быть сосредоточены на разработке новых стратегий и изучении сложных социоэкологических факторов, лежащих в основе AMR. Данная статья представляет собой всесторонний ресурс для исследователей, законодателей и медицинских работников, стремящихся понять сложный ландшафт AMR и разработать практические меры по его снижению.

Introduction. One of the biggest dangers to global public health and development is antimicrobial resistance (AMR). According to estimates, bacterial AMR led to 4.95 million fatalities worldwide in 2019 and was directly responsible for 1.27 million deaths. Drug-resistant infections are mostly caused by the abuse and overuse of antibiotics in people, animals, and plants. All regions and all income levels are impacted by AMR. Poverty and inequality worsen its causes and effects, with low- and middle-income nations being the most impacted. Many of the advances in contemporary medicine are at danger because to AMR. It increases the danger of certain medical procedures and treatments, including surgery, caesarean sections, and cancer chemotherapy, and makes infections more difficult to treat.Since the 1940s, when antibiotics were first used in therapeutic settings, concerns about their use have been acknowledged. Since then, there has been an increase in the usage of antimicrobials and their frequently improper use [1-6]. In the US, antibiotic resistance results in over $20 billion in increased medical costs and the deaths of almost 23,000 patients annually. In order to counteract this tendency, antibiotic stewardship was developed in 1996 to raise awareness of the growing number of deaths and illnesses linked to the improper use of antibiotics. Serious infections including Staphylococcus aureus, vancomycin-resistant enterococci, extended-spectrum B-lactamase-producing Enterobacteriaceae and other infectious organisms are at least partially caused by antimicrobial agents. Improving clinical outcomes, reducing antibiotic resistance, and lowering healthcare costs are the main goals of stewardship initiatives. The Infectious Disease Society of America (IDSA) and the Society of Healthcare Epidemiology of America (SHEA) published stewardship guidelines in 2007, which strengthened and acknowledged stewardship programs countrywide. An institutional program to improve antimicrobial stewardship was developed with the use of these principles. Strong medications called antibiotics are used to treat once-fatal illnesses. Antibiotics have a variety of side effects, just like any potent drug. When these medicines are used appropriately, the benefits outweigh the hazards [7-13]. Antimicrobials are medications used to prevent and cure infectious infections in people, animals, and plants. They include antibiotics, antivirals, antifungals, and antiparasitics. When bacteria, viruses, fungi, and parasites stop responding to antimicrobial medications, this is known as antimicrobial resistance, or AMR. Drug resistance increases the risk of disease transmission, serious sickness, disability, and death by making antibiotics and other antimicrobial medications ineffective and making infections difficult or impossible to cure. AMR is a natural mechanism that develops over time as a result of pathogen genetic alterations. Human activity, particularly the abuse and overuse of antimicrobials to treat, prevent, or control illnesses in humans, animals, and plants, has increased its emergence and spread. However, when antibiotics are overused, people do not benefit and are still vulnerable to the negative effects. Additionally, antibiotics alter the infectious agent's makeup, which causes bacterial mutations or adaptability and, ultimately, the emergence of new strains that are resistant to the existing antibiotic treatment. This is a serious public health concern since improper antibiotic usage in one patient may result in the development of a resistant strain that spreads to other patients who do not use antibiotics. 30% of outpatient antibiotic prescriptions in 2015 were unwarranted, with acute respiratory illnesses accounting for 50% of these prescriptions [14-21].

The main purpose of the presented manuscript is a brief analysis of the importance of antibiotic resistance in medical practice and the relevance of its prevention based on the results of reputable scientific research.

Antimicrobial resistance epidemiology. AMR threatens to undo decades of advancements in the treatment of infectious diseases and has an impact on both human and veterinary medicine. Therefore, in order to comprehend the burden, distribution, and drivers of AMR as well as to create efficient preventative and management measures, population-based studies are necessary. These investigations will overcome the drawbacks of laboratory-based surveillance, such as inadequate laboratory capacity, subpar health systems, and little resources, which are prevalent in LMICs, and give objective prevalence estimates. The WHO has created action plans to promote novel antibiotics, lessen antibiotic abuse, and enhance surveillance in order to address this worldwide issue. Urban sewage metagenomic analysis has been suggested as a financially viable method for ongoing worldwide AMR surveillance [3-9].

Antimicrobial Resistance Mechanisms. The efficacy of medications that fight microorganisms (such as bacteria, viruses, fungi, and parasites), which have evolved a variety of biological strategies to avoid the effects of antimicrobial agents, is threatened by antimicrobial resistance (AMR), a major worldwide health concern. Mechanisms of Antimicrobial Resistance: Microorganisms. Bacteria are among the most researched microorganisms in the context of antimicrobial resistance (AMR), mostly because of their ability to generate many defense mechanisms that allow them to withstand exposure to antibiotics. One of these strategies, called target modification, involves bacteria changing the molecular targets of antibiotics so that the medications cannot adhere to them. For example, mutations in bacterial ribosomal RNA (rRNA) prevent aminoglycosides from binding, allowing the bacteria to continue producing proteins in spite of the antibiotic [4-10]. In addition to suggesting that differential translation and codon decoding are crucial to the stress response, Babosan and colleagues' recent study highlighted the significance of nonessential transfer RNA (tRNA) and rRNA alterations in the bacterial response to antibiotic stress. Efflux pumps actively move a variety of medications outside the cytoplasm in certain bacteria, lowering their intracellular concentrations and enabling the cells to endure higher antibiotic doses. When it comes to antibiotic resistance to tetracyclines, fluoroquinolones, and macrolides, these membrane proteins are very important (figure 1). Certain bacteria, particularly those that are Gram-negative, have a mechanism that lowers the permeability of the cell membrane, keeping antibiotics out of the cell. As a result, the bacterial outer membrane functions as a selective diffusion barrier, preventing the entry of antibiotics through two primary pathways: a lipid-mediated mechanism (for hydrophobic antibiotics) and diffusion via protein channels (for hydrophilic antibiotics). Changes in the outer membrane's protein and lipid composition can have a big effect on how sensitive bacteria are to antibiotics. Fighting antibiotic resistance requires a deeper understanding of the physicochemical factors influencing antibiotic translocation through porins and the molecular underpinnings of outer membrane permeability. Lastly, some bacterial strains develop biofilms, which become extremely resistant to antibiotics because they produce a protective extracellular matrix that restricts drug entry [13-20].

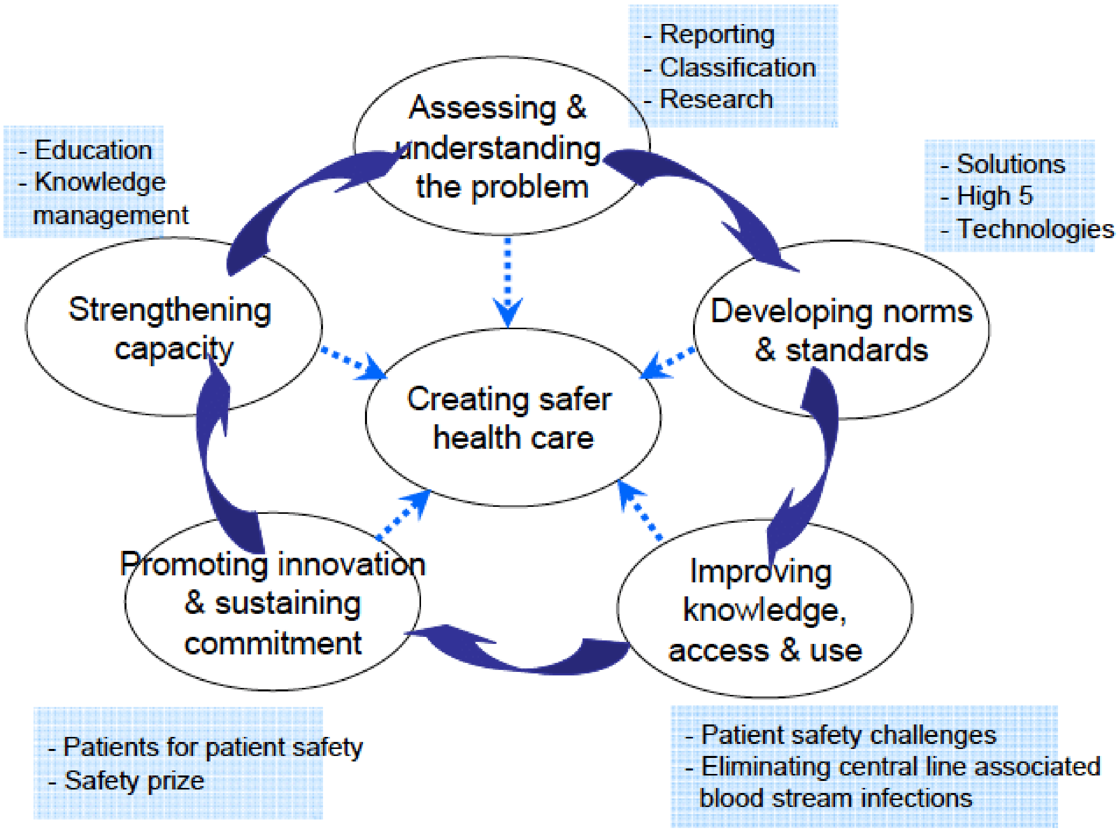

Figure 1. The WHO Patient Safety Program introduced infection control as a means of preventing antimicrobial resistance [20].

The bacteria within these biofilms, which frequently exhibit lower metabolic activity and longer doubling rates, are less vulnerable to antibiotics that target actively dividing cells. In terms of bacterial survival, the biofilm structure has two benefits: it facilitates HGT and increases mutation rates while producing gradients of nutrients and oxygen that result in a variety of metabolic states and antibiotic tolerance. These processes offer vital information for the creation of fresh approaches to treat antibiotic resistance and fight infections linked to biofilms [4-9].

Antimicrobial Resistance's Genetic Mechanisms. Several genetic processes that allow bacteria to adapt and survive in the presence of these chemicals mediate the development of AMR. The ensuing sections will discuss these mechanisms. An organism's DNA sequence is randomly altered by mutations, a basic genetic process. These can happen on their own or be brought on by outside influences such exposure to antibiotics. Naturally occurring during DNA replication, spontaneous mutations can lead to the formation of resistant strains if they impact a gene implicated in drug resistance. Temporal limitations prevent some errors from being repaired despite the efforts of replication error repair systems. For instance, resistance to quinolones is conferred by a point mutation in the bacterial DNA gyrase gene, which lowers the drug's binding affinity. Even among closely related microbes, the rate of spontaneous mutation during reproduction varies [6-11]. For example, the mutation rate of herpes simplex virus type 2 (HSV-2) is higher than that of HSV-1 (laboratory strains: 9–16-fold; clinical isolates: over 30-fold). However, changes in many genes frequently lead to the formation of resistance. For example, mutations in genes linked to prodrug activation and the F420 biosynthesis pathway (genes: ddn, fgd1, fbiA, fbiB, and fbiC) are linked to resistance to PA-824 in M. tuberculosis, leading to decreased sensitivity. Antimicrobial agent exposure at sub-lethal concentrations causes genomic instability and DNA damage, which increases the rate of mutation in bacteria and may result in the formation of novel AMR—antibiotic-induced mutagenesis. This condition is caused by the generation of reactive oxygen species (ROS) and the ensuing oxidative stress, which causes error-prone polymerases and either directly affects DNA or throws nucleotide metabolism out of balance. Because of this, a variety of genetic abnormalities can be seen, ranging from serious chromosomal rearrangements to single-nucleotide polymorphisms (SNPs). The possible involvement of environmental pollutants in generating antibiotic resistance has been highlighted by the suggestion that heavy metals also raise mutation rates and permit the creation of mutants resistant to several drugs. In addition to these two, chemical pollutants (such as biocides, nanoparticles, and disinfection byproducts) and non-chemical stressors (such as UV radiation, electrical stimulation, and starvation) may also contribute to the higher rate of mutation in bacteria and the possible emergence of antimicrobial resistance [12-19].

Interaction between selection pressure and genetic mechanisms. In AMR, genetic mechanisms and selective pressure interact in a complicated and multidimensional way. On the one hand, bacteria use a variety of methods (such as structural modifications, enzymatic activities, and gene regulation) to adapt to host defense systems and antimicrobial drugs. However, ARGs are spread by mobile genetic elements like plasmids and transposons, and the development of genetic drug resistance is aided by non-genetic factors such transcriptional heterogeneity. Furthermore, bacterial adaptability and antibiotic resistance are influenced by epigenetic changes (such as DNA methylation and non-coding RNA control). Lastly, mechanisms of genetic recombination and selective evolutionary pressure brought on by the improper use of antimicrobial medications further accelerate the spread of AMR. Whole-genome sequencing (WGS) and other high-throughput bioinformatics techniques have recently emerged as useful instruments for the investigation of AMR processes and the identification of novel resistance signatures [7-12].

Discussion. Humanity is in a challenging position due to the growing threat of antibiotic resistance and the decline in illness treatment choices. There is a pressing need to preserve and safeguard the effectiveness of antibiotic therapy due to the impending threat of the return of the pre-antibiotic period. The spread of antibiotic resistance's causative agents from non-clinically significant strains to clinically significant strains and vice versa is one of its paradoxical outcomes.

When it comes to combating antibiotic resistance, the adage "prevention is better than cure" is appropriate. On the one hand, new and efficient antibiotics are needed; on the other hand, improved antibiotic usage protocols and more public awareness of antibiotic use are crucial. Strong medications called antibiotics are used to treat once-fatal illnesses. Antibiotics have a variety of side effects, just like any potent drug. When these medicines are used appropriately, the benefits outweigh the hazards [1,4,5,6]. However, when antibiotics are overused, people do not benefit and are still vulnerable to the negative effects. Additionally, antibiotics alter the infectious agent's makeup, which causes bacterial mutations or adaptability and, ultimately, the emergence of new strains that are resistant to the existing antibiotic treatment. This is a serious public health concern since improper antibiotic usage in one patient may result in the development of a resistant strain that spreads to other patients who do not use antibiotics. 30% of outpatient antibiotic prescriptions in 2015 were unwarranted, with acute respiratory illnesses accounting for 50% of these prescriptions. This exercise goes over the factors to take into account when using antibiotics and talks about the interprofessional team's role in teaching patients and healthcare professionals when to use them and when not to. Controlling the use and abuse of antibiotics as well as the containment of antibiotic resistance can be substantially aided by awareness, particularly regarding appropriate antibiotic usage, antibiotic resistance, its dissemination, and potential dangers. By creating new antibiotic analogs or supplementing existing antibiotics with adjuvants, the efficacy of antibiotic medications can be increased [7,8,10]. Multidrug-resistant (MDR) bacterial infections have been successfully treated with antibiotic combinatorial therapy. In order to combat antibiotic resistance, this review will highlight the present state of antibiotic resistance worldwide and go over strategies for tracking, preventing, inhibiting, or reversing bacterial resistance processes. Antimicrobial resistance, which allows germs to withstand exposure to medications intended to inhibit or kill them, is caused by genetic alterations and environmental stressors. This complexity emphasizes the necessity of all-encompassing approaches, such as careful use of antibiotics, effective infection management, and continuous research into new treatments. The widespread and rising incidence of AMR across many diseases, geographical areas, and industries is revealed by its epidemiology, underscoring the critical need for a concerted worldwide response. Without coordinated action, the world runs the possibility of common illnesses becoming incurable in the future, significantly weakening the advancements made in contemporary medicine [15-19]. As mentioned earlier, combating antimicrobial resistance (AMR) is a crucial issue of our day, necessitating a coordinated worldwide effort across disciplines, industries, and national boundaries. We can create long-lasting answers to this expanding threat by comprehending the processes of resistance, tackling its epidemiological complexity, and embracing creative ways through the One Health framework. Maintaining the efficacy of antibiotics and guaranteeing the health and safety of future generations require a cooperative strategy that incorporates policy, legislation, research, and public involvement. The stakes are extremely high, and now is the moment to take action [20-24].

Conclusions. Antimicrobial resistance is a complicated, multidimensional problem that calls for a concerted international response. The need for new antimicrobial drugs and alternative treatment approaches is highlighted by the growth of multidrug-resistant organisms and novel resistance mechanisms. To guarantee that the advantages are distributed fairly, the ethical and societal ramifications of AMR treatments must be properly taken into account. The battle against AMR must include strengthening international surveillance, including AMR into larger health agendas, encouraging cross-sectoral cooperation, and raising public awareness. We can preserve the effectiveness of antibiotics and defend global public health for future generations by adopting a thorough and cooperative approach.

Every hospital in the US must have a stewardship program, according to new stewardship guidelines established by the Joint Commission in 2017. However, many hospitals have not yet implemented these programs, and many organizations worry that smaller hospitals might not be able to create stewardship programs that work. Some potential ways to get beyond these obstacles include pooling resources from neighboring hospitals, promoting the use of their state's health department resources, and joining a larger healthcare system to take advantage of their resources. One aspect of a health system that is typically run by the government to monitor and control healthcare is stewardship. In order to promote the best use of antibiotic agents, including their selection, dosage, route, and duration of administration, antimicrobial stewardship programs necessitate systematic measurement and coordinated interventions between clinicians, infection control staff, pharmacists, and informational technology.

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