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The Looming Threat of Bacterial Resistance and Immune Response Disruption: A Review

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Abstract: A broad range of antibiotics are prescribed and used too often and too readily, driving the spread of antimicrobial resistance (AMR) which is a threat to human health, animal welfare and food security all over the world. The multifactorial aspects of antibiotic misuse that include the influence on resistant bacterial strains and the resulting immunocompromise of the host are reviewed. Bacterial resistance mechanisms such as decreased uptake, target modification, destruction of antibiotics by enzymes, and the activation of efflux pumps are discussed, as are the effects of antibiotics on the innate and adaptive immune systems. Special focus is given to the importance of gut microbiota in maintaining immune homeostasis, and antibiotic-induced dysbiosis in disrupting mucosal immunity and increasing the susceptibility to recurrent difficult-to-treat infections. In addition, the review examines the co-evolution of resistance and immune evasion mechanisms, which help to enable pathogen persistence and disease recurrence. Lastly, new solutions like antibiotic stewardship programs, microbiome recovery strategies and innovative therapeutic strategies are explored as key interventions to prevent antibiotic overuse and reduce the long-term immunological and epidemiological impacts of antibiotic use.

Keywords: Antibiotic Resistance, Antimicrobial Stewardship, Immune System Disruption, Gut Microbiota, Efflux Pumps, β-lactamases

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1. Introduction

Antibiotics have played a crucial role in decreasing mortality rates due to infectious disease and have revolutionized modern medicine. But they have been used indiscriminately with unintended consequence that poses threats to global health. AMR is one of the top 10 health threats in the world, according to the World Health Organization [1]. In addition to resistance, there is increasing evidence that antibiotics can also have a negative effect on the immune system, particularly by destroying the commensal microbiota, reducing immune surveillance, and inducing chronic inflammation [2], [3].

Antimicrobial drugs are essential drugs in today's healthcare. In addition to their use for treating common bacterial infections, they are also the basis for many of the most important medical procedures and treatments, including cesarean sections, orthopedic surgery such as joint replacement, and cancer chemotherapy and organ transplantation. These procedures are based on the use of efficient prophylactic and therapeutic antibiotic treatments to prevent and treat infections. However, rising cases of antimicrobial resistance (AMR) are jeopardizing advances of the past few decades that are vital to

healthcare, with the potential for once treatable infections to become deadly, and the safety of essential medical procedures to be compromised.

The impact of AMR extends beyond human health to animal health, agriculture and the environment. Resistant pathogens reduce livestock productivity and plant health, thus impacting food systems and food security. AMR has a heavy economic impact on national health systems and economies. The use of second or third line of antibiotic, extended hospital stays, intensive care and long convalescent periods contribute to higher health care costs, lower productivity of the workforce and higher burdens on caregivers.

The discovery of antibiotics can be regarded as one of the biggest developments in 20th-century medicine. Medications started with the sulfonamides during the 1930s, and the production of penicillin and streptomycin were taken to mass scale in the 1940s. In the 1950s, the broad-spectrum bacteriostatic agents were introduced, and in the 1960s, potent bactericidal compounds and synthetic antimicrobials were added [4]. These developments had a dramatic impact on the death toll in infectious diseases. The indiscriminate and overuse of these life-saving agents, however, led to the development and proliferation of resistant bacterial strains and to a worldwide public health crisis.

This threat is so severe that there are urgent discussions and coordinated response from international agencies. The World Health Organization (WHO), the United States Institute of Medicine (IOM), and the British House of Lords (HOL) have all held high-level panels to discuss AMR [5], [6]. To foster AMR research and policy, the European Union has also been actively involved in organizing scientific sessions and has published several reviews [7]. National programmes have also risen to become important elements of surveillance and response. In India, for example, the Indian Council of Medical Research (ICMR), All India Institute of Medical Sciences (AIIMS) and CDC India have established large scale antimicrobial surveillance networks. The healthcare-associated infection (HAI) surveillance initiative was launched in 2016 with only five hospitals and is now in place in 36 hospitals across 24 states as of 2021. At the same time, there are now 35 laboratories from 26 states and 3 union territories in the National Antimicrobial Resistance Surveillance Network (NARS-Net).

CDC India has also supported the global AMR data by integration with the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS), which has assisted in monitoring emerging AMR trends and outbreaks of multidrug-resistant pathogens globally. During the COVID-19 pandemic, these initiatives were built upon to promote infection prevention and control (IPC) messages and to maintain continuity of AMR surveillance activities.

However, while these developments are positive, multidrug-resistant strains are on the rise and are outpacing the development of effective treatment, particularly of Gram-negative bacteria such as Klebsiella pneumoniae, Acinetobacter baumannii and Pseudomonas aeruginosa and Gram-positive bacteria such as MRSA. Lack of timely microbiological diagnosis leads to the empirical use of broad spectrum antibiotics in severe infections like Sepsis or Bacteremia in many health care facilities. This practice, along with the lack of infection control measures, leads to development of resistance and nosocomial transmission [8].

Thus, the review highlights the compelling need to tackle the clinical and immunological challenge of antimicrobial resistance. When left unchecked, AMR poses a risk to the effectiveness of routine and advanced medical care and is a threat to the advancement of public health, especially in low- and middle-income countries where it is needed most: in areas with limited surveillance, weak laboratory capacity, and insufficient regulation.

2. Factors Behind Antimicrobial Resistance

There are many interconnected factors driving antimicrobial resistance (AMR) that manifest in a wide variety of ways in health care, the environment, veterinary health and human health. Antibiotics are used extensively in humans and in agriculture. Two to five decades of antibiotics have been used in human medicine and 40%–80% in animal medicine, mainly for growth promotion and prophylaxis [9]. It has been found to be associated with the development of antibiotic-resistant bacteria, including vancomycin-resistant enterococci (VRE) that can colonize the gut of animals and spread to humans through the food chain or environmental contact [10]. Furthermore, the widespread use of broad-spectrum antibiotics in the hospital setting creates strong selection pressure for survival and proliferation of resistant organisms and contributes to the risk of nosocomial transmission and outbreaks [11].

AMR is also greatly influenced by environmental factors, which have been a significant driver of its worldwide dissemination. Community-acquired resistant infections are a risk from poor sanitation, overpopulation and urbanisation. In some overcrowded regions, insufficient waste disposal practices lead to environmental reservoirs of resistance genes [12] in water and soil. Resistant pathogens are spread further at the global level by global travel as well as migration. Furthermore, the use of antibiotics for non-therapeutic purposes in agriculture and aquaculture and the presence of antimicrobial agents in household cleaning products lead to contamination of the environment and to low-level exposure of antibiotics in ecosystems [8], [13]. Drug-related issues play an important role in the issue. Self-medication and inappropriate use of antibiotics is widespread in many LMICs, as these are easily purchased without a prescription. Subtherapeutic dosing or antagonistic drug interactions may occur because of irrational marketing and use of fixed dose combinations (FDCs) of antimicrobials, many of which are not supported by sufficient clinical evidence [14]. In addition, substandard and fake drugs often found in weak regulatory markets may be poorly formulated with inadequate concentrations of active pharmaceutical ingredients, which can result in incomplete elimination of bacteria and the emergence of resistant strains [15].

Patient-related factors also contribute to antimicrobial misuse and spread of antimicrobial resistance. Missed doses of prescribed medication is a universal problem, particularly among groups with poor access to health services and low health literacy. In some cases, patients are unable to finish the course of antibiotics, allowing some of the bacteria to develop resistance. Patients are also pushed to visit informal or OTC health providers without proper guidance due to the poverty, lack of sanitation and limited access to diagnosis services [16]. Besides, cultural beliefs about antibiotics use, such as their effectiveness for viruses, make it difficult for the right patterns of use.

Healthcare providers and prescribers haven't been spared of contributing factors. Prescribing antibiotics when they are not indicated continues to be a problem in clinical practice: often a clinician will prescribe a broad antibiotic when a specific diagnosis is not suspected. The selection of resistant organisms is due to empirical treatment with more than one antimicrobial, inadequate dosage and resistance from the antimicrobial therapy not being adjusted based on cultures [17]. Furthermore, current medical curricula, especially in rural and resource-limited areas, do not provide continuous medical education, which is a major challenge for the rational use of antibiotics [18]. Lack of strong antimicrobial stewardship programs in many healthcare systems also contributes to this issue and resistance can spread freely.

3. Mechanisms of Antimicrobial Resistance

Antimicrobial resistance (AMR) is the result of multiple molecular and cellular mechanisms evolved by bacteria that help them to resist the effects of antimicrobials. These mechanisms can be broadly classified

as follows: Limits the uptake of the drug in the cell; Drug target modification; Enzymatic inactivation of the drug; Active transport of the drug from the cell. Resistance mechanisms can be intrinsic (encoded in the bacterial genome) or acquired, either by horizontal gene transfer, spontaneous mutation or by the transfer of mobile genetic elements (plasmids and transposons) [11]. The deployment of these mechanisms is also affected by the difference in cell wall structure of the bacteria. For example, all four mechanisms are typical in Gram-negative bacteria, which have a complex outer membrane, while modification of the target and enzymatic inactivation are typical in Gram-positive bacteria.

3.1 Genetic Adaptations and Selection Pressure

3.1.1 Reduced permeability via altered porins

One of the basic mechanisms of intrinsic resistance is the prevention of entry of the drug into the bacterial cell. Gram-negative bacteria have an outer membrane of lipopolysaccharides (LPS) that protect them from many hydrophilic and large molecules [19]. In these organisms, the antibiotics usually enter via porin channels, and their permeability can be greatly reduced by mutations, such as loss of porins, or decrease in their abundance. For instance, Enterobacteriaceae have been linked to carbapenem resistance through decreased expression of porins. Mycobacteria have a lipid-rich outer membrane that impedes the penetration of hydrophilic drugs and facilitates that of lipophilic drugs such as rifampicin. Organisms like Mycoplasma, on the other hand, do not have a cell wall and are intrinsically resistant to all β-lactam and glycopeptide antibiotics. Intrinsic resistance is also due to a dense cell wall in some Gram-positive organisms such as Enterococcus faecalis that limits aminoglycoside penetration.

3.1.2 Biofilm formation, enhancing collective resistance

Biofilm formation is another mechanism of resistance to antibiotics. The bacteria in biofilms are surrounded by an extracellular polymeric matrix which is produced by the bacteria themselves and resists the penetration of antimicrobial agents, as well as immune system attack [20]. In addition, horizontal gene transfer is more likely to occur in the biofilm environment, which may speed the transfer of resistance genes. Plasmids, transposons, or integrons are potential mechanisms for transfer of resistance genes, and they may be accompanied by mobile genetic elements in polymicrobial communities [11].

3.1.3 Altered drug targets

Target modification is one of the most frequent resistance mechanisms of Gram-positive and Gram-negative bacteria. This mechanism includes conformational changes to the antibiotic binding site to decrease the affinity of the binding site for the antibiotic, but not affecting the normal function of the binding site. For example, mutations that lead to the acquisition of PBP2a encoded by the mecA gene in methicillin-resistant Staphylococcus aureus (MRSA) make the organism resistant to almost all β-lactam antibiotics [21]. Likewise, van genes in Enterococcus faecium make the terminal D-Ala-D-Ala recognition sequence of vancomycin susceptible to binding with D-Ala-D-Lac, which results in vancomycin-resistant enterococci (VRE) [22].

Point mutations disrupting the action of the DNA gyrase (gyrA) and topoisomerase IV (parC or grlA) genes essential for the activity of the fluoroquinolones are common causes of resistance [23]. Protein Synthesis Inhibitors including macrolides and aminoglycosides are mediated by erm genes which cause methylation of 23S rRNA so that the antibiotic cannot bind but the ribosome can still function, or by mutations which modify the ribosome so the antibiotic cannot bind to it. Resistance to tetracyclines can result from the displacement of the antibiotic from its binding site, and/or by preventing binding of the antibiotic to the ribosome. Similarly, resistance to sulphonamides and trimethoprim (which both inhibit folate biosynthesis) is mediated by point mutation or by picking up resistant variants of two enzymes, dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR).

3.1.4 Enzymatic inactivation

Enzymatic inactivation of antimicrobial agents is another common mode of resistance. The most common way to be deactivated is by hydrolysis or chemical modification, the latter happening most frequently to β-lactam antibiotics through the action of β-lactamases which deactivate the β-lactam ring. This is common not only to Gram-negative pathogens, but to Gram-positive pathogens as well [24]. For example, the TEM, SHV and CTX-M families of extended-spectrum β-lactamases (ESBLs) have been found in a large fraction of resistance to penicillins and cephalosporins in Escherichia coli and Klebsiella pneumoniae.

Some bacterial enzymes chemically modify antibiotics in addition to hydrolysis. Chemical modification of aminoglycosides occurs by acetyltransferases, phosphotransferases and nucleotidyltransferases which decrease the ability of the antibiotics to bind to the ribosom. The genes tet (X) are flavin-dependent monooxygenases which hydroxylate tetracycline resulting in its inactivation. These enzymatic defenses make a significant contribution to the multidrug resistant phenotypes.

The β-lactamases belong to a large family of enzymes with a wide variety of properties, and are the most common mechanism of resistance among Gram-negative microbes. These enzymes can be classified into four structurally distinct groups (A-D), cephalosporinases, serine β-lactamases and metallo-β-lactamases (MBLs) [25]. TEM, SHV and KPC carbapenemases are classified as Class A enzymes. Like other class B MBLs, VIM, IMP and NDM break down all β-lactam classes, including carbapenems, and are not inhibited by the usual β-lactamase inhibitors. Class C (AmpC) enzymes are typically chromosomally mediated and cause resistance to cephalosporins in organisms such as Enterobacter cloacae. The OXA-type β-lactamases are enzymes found in Acinetobacter baumannii and related to carbapenem resistance, and are classified as class D enzymes. The plasmid mediated β-lactamases, such as ESBLs and carbapenemases are clinically relevant because of their high transmissibility and co-resistance with other classes of antibiotics [26]. Novel combinations of β-lactamase inhibitors, including ceftazidime-avibactam and meropenem-vaborbactam, are effective against some ESBLs and KPCESBLs but not against MBL producers.

3.1.5 Efflux pumps reducing intracellular drug concentration

Efflux pumps are membrane-bound transport proteins which actively pump antimicrobial agents out of the cell, decreasing their intracellular concentration below therapeutic levels. These systems can be chromosomally encoded in the cell or acquired through the plasmid; and their overexpression is often associated with multidrug resistance [27]. Efflux activity is controlled by environmental conditions and substrates, and frequently leads to increased survival in antimicrobial-rich environments. Bacteria have five main families of efflux pumps: ATP-binding cassette (ABC) superfamily, major facilitator superfamily (MFS), resistance-nodulation-division (RND) family, multidrug and toxic compound extrusion (MATE) family and small multidrug resistance (SMR) family [28]. Many gram-negative organisms, including Pseudomonas (P.) aeruginosa and E. coli, are known to have pumps belonging to the RND family, such as MexAB-OprM and AcrAB-TolC, that provide resistance to β-lactams, macrolides, fluoroquinolones and beyond [27]. These pumps traverse the entire cell envelope and pump a wide variety of drugs by means of proton-motive force.

On the contrary, MFS and SMR pumps are the main contributors of Gram-positive bacteria. The NorA pump in S. aureus is associated with fluoroquinolone resistance, and the LmrS pump is involved in the removal of several drugs, such as linezolid and chloramphenicol. These pumps, which are less structurally complex than their Gram-negative counterparts, are important for intrinsic and acquired resistance. There are newer classes of efflux inhibitors and pump blockers under development, especially

those that target RND systems. But clinical efficacy has been hampered by toxicity and low spectrum.

3.2 Emergence of Multidrug-Resistant Pathogens

One of the worst effects of non-responsible antibiotic use is the advent of multidrug resistant (MDR) and extensively drug resistant (XDR) pathogens around the world. They are multidrug resistant, limiting the treatment options considerably, resulting in extended periods of sickness, deaths and increased health care expenses. In addition to adding to the difficulty of treating these infections, MDR pathogens also pose difficulties during infection control, particularly in hospital and intensive care environments. The most clinically relevant MDR pathogens are Staphylococcus aureus (MRSA), Pseudomonas aeruginosa, carbapenem-resistant Klebsiella pneumoniae (CRKP) and extensively drug-resistant Mycobacterium tuberculosis (XDR-TB).

3.2.1 Methicillin-Resistant Staphylococcus aureus (MRSA)

Staphylococcus aureus is well known to cause skin and soft tissue infections, pneumonia and bloodstream infections. MRSA was first identified in the 1960s and was another big milestone in the field of antimicrobial resistance (AMR) [21]. MRSA strains are resistant to β-lactam antibiotics due to the presence of the mecA gene which encodes penicillin-binding protein 2a (PBP2a) that has a low affinity for β-lactam antibiotics. MRSA has become endemic in HA-MRSA and CA-MRSA settings and there have been reports of resistance to non-β-lactam antibiotics, such as clindamycin and fluoroquinolones. This pathogen is also highly unusual because it can escape immune responses through the production of immune-modulating toxins and formation of biofilm [29].

3.2.2 Pseudomonas aeruginosa

P. aeruginosa is a gram-negative pathogen, which tends to cause opportunistic infections in patients with compromised host defenses or in the presence of nosocomial factors like ventilator-associated pneumonia (VAP), urinary tract infections (UTI), and infections in burn and immunocompromised patients. The resistance profile is beyond formidable because of its ability to form biofilms, reduce the uptake of drugs (e.g., decrease in porins) and overexpress efflux pumps, especially MexAB-OprM [27]. Furthermore, P. aeruginosa often possesses the ability to produce β-lactamase enzymes such as AmpC and metallo-β-lactamase (MBM) that provide resistance to cephalosporin and carbapenems. It is a key organism in the ESKAPE group of pathogens prioritised by the WHO for the urgent development of new antimicrobials, and also has inherent adaptability and genetic plasticity [30].

3.2.3 Carbapenem-Resistant Klebsiella pneumoniae (CRKP)

Klebsiella pneumoniae is a member of the Enterobacteriaceae family and is an important cause of pneumonia, blood stream infections and surgical site infections. CPEs have emerged as a serious public health threat, particularly in ICUs. The production of carbapenemases like KPC, NDM-1, VIM and OXA-48 enzymes, which break down the carbapenem antibiotics, is the main basis of resistance in CRKP. These resistance determinants are frequently plasmid mediated and linked to other genes such as those for resistance to aminoglycoside, fluoroquinolone and colistin, conferring pan resistance. The mortality rate of CRKP can be over 50%, especially in susceptible groups of patients [31].

3.2.4 Extensively Drug-Resistant Mycobacterium tuberculosis (XDR-TB)

Mycobacterium tuberculosis is the cause of tuberculosis (TB) and is still one of the most important infectious disease killers in the world. The emergence of drug-resistant TB, particularly multi-drug resistant TB (MDR-TB), and XDR-TB (extensively drug resistant TB) which is resistant to isoniazid, rifampin, fluoroquinolones and at least one injectable second-line drug, has severely compromised TB control programs around the world [32]. XDR-TB is linked to sub-optimal treatment outcomes, longer treatment (usually >18 months) and higher mortality. Treatment is inherently complex because M.

tuberculosis is slow growing and can persist intracellularly, forming granulomas that make the bacteria shielded from detection and treatment, making it vulnerable to the development of resistance when drugs are interrupted or taken incorrectly. This has the potential to drastically limit treatment choices, and is shown to be a factor in increased morbidity, mortality, and healthcare costs [18].

4. Immune System Disruption by Antibiotics

In addition to the promotion of antimicrobial resistance, antibiotics have the capacity to have profound and underappreciated effects on the host immune system. These disruptions act, in part, via their influence on the gut microbiota, one of the most important regulators of immune development and function, but can also have direct immunomodulatory effects on both innate and adaptive immune responses. Evidence is growing that antibiotic-induced disruption of immune homeostasis can lead to both increased susceptibility to recurrent infections and chronic inflammatory diseases, as well as poor vaccine response [3].

4.1 Gut Microbiota and Immune Crosstalk

Gut flora is a complex and abundant microbial community that is important for regulating mucosal and systemic immune responses. Antibiotics, particularly broad-spectrum antibiotics, that disrupt this delicate balance by eliminating beneficial commensals, such as Bifidobacterium and Lactobacillus, and decrease the diversity of microorganisms, allowing opportunistic pathogens, including Clostridioides difficile [2], to grow. These changes disrupt the integrity of the gut barrier, the production of immunoglobulin A (IgA) and the availability of microbial metabolites, including short-chain fatty acids (SCFAs), which are essential for regulatory T cells (Tregs) differentiation and immune tolerance [33].

It also causes increased risk of autoimmune and allergic diseases. For example, early-life exposure to antibiotics has been associated with an increased risk of asthma, eczema, and inflammatory bowel disease-like conditions associated with dysfunctions in the immune system [34]. Additionally, microbiome depletion leads to decreased colonization resistance and allows pathogenic organisms to thrive and to be more susceptible to new infections.

4.2 Effects on Innate Immunity

Antibiotics can directly affect elements of the innate immune system. Fluoroquinolones and macrolides are some classes of antimicrobials that have been shown to modulate neutrophil and macrophage activity. They can inhibit chemotaxis, phagocytosis and oxidative burst, which reduces the ability of innate cells to mediate pathogen clearance [35]. In mice, like in humans, exposure to antibiotics was also linked to decreased levels of Toll-like receptors (TLRs) and their signaling pathways, resulting in an impaired recognition of pathogens and inflammatory response [36]. Some medicines, such as beta-lactam antibiotic drugs and chloramphenicol, also suppress the immune system naturally, as do the use of antibiotics (innate suppression). This is particularly relevant in chemotherapy patients and in immunocompromised patients and could seriously compromise the host's ability to resist bacterial and fungal infections, demonstrating the fine line between antimicrobial activity and host immunity.

4.3 Impact on Adaptive Immunity

Adaptive immune system is not spared of immunomodulatory effects of antibiotics. Loss of gut microbiota has been demonstrated to affect mucosal lymphoid structures development and function, T-helper cell differentiation and the production of antigen-specific memory T and B cells [37]. This is especially true of the efficacy of oral and intranasal vaccines that depend on strong mucosal immunity for protection. Furthermore, macrolides and tetracyclines have been shown to have immunosuppressive effects other than their antibacterial properties. These antibiotics can alter cytokine production, including

the decrease of interleukin-12 and tumor necrosis factor-alpha (TNF-α) that shift the immune response towards a Th2 or regulatory phenotype [38]. This can be advantageous in chronic inflammatory diseases such as CF, but is a concern when it comes to immune suppression in otherwise healthy people or during acute infections.

5. Interactions Between Resistance and Immunity

The battle for antimicrobial resistance and host immunity is an intricate and dynamic landscape. Resistance decreases the effectiveness of antibiotics as the infection is treated and will influence the host-pathogen interaction. Resistant organisms tend to occupy niches within the immune system, thrive in inflammatory environments, and acquire traits that aid in evading the immune system.

5.1 Infection Recurrence and Immune Evasion

Recurrent infections result from a permissive environment for them, due to antibiotic induced dysbiosis and immune suppression. For instance, altering gut microbiota with antibiotics can increase colonization resistance and lead to the re-infection of C. difficile or uropathogens such as uropathogenic E. coli [39]. The use of antibiotics may not curb these recurrent infections, because that is not enough to stop the growth of antibiotic resistant bacteria and the host immune system is not enough to stop them. The immune clearance of pathogens in biofilms is very efficient. Biofilm-associated bacteria have low metabolic rates, lowered expression of antigens and a protective extracellular matrix that protects them from phagocytosis and antibody mediated killing. These properties enable pathogens, such as Pseudomonas aeruginosa in CF patients or Staphylococcus epidermidis on indwelling devices to survive for long periods despite host immune activation and antibiotic treatment [20].

5.2 Evolution of Immune-Evasive Traits

Immune evasion is part of the arms race between antibiotics and microbes. The selection of resistant phenotypes by antibiotics also indirectly promotes immune escape phenotypes. For example, it has been noted that MRSA strains are capable of inhibiting immune cell surface proteins, producing stronger biofilms, and secreting toxins that affect the function of neutrophils [29]. Likewise, MDR Klebsiella pneumoniae often possess thick capsules and siderophores which render them complement-inactivating and phagocytosis-resistant [40]. Not all of these evolutionary adaptations are hospital specific. Agricultural and sub-therapeutic antibiotic use in the community has been suggested to be a cause of zoonotic strains with increased ability to evade immune system responses, and of potential infections that will be more difficult to treat that will be spreading between strains and species [12].

6. Emerging Solutions to Curb Antibiotic Abuse

The battle against the global problem of antimicrobial misuse needs to be undertaken through multiple approaches, not just to minimize unnecessary exposure to antimicrobials, but also to restore the body's natural barriers. One institution of this approach is antibiotic stewardship programs (ASPs). These coordinated interventions are designed to optimally use antibiotic choice, dosing, route, and duration of treatment, based on microbiological data and clinical evidence. Use of broad-spectrum agents should be minimized and replaced with targeted therapy, and de-escalation and discontinuing therapy should be considered at an early stage when infection control has been reached. The use of ASPs in the hospital setting has been proven to substantially decrease the use of antibiotics and the number of infections caused by resistant organisms, in some settings by up to 40% [41]. While stewardship, the recovery of microbiomes is also becoming a focus of interest, particularly because of the pivotal role of the gut microbiome in immunity and resistance to infections. Examples of restorative approaches include use of

probiotics and synbiotics to promote beneficial bacteria and prebiotics to support the endogenous microbial populations. FMT has been shown to be a highly effective therapy for severe dysbiosis and is effective in restoring microbial diversity and function, especially in recurrent Clostridioides difficile infections (rCDI). With stewardship initiatives, these strategies represent an exciting opportunity not only to help roll back the immunological and ecological damage wrought by antimicrobial overuse but also to prevent the generation of further resistance.

7. Conclusion

The problems of antibiotic resistance and immune disruption are linked and stem from overuse of antibiotics for decades in human medicine, agriculture, and veterinary medicine. Currently, there are new resistant pathogens emerging and the effectiveness of the medications used to treat them is rapidly declining, resulting in increased hospital stays, morbidity and mortality, and healthcare costs. Furthermore, the collateral damage of antibiotics on the immune system, particularly the disruption of the microbiome weakens the host's immune response to infection and vaccine success. This dual threat demands a global response, including the implementation of effective antibiotic stewardship programmes, regulation of antibiotic usage in animal husbandry, public awareness campaigns and investment in new and improved antimicrobials and microbiome-friendly therapies. If action is not taken, there is a possibility of getting back to the pre-antibiotic days when minor infections were once fatal and medical innovations were rendered useless.

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