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Superbugs (Multi Drug Resistant Bacteria to Antibiotics): A Review

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ABSTRACT

This paper aims to focusing on the antimicrobial resistance, causes, mechanisms of resistance and some kinds of multidrug resistance bacteria that causes health problems and may leads to death. The Superbugs resist to several antibiotics and other medications commonly suggested treating the health problems they cause. They involve strains of fungus, bacteria, viruses, and parasites. Among the resistant bacteria include those that cause respiratory infections, infections in the urinary tract, and skin infections. Antimicrobial resistance, or drug resistance, is an occurrence that happens naturally and can be delayed but not halted. Drugs used to kill bacteria, viruses, parasites, and fungi cause these microorganisms to evolve over time in order to survive this reduces the efficacy and occasionally eliminates the need for some recommended treatments or infections. Researchers are currently analyzing how these resistant bacteria proliferate. Additionally, they investigate the background of antibiotic resistance, its signs, and therapeutics. A few things that might accelerate the evolution and dissemination of bacteria that are resistant to antibiotics include the abuse and overuse of antibiotics, insufficient infection prevention and control measures, residing or employed in contaminated conditions, and incorrect handling of foods.

Keywords: Superbugs, Bacteria, Multidrug resistance bacteria, Antibiotics

1. Introduction

Superbugs are harmful microorganisms, particularly bacteria that have become resistant to the drugs typically used to treat them. A new danger to food security, human health, and economic growth is arising: antimicrobial resistance (AMR). The World Healthcare Organization (WHO) states that superbugs and multidrug-resistant pathogens pose a major global health risk. The Intergovernmental Working Team on AMR has projected that by 2050, the number of deaths rise to nearly 10 million yearly (Painuli et al, 2023).

The definition of "multidrug resistant pathogens" refers to bacteria, viruses, fungi, or parasites that develop resistance to current therapy and cease to respond to it as a result of improper antibiotics use, eating filthy food, maintaining unsanitary conditions, improper infection prevention, and other factors (Tanwar et al., 2014).

On the basis of the predictive statistical models done by Antimicrobial Resistance Collaborators in 2022 ; Approximately four million fatal incidents were attributable to bacterial AMR in 2019, with one million (95 %) of those deaths being directly related to AMR. Under the magnitude of the region, was calculated that the all-age death rate due to resistance was 6 deaths per one hundred thousand in Australasia and about 27 deaths per one hundred thousand in Africa. Among infectious conditions, lower respiratory infections are the most prevalent, with nearly one million resistance-related deaths in 2019, and nearly 3 million deaths related to (AMR) were attributed to relate with resistance: *Escherichia coli*, then *Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa.*

1. Multi -Drug Resistant Bacteria and Nosocomial Infections

In hospital-acquired infections as well as community-acquired illnesses, antibiotic resistance (AMR) is a significant issue. Nosocomial-acquired infections (HAIs), often referred to as nosocomial infections (NIs), are illnesses that have been picked up in a hospital or other healthcare setting. They can originate from a number of things, such as medical staff, tainted bedding, infected equipment, and air droplets (Spellberg et al ,2008). In hospitalized patients, these superbugs linked to healthcare typically result in opportunistic infections and illness outbreaks. Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), carbapenem-resistant enterococci (CRE), MDR *Pseudomonas aeruginosa*, and vancomycin-resistant enterococci (VRSA) are the main culprits. When antimicrobial resistant bacteria are not effectively treated, medical care is no longer sufficient, and the illness continues to exist in the body, raising the possibility that it may spread to other people. Worse still, growing global connectedness makes it easier for infectious pathogens and the genes that confer resistance to spread quickly over the globe (Grundmann et al.; Jevons, 1961).

National institutions heavily burden health care in rich and developing nations (Ayliffe, 1997). The global development of multidrug-resistant organisms (MDROs) makes this issue worse by making infection control more difficult, reducing the number of treatment choices available, and increasing poverty (Livermore,1995; Barriga, 2001; Chopra et al.,2001). The need for alternate methods of treating and preventing these illnesses has arisen due to the growing resistance of antibiotic-resistant bacteria, which has renewed interest in therapeutic phages for these objectives. Phages are viruses that only infect bacteria, they are utilized to treat bacterial illnesses as soon as they are identified.

3. Causes of Antibiotic Resistance

3.1. Overuse

It is evident that antibiotic usage contributes to the emergence of resistance. Genes of microorganisms can be inherited via related organisms or obtained from unrelated organisms on plasmids, which are movable genetic elements. Many studies have shown a clear correlation between antibiotic intake and the cause and transmission of resistant bacterium strains (Garcia-Bustos and Tomasz ,2020; Tomasz and Munoz ,2022). Through a process known as horizontal gene transfer, different bacterial species may be able to acquire resistant genes to antibiotics. Furthermore, resistance might develop spontaneously as a result of mutation. Antibiotics destroy drug-sensitive opponents, allowing natural selection to promote the spread of resistant microbes. Worldwide, antibiotics are routinely prescribed despite cautions against abuse (Michel and Gutmann ,2021). In a number of other countries, antibiotics are available without charge and unrestricted (Leclercq and Courvalin ,2020; Craig ,2022). Antibiotic misuse is encouraged by the easy accessibility, abundance, and low cost of these drugs as a result of the absence of control. The availability of these drugs in nations where antibiotics are restricted has also been facilitated by their online purchase (Levy, 2022).

3.2. Unsuitable Treatment

Antibacterial when incorrectly given also increases the rate of bacterial resistance (Cohen, 2019). Research has indicated (30 to 50) % Many cases include the use of agents, improper treatment reasons, or prolonged use of antibiotics (Vincent et al ,1999). Of the 17 .000 patients diagnosed with pneumonia, only 7.5% had a pathogen detected (Vandenbroucke-Grauls, 2017). Additionally, research has shown that between (30) % to (60) % of the antibiotics used in the treatment are unimportant, inappropriate, and not acting as well as they should (Gold and Moellering, 1999). Antibiotic treatment problems may arise when patients get antibiotics given incorrectly, and their therapeutic efficacy is debatable (Livermore and Yuan, 1998). By encouraging genetic abnormalities such as mutagenesis, HGT, and changes in gene expression, sub inhibitory and sub -therapeutic antibiotic doses might accelerate the emergence of antibiotic resistance (Chow et al., 1999).

3.3. Wide-ranging Use in Agriculture

Around the world, antibiotics are frequently employed as growth additives for livestock (De Cheldre et al, 2010). Animals are the primary users of an estimated (80%) of antibiotics, mainly used to encourage growth and prevent disease (Towner, 1997). Animals treated with antimicrobial treatment are believed to be healthier overall, giving better-quality products and larger yields (Struelens et al, 2020). Antibiotics used on cattle are included in the food that humans eat. The intestinal microbes of agricultural workers and agricultural livestock were found to have high rates of resistant to antibiotics (McGowan, 1983).

4. Some Genera of Multi Drug Resistant Bacteria

A list issued by the World Health Organization (WHO) indicates that a number of bacteria are increasingly resistant to antibiotics. These bacteria are divided into: *Acinetobacter baumannii and P. aeruginosa*, Enterobacteriaceae (resistant to carbapenem), and *Neisseria gonorrhoeae* (resistant to cephalosporin and fluoroquinolones), *Enterococcus faecium* (resistant to vancomycin), *Staphylococcus aureus* (resistant to methicillin and vancomycin), and *Haemophilus influenzae* (resistant to ampicillin), with many other bacteria which are highly resistant to antibiotics (Painuli et al., 2023).

4.1. Methicillin -Resistant *Staphylococcus Aureus*

Methicillin- intolerant *Staph. aureus* is a common pathogen on a healthy person's skin or nose. Although these bacteria are usually benign, they can become infected when they get into a wound. Numerous medications, including methicillin, cannot kill this bacterium (Ming-Feng, & Chung-Yu, 2019). The majority of infections caused by methicillin resistant *Staph. aureus* (MRSA) acquired from the community are skin infections. MRSA causes pneumonia, post operation infections, and potentially fatal blood-stream infections in hospitals; MRSA may enter the body and cause potentially fatal infections in the heart, lungs, joints, and bones (De Cheldre et al, 2010).

4.2. *Streptococcus Pneumoniae*

Pneumonia is one of the numerous diseases caused by the S*treptococcus pneumoniae* bacterium (Towner,1997). In addition to meningitis, an infection of the membranes around the brain and spinal cord, these bacteria can also cause sinus and ear infections. Another bloodstream infection that can be brought on by *Strep. pneumoniae* is bacteremia (Chow et al, 1999). Coughing, sneezing, and intimate touch with an infected individual can all transmit this kind of bacterium. The affected bodily portion determines the symptoms. These symptoms may include chills, insomnia, irritability, fever, coughing, shortness of breath, chest discomfort, stiff neck, light sensitivity, confusion, and disorientation. Severe infections with *Strep. pneumoniae* can result in mortality, brain damage, and hearing loss (McGowan ,1983).

4.3. Carbapenem-Resistant Enterobacteriaceae

Escherichia coli, *Salmonella*, *Shigella*, and other pathogens prevalent in the environment and digestive system are members of the Enterobacteriaceae family of bacteria. The bacteria are able to survive in the intestines without harming people. Nonetheless, certain Enterobacteriaceae strains can contaminate food or water and lead to food poisoning or gastroenteritis, which primarily manifests as diarrhea and vomiting (Read and Woods, 2014). These microorganisms can occasionally go outside the stomach and resulting in dangerous bloodstream, wound, or urinary tract infections. The majorities of these infections are related to catheter use and surgical operations and happen in hospitals and other healthcare environments. Enterobacteriaceae infections that are resistant to antibiotics can be treated with carbapenem, an antibiotic. Nevertheless, the bacteria may develop a resistance to carbapenem. Bacteria classified as carbapenem-resistant Enterobacteriaceae are those that cause this (The antimicrobial alarm, 2013).

4.4. Carbapenem Resistant *Acinetobacter Paumannii*

Gram-negative *Acinetobacter baumannii* is a rod-shaped, almost spherical, and usually short bacterium (coccobacillus). It can cause many dangerous diseases around the world. It is becoming increasingly significant as a hospital-derived (nosocomial) and can infect people with compromised immune systems. Although *A. baumannii* is almost exclusively isolated from hospital surroundings, other species can be isolated from soil (Ming-Feng, & Chung-Yu, 2019).

5. Mechanisms of Antibiotic- Resistant

There are many mechanisms that bacteria use to protect themselves from antibiotics which can be divided in to four types as shown in **Figure 1**. Antibiotic modification is the best known: the resistant bacteria retain the same sensitive target as antibiotic sensitive strain, but the antibiotic is prevented from reaching it. This happens, for example, with β lactamases-the β lactamases enzymatically claves the four membered β latam ring, rendering the antibiotic inactive. Certain bacteria resistant to antibiotics shield the target of the antibiotic's action either by blocking the antibiotic's entry into the cell or expelling it more quickly than it can enter (much like a boat's bilge pump). Porin, a hollow membrane protein filled with water, allows β- lactam antibiotics in G-ve to enter cells (Lushniak ,2014). Some β -lactamases are more specific than others; they work specifically against penicillinases like *Staphylococcus aureus* penicillinase or cephalosporinase like *Enterobacter spp*. (AmpC enzyme). Most β lactamases work in some manner against both types of antibiotics. A wide range of bacterial species, both Gram positive and negative bacteria, can produce β lactamases; which are suppressed by β lactamase inhibitors such as clavulanic acid (Gross, 2021).

Since Imipenem is unable to enter the cell, *Pseudomonas aeruginosa* that is resistant to it possesses resistance due to the absence of a particular Porin. Low levels of resistance to aminoglycosides and fluoroquinolones have also been seen to use this route. One established route for resistance to Tetracycline is increased efflux through an energy-consuming transport pump. Although, the modified enzyme still synthesizes peptidoglycan. *Strep. pyogenes* mutants that express changed and are resistant to penicillin have not been observed in patients; this may be due to the cell wall's inability to interact with the anti-phagocytic M protein. The last defense strategy bacteria use against antibiotics is the development of a new target, often an enzyme, that is resistant to the antibiotic's suppressive action while the maintaining previous, sensitive target (Piddock, 2018).

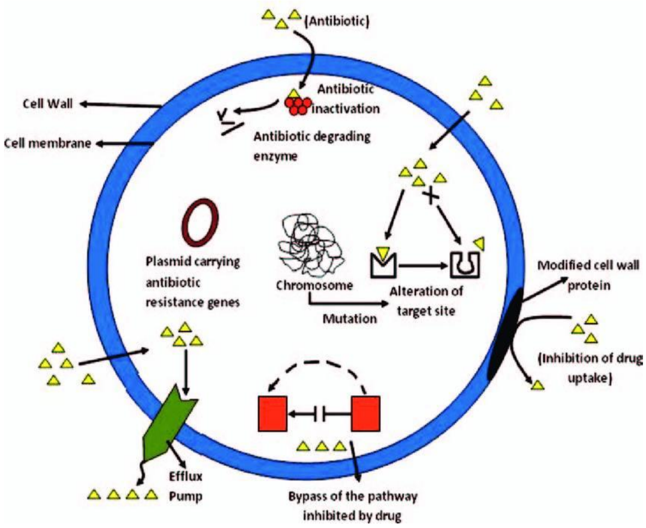

Figure 1. Mechanisms of Resistance to Antibiotics in Bacteria (Lushniak, 2014)

6. Transfer of Antibiotic Resistance

Horizontal gene transfer is an approach through which bacteria may exchange genes. Under proper conditions, this can happen via a various pathways between bacteria of the same species and between different genera. Gene transfer assists substantially in disseminating antibiotic resistance genes by creating genetic variety in bacteria. Modes of gene transmission among bacteria include: Conjugation, which is the process by which two bacteria join together and exchange DNA from one bacterial cell to the other. Transduction: is when Bacteriophage viruses infect the bacteria; occasionally, genes that these viruses acquired by infecting another bacterium are transmitted. through this process, the bacteria' DNA may have these genes (Bartlett, 2016).

Bacteria may be harmed by foreign DNA; thus mechanisms are in place to break down incoming DNA. However, these systems are not entirely effective; they are more likley to be sustained if the entering DNA is absorbed and benefits the bacteria. For instance, bacteria that acquire a resistance gene to antibiotics and are exposed to antibiotics will benefit more than their susceptible partners and may proliferate, as shown in **Figure 2** (Live et al., 2014).

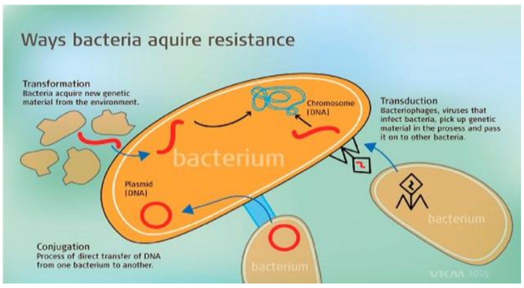

Figure 2. Main Mechanisms Used to Transfer Resistance Genes Between Bacteria (NesseAnne et al., 2014).

7. New Drugs used Against MDR

Antibiotic clinical trials are challenging due to changes in many trials to design criteria implemented by the Food and Drug Administration (FDA) over the past 20 years. Studies that compare antibiotics with placebo are deemed unethical; as a result, studies are planned to show that new treatments are not inferior to current medications, within a given statistical range (Terreni et al.,2021). A WHO reported in 2020 that just 52, novel antimicrobial agents were undergoing experimental and medical evaluation; worse yet, just 32 obtained approval to treat diseases resistant to numerous medicines (The Lancet, 2020). Certain antibiotics, such as cefiderocol, probenecid, durlobactam, murepavadin, cestobiprole, and others, are effective against organisms resistant to different medicines (Parmanik et al.,2022).

8. New Strategies Against MDR

Natural determinants of bactericidal usage may be found in our surroundings and inside our bodies because of the extraordinary number and richness of bacteriophages. These variables could be crucial in mitigating the issue of antimicrobial resistance. Phage treatment still faces obstacles, such as bacterial resistance to phages and regulatory concerns, but efforts to commercialize it as a contemporary medication are still underway (Jevons, 1961; Tomasz and Munoz, 2022). Phages have the potential to play a significant role in nosocomial infection control throughout the whole process of clinical practice, even beyond their use in therapeutic applications.

Several studies have been conducted focusing using natural products against AMR. Similar substances discovered from *Zingiber officinale* have proven antibacterial activity against eighteen resistance pathogens (Vaz et al., 2022). *Vernonia auriculifera Hiern* contains phenols and flavonoids that have demonstrated efficacy against *Enterobacter aerogenes*, *K. pneumoniae, P. aeruginosa, S. aureus, and E. coli* (Jepkoech et al., 2022). ***Salvia officinalis*** alcoholic extract have antimicrobial activity against MDR *P. aeruginosa* (Sweedan, 2021). Metal oxide nanoparticles have also demonstrated remarkable antibacterial action. The antibacterial activity of silver Nano sheet against a multidrug resistant (superbugs) (Tamkeen and Al-Bahrani, 2019). Morever the significant activity of photo thermal treatment against superbugs was reported by Roy et al. (Roy et al., 2023). Nanoparticles of Zinc oxide made from *Limonia acidissima* extract have demonstrated efficacy against *S. paratyphi*, *K. pneumonia*, *Shigella*, *Streptococus spp.*, and *staphylococcus spp.* (Singh et al., 2014). Aloe-vera extract used to produce nanoparticles of silver have demonstrated antibacterial efficacy against strains of S. *aureus*, *E. coli*, *P. aeruginosa*, and *A. baumannii* (Arshad et al., 2022). The resistant bacteria also appeared in *K. pneumoniae* isolated from water (Hasan and Aburesha, 2021).

9. Conclusion:

The area of antibiotics research is unquestionably in a hazardous predicament due to years of advancing promotion and the frightening rise in bacterial resistance caused by reckless policies and practices. However, this dilemma has been clarified, by recent initiatives by a various organizations, including scientists, physicians, and occasionally even officials. The development of new antibiotic classes and the refinement of current varieties were made available by technological developments, which are essential to counteract the primarily unregulated increase of resistant gram-negative bacterial infections.

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