ANTIBIOTIC RESISTANCE IN BACTERIA

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❖ *ABSTRACT:*

Beginning in the 1940s, the antibiotic era altered human demography and the characteristics of infectious diseases. Eliminating this primary cause of sickness in humans and animals seemed feasible, and the growing classes and numbers held great promise. Numerous studies have been conducted on bacterial antibiotic resistance, which was discovered shortly after antibiotics were introduced. The genetic foundation has been clarified and a variety of methods have been shown. It has been established that prokaryote ecosystems are resistant to antibiotic stress. To provide an overview, these topics are briefly covered throughout the study. Community behavior in many nations are described, together with the epidemiology of antibiotic resistance. Environments with excessive antibiotic usage are implicated. It has been noted that the widespread use of antibiotics in animals has implications. Decreases in the quantity of newer drugs and steadily rising antibiotic resistance seem to indicate a post-antibiotic era where treating illnesses would become more challenging. This article reviews the state of antimicrobial resistance around the world and compares it to India's experience. It describes the frequency of antibiotic resistance in India across the main pathogen groups. The factors that contribute to the high rates of antibiotic resistance that are common have been emphasized. Future studies have been suggested to guarantee the antibiotics' ongoing effectiveness in infection control.

❖ **Key Words:** Antibiotic resistance; Bacteria; Mechanism; Infections; public health

❖ INTRODUCTION:

One of the greatest medical achievements of the 20th century must undoubtedly be the discovery of antibiotics. One might have believed that the groundwork for a revolution in the treatment of bacterial diseases had been laid with the introduction of sulfonamides into medical practice in the 1930s, penicillin and streptomycin in the 1940s, broad spectrum bacteriostatic antibiotics in the 1950s, and bactericidal antibiotics in the 1960s, along with other significant synthetic chemicals and highly specific narrow spectrum antibiotics during these years.[1] However, these achievements were steadily followed by the slow formation of populations of antibiotic-resistant bacteria brought on by human use, misuse, and blatant abuse of antibiotics. As a result, drug-resistant bacteria are now a significant global public health concern. Antimicrobial resistance has emerged as a phenomenon. In the past four years, the United States Institute of Medicine has released a report on emerging illnesses caused by antibiotic resistance, and the British House of Lords has also discussed the issue.[2,3] These two WHO sessions have been spurred by the problem of antimicrobial resistance. In addition to several review articles on antimicrobial resistance, the European Union has sent three scientific sessions in the past two years.[4,5,6] This review paper aims to raise awareness of a new public health issue that, if left unchecked, might have a detrimental effect on healthcare delivery, especially in poor nations.

Resistance gene origins and molecular epidemiology

A resistant microorganism is one that is not eliminated by an antimicrobial agent during a regular course of treatment. This is because antibiotic resistance should be defined in terms of clinical outcomes rather than laboratory approaches and in the medical in vivo context.[7] Microbes are forced to adapt or perish (selective pressure) when antimicrobials are used for any infection, real or imagined, in any dosage over time.[8] The surviving microbes carry drug resistance genes that can be passed on to other strains within their own genus and species, as well as to unrelated species.[2]

Bacteria may have acquired or innate resistance. Acquired resistance happens when a bacterium that was once sensitive to antibiotics acquires resistance, whereas intrinsic resistance is a characteristic that naturally arises from the biology of the organism, such as vancomycin resistance in Escherichia coli.[7] This usually occurs as a result of DNA mutation or acquisition.[9] The most frequent way that resistance develops in bacteria, particularly in Mycobacterium tuberculosis, is mutation, which happens whether or not antibiotics are present.[10] Multi-drug resistant tuberculosis, which has now been found in more than 100 countries worldwide, is the result of resistance genes created throughout the process being reproduced and passed to in-contact individuals via plasmids and transposons.[11] Apart from mutation, bacteria have evolved a wide range of genetic and metabolic processes to guarantee the development and spread of antibiotic resistance. B-lactamases, which enzymatically split the four-membered b-lactam ring, are one example of how antibiotics can be modified so they do not react with the target site, making the antibiotic ineffective. [12] As is the situation with b-lactam antibiotics and Gram-negative bacteria, antibiotic-resistant bacteria can occasionally shield the target of antibiotic action by decreasing drug uptake and/or causing a rapid efflux of it.[10] Additionally, the antibiotic's target action may be changed, making it useless (for example, enterococci's resistance to cephalosporin's).[12] The last way that bacteria can defend themselves against the effects of antibiotics is by producing a different target, typically an enzyme, that the antibiotic cannot inhibit while the cells still generate the original sensitive target. Because the alternative enzyme avoids the antibiotic's effects, bacteria are able to persist in the face of selection. The most well-known example is the alternative penicillin building protein (PBP2a), which methicillin-resistant Staphylococcus aureus

(MRSA) produces in addition to the regular penicillin building proteins. However, a bacterium displaying multiple of these mechanisms is not unusual.[7]

Mechanism of Antibiotics on Bacteria

1. Inhibition of Cell Wall Synthesis:
   Mechanism: Peptidoglycan, a polymer made of sugars and amino acids, makes up the cell walls of bacteria. To provide the cell wall strength, enzymes such as trans peptidases (penicillin-binding proteins) cross-link the peptidoglycan strands. These enzymes are inhibited by beta-lactam antibiotics (like penicillin), which results in inadequate cell wall production and increases the cell's susceptibility to osmotic lysis.
   Examples:

- Beta-lactams: Penicillin's, Cephalosporin's, Carbapenems, Monobactams
- Glycopeptides: Vancomycin (binds D-Ala-D-Ala termini, blocking peptidoglycan synthesis)[13,14]

2. Inhibition of Protein Synthesis
   Mechanism: Bacterial ribosomes are selective targets because they are 70S (50S + 30S) in contrast to eukaryotic 80S. Antibiotics attach to either sub-unit and disrupt the initiation, elongation, and termination phases of translation.
   Examples:

- Aminoglycosides (e.g., streptomycin): Bind to 30S → misreading of mRNA
- Tetracycline's: Block tRNA binding to the 30S A-site
- Macrolides (e.g., erythromycin): Bind 50S → block translocation
- Chloramphenicol: Inhibits peptidyl transferase activity on 50S
- Linezolid: Prevents initiation complex formation on 50S[15,16]

3. Inhibition of Nucleic Acid Synthesis
   Mechanism: Inhibits enzymes essential for DNA replication or RNA transcription.
   Examples:

- Fluoroquinolones (e.g., ciprofloxacin): Inhibit DNA gyrase (topoisomerase II) and topoisomerase IV
- Rifamycins (e.g., rifampin): Bind DNA-dependent RNA polymerase → block RNA synthesis

4. Inhibition of Metabolic Pathways (Folate Synthesis)
   Mechanism: Folic acid, which is necessary for the production of nucleic acids, is produced by bacteria. Folate is a selective bacterial target because humans obtain it through their food.
   Examples:

- Sulphonamides: Compete with PABA, inhibit dihydropteroate synthase
- Trimethoprim: Inhibits dihydrofolate reductase. Used together as co-trimoxazole for a synergistic effect.[17,18,19]

5. Disruption of Cell Membrane Integrity
   Mechanism: These antibiotics bind to bacterial membranes and disrupt membrane potential or structure, leading to leakage of ions and death.
   Examples:

- Polymyxins: Bind LPS and phospholipids in Gram-negative membranes
- Daptomycin: Inserts into Gram-positive membranes → causes depolarization[20,21]

The four principal forms of antibiotic resistance evolve as:

1. Natural resistance (Intrinsic, Structural):
   This kind of resistance is brought on by the structural characteristics of the bacteria rather than the use of antibiotics [22]. This happens because of intrinsic resistance, microorganisms that don't adhere to the target antibiotic's structure, or antibiotics that don't interact with their target because of their properties [23]. Gram-negative bacteria are inherently resistant to vancomycin because, for instance, vancomycin antibiotics do not pass past the outer membrane of these bacteria [24]. Similarly, L-form bacteria, which are bacteria without cell walls, such Mycoplasma and Urea plasma, inherently possess resistance to beta-lactam antibiotics [25].
2. Acquired resistance:
   It is acquired because it is not impacted by the antibiotics to which it was previously sensitive, regardless of the development of resistance brought on by changes in the genetic characteristics of bacteria [26]. The primary chromosome or other chromosome structures (plasmids, transposons, etc.) are the source of this type of resistance [27]. Mutations that alter the bacterial chromosome at random are the cause of chromosomal resistance; these mutations can be brought on by specific physical and chemical conditions [28]. This could result from modifications to the medication's target within the cell or from alterations in the makeup of the bacterial cells, which could lead to lower bacterial drug permeability [29]. Resistance to these forms can arise in streptomycin, aminoglycosides, erythromycin, and lincomycin [30].
   Extrachromosomal resistance is achieved through the transmission of genetic components such as plasmids, transposons, and integrons [31]. Plasmids are DNA fragments that can replicate independently from chromosomal DNA [32]. Plasmids are often responsible for the creation of antibiotic-inactive enzymes [33]. Bacterial cells can maintain genetic material (resistance genes and plasmids) through many methods, including transduction, transformation, conjugation, and transposition [34]. Antibiotic-resistant genes on chromosomes or plasmids are linked to several integration groups, or integrons. Recombination is relatively common in integrons [35].
3. Cross-resistance:
   It refers to the resistance of particular germs to a particular antibiotic that function through similar or comparable mechanisms and are also resistant to other drugs [36]. This typically occurs when antibiotics share structural characteristics, such as resistance to

cephalosporin’s, penicillin’s, erythromycin, neomycin, and kanamycin [37]. But occasionally, cross-resistance can also be observed in a totally other class of medications, such as the cross-resistance between erythromycin and lincomycin, which may or may not have a chromosomal origin [38].

4. Multi-drug and other types of resistance:

   In order to guarantee that the bacteria cannot be eradicated or controlled by a single medication, multidrug-resistant species are usually pathogens that have developed resistance to their medications [39]. Multidrug-resistant pathogenic microorganisms were introduced as a result of improper antibiotic use for treatment [40]. Bacteria can develop multidrug resistance by either of the two processes [41]. First, these bacteria will develop a number of genes that code for distinct drug resistance; these resistances typically occur on R-plasmids [42]. Second, alterations in target structure, enzymatic inactivation of antibiotics, increased gene expression encoding efflux pumps, and other factors can also result in multidrug resistance [43].Multidrug-resistant (MDR) bacteria are those that are resistant to three or more different types of antibiotics. Pan-drug resistant organisms are those that are resistant to all useable drugs, or to all but one or two classes of antibiotics, and are considered highly resistant to medications [44,45]. For instance, bacteria that are resistant to at least three kinds of antibiotics, such as all cephalosporin’s, aminoglycosides, quinolones, and penicillin’s, are known as Acinetobacter species with multidrug resistance (MDR) [46]. Numerous Acinetobacter species that are drug-resistant (XDR), isolate resistant to the three classes of antibiotics listed above (MDR), and even carbapenem-resistant Acinetobacter species that are pan-, drug-, or polymyxin-resistant (PDR) may be XDR in addition to being tigecycline- and polymyxin-resistant [47,48].

Mechanisms of Antibiotics Resistance

1. The modifications:

   The target regions of the relationship with the antibiotics and the changes that occur in the drug-related receptor are different; these may include complicated enzymes and ribosomes [49]. Macrolide antibiotics have the most commonly seen resistance that is associated with changes in the ribosomal target [50]. The most well-known examples of this are the development of penicillin resistance in strains of Staphylococcus aureus, Streptococcus pneumonia, Neisseria meningitides, and Enterococcus fecium as a result of changes in the beta-lactamase enzymes of penicillin-binding proteins [51].
2. Enzymatic inactivation of antibiotics:

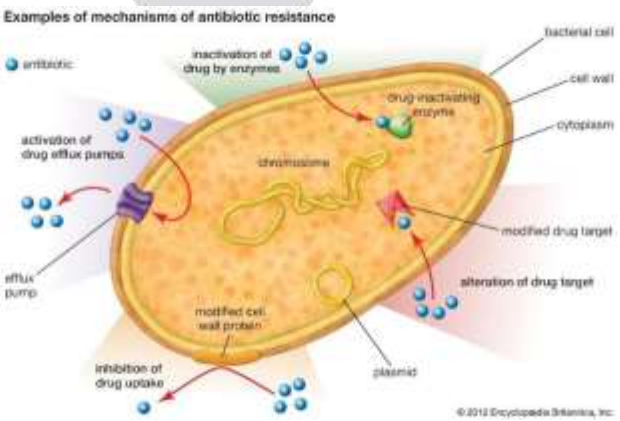
   The majority of bacteria produce enzymes that break down antibiotics, and one of the most significant routes of antibiotic resistance is enzymatic inactivation [52]. The most well-known examples in this category include erythromycin-modifying enzymes, beta-lactamases, amino glycosidase, and chloramphenicol [53].
3. Reduction of the inner and outer membrane Permeability:

   Reduced drug uptake into the cell or quick ejection from the pump systems are the outcomes of this mechanism, which is caused by changes in the permeability of the internal and exterior membranes [54]. Porin mutations in proteins of resistant strains can result in a decrease in membrane permeability; for instance, a mutation in a particular porin known as OprD might make a strain of Pseudomonas aeruginosa resistant to carbapenem [55]. A decrease in outer membrane permeability may be a significant factor in resistance to aminoglycosides and quinolones [56].
4. Active Pumps System:

   The active pump systems of the tetracycline class of antibiotics are where resistance most frequently arises [57]. Tetracycline’s are expelled and unable to concentrate inside the cell when using an energy-dependent active pumping system [58]. This mechanism Osmolar control of resistance to is in plasmid and chromo. For instance, active pumping systems work well against beta-lactam antibiotics, quinolones, 14-membered macrolides, and chloramphenicol [59].
5. Using an alternative metabolic pathway:

   The most recent drug-susceptible pathway does not require objective development, in contrast to several of the target modifications in bacteria [60]. Instead of manufacturing folic acid, bacteria can produce it from the environment, making it resistant to trimethrim and sulphonamide [61].

Fig. 1: Mechanism of Antibiotic Resistance



Common Antibiotics Resistant Pathogens (ESKAPE Pathogen)

Pathogens	***Resistance Traits***
Enterococcus faecium	Vancomycin-resistant enterococci (VRE)
Staphylococcus aureus	Methicillin-resistant (MRSA)
Klebsiella pneumoniae	ESBL, Carbapenem-resistant (KPC)
Acinetobacter baumannii	MDR, XDR strains
Pseudomonas aeruginosa	Efflux pumps, porin mutations
Enterobacter spp.	AmpC beta-lactamase production

Table no.1 : ESKAPE Pathogen

Mechanisms of Transfer of Resistance Based on Examples of Various Species Of Bacteria

1. Campylobacter spp.

   One of the most frequent causes of food-borne gastroenteritis in humans is known to be Campylobacter, particularly C. jejuni [62,63]. It has been demonstrated that poultry is the primary source of these bacteria, and handling contaminated food—particularly chicken meat—is the primary way that Campylobacter is spread to humans [64]. However, human C. jejuni and, to a lesser extent, C. coli infections are also caused by ruminants, particularly cattle and pigs [65,66]. Most instances of campylobacteriosis resolve on their own and don't need to be treated with antibiotics. Nonetheless, medical interventions are required for pregnant women, very young or elderly individuals, and when complications like Guillain-Barre syndrome arise [67].In these situations, fluoroquinolones (like ciprofloxacin) or tetracycline's are other alternatives, whereas macrolides (like erythromycin) are typically the first-choice antibiotics [68].

- Resistance to Fluoroquinolones : AMR of Campylobacter has only surfaced, particularly to fluoroquinolones (e.g., ciprofloxacin) [69]. Furthermore, co-resistance to macrolides (like erythromycin) and fluoroquinolones, which are additional preferred antimicrobials for treating Campylobacter infections, has been observed recently [70]. Additionally, some research has demonstrated that infections with Campylobacter that are resistant to erythromycin or quinolones result in more severe and prolonged sickness, as well as a higher chance of developing an invasive form of the illness or even dying [71]. Campylobacter has been found to exhibit a number of molecular pathways of resistance to antibiotics [72,73,74]. One entails genetic alterations that result in the development of complete or at least partial resistance to different antimicrobials [75]. By horizontally transferring genes from other bacteria of the same or different species, Campylobacter can acquire sequences that encode antibiotic resistance. Additionally, spontaneous gene changes that produce genetic markers for chromosomally encoded resistance to fluoroquinolones or macrolides can also result in antimicrobial resistance [76]. The quinolone resistance-determining region (QRDR) of DNA gyrase (topoisomerase II), which is encoded by the gyrA and gyrB genes and is in charge of the synthesis of two subunits of the enzyme (subunits A and B, respectively), is primarily where mutations that cause Campylobacter resistance to fluoroquinolones are found [77].Fluoroquinolone resistance in C. jejuni has been associated with point mutations in the gyrA sequence at positions Thr-86, Asp-90, and Ala-70 [78]. While the Thr-86-Lys and Asp-90-Asn mutations are less frequent and linked to intermediate fluoroquinolone resistance, the Thr-86-Ile mutation in the gyrA gene is the most frequently observed mutation that causes high-level resistance in fluoroquinolone-resistant Campylobacter [33]. There have also been reports of double point mutations of the gyrA gene in conjunction with Asp-85-Tyr, Asp-90-Asn, or Pro-104-Ser [79].The synergistic effect of the gyrA mutation and the CmeABC multidrug efflux pump, which is encoded by an operon made up of three genes (cmeA, cmeB, and cmeC) that express an outer membrane protein, an inner membrane drug transporter, and a periplasmic fusion protein, respectively, may also be the cause of Campylobacter's high level of fluoroquinolone resistance [80]. Highly conserved in nature, the CmeR repressor controls the CmeABC efflux pump. The intracellular concentration of antibiotic decreased in an insertional cmeR Campylobacter mutant strain due to overexpression of CmeABC pump components. Moreover, even in the presence of gyrA gene alterations, the minimum inhibitory concentration (MIC) values for fluoroquinolones (such as ciprofloxacin) were lowered to the level found in susceptible strains when this efflux pump was blocked. The cmeABC genes are widely distributed in human and poultry C. jejuni, and they may be horizontally transferred across strains of various origins, according to recent research by Yao et al. employing whole genome sequencing [81].
- Resistance to Macrolides: In contrast to fluoroquinolone resistance, Campylobacter mutations of the genes causing macrolide resistance are far less frequent. Furthermore, it may take several mutation steps for high-level resistance to emerge. As a result, macrolide-resistant Campylobacter mutants typically develop more slowly when subjected to selective antibiotic pressure as opposed to fluoroquinolones, necessitating extended exposure to macrolide antimicrobial agents [82]. A mutation of 23S rRNA at positions 2074 (A2074C, A2074G, or A2074T), 2075 (A2075G or A2075C), or both of the adenine residues in all three copies of this gene (rrnB operon) typically modifies the ribosome target binding site, resulting in Campylobacter resistance to this class of antibiotics [83]. However, a change at A2075G in 23S rRNA's domain V is mostly linked to high-level macrolide resistance. Cross-resistance to other macrolides and related medications of the lincosamide and streptogramin families has also been demonstrated to correlate with such erythromycin resistance mechanisms. Changes in the ribosomal subunit proteins L4 and L22 of the 50S ribosome, which are encoded by the rplD and rplV genes, respectively, may also contribute to the resistance of Campylobacter isolates to macrolides. At position 74 of the L4 protein sequence, glycine is substituted with asparagine due to the G-to-A transition at nucleotide 221 of the rplD gene [84]. Duplication at locations 292 and 256 in the rplV gene is the primary

source of macrolide resistance in the instance of the L22 protein [85]. Furthermore, Campylobacter's resistance to macrolides has been connected to the presence of the newly discovered ermB gene.

2. Enterococcus spp

The normal gut microbiota of both humans and animals includes bacteria belonging to the genus Enterococcus. Enterococcus species are the second most prevalent cause of infection in humans and are typically linked to intra-abdominal infections (IAI). Humans with endocarditis, bloodstream infections, wound and surgical site infections, as well as intra-abdominal and urinary tract infections, have been found to harbour Enterococcus bacteria [86]. Prolonged endodontic infections and chronic periodontitis have also been linked to this bacteria [87]. One antibiotic that targets enterococci is usually used to treat simple wound infections, urinary tract infections, and the majority of intra-abdominal infections. Because Enterococcus species infections are difficult to treat, they pose a major risk to both human and animal health. These bacteria are frequently resistant to numerous antimicrobials because they are very capable of transmitting genes that confer resistance to antibiotics [88]. Combination therapy using a cell wall-activating agent (such as ampicillin or penicillin) and a synergistic aminoglycoside (such as high doses of gentamicin) is used in clinical practice to treat severe enterococci infections in patients who are critically ill, show signs of sepsis, have endocarditis, meningitis, or osteoarthritis. Vancomycin is the medication of "last resort" when resistance develops to one of these antibiotic classes. Linezolid, diptomycin, quinupristin/dalphopristin, and tigecycline are used to treat infections caused by vancomycin-resistant Enterococcus strains [89].Monotherapy with antibiotics chosen depending on the area of the illness, the species of the afflicted animals, and the findings of drug susceptibility testing is the primary therapeutic management of Enterococcus spp. Infections in veterinary medicine [90]. This has to do with the restricted use of antibiotics in animals, particularly those used for human consumption [91]. Despite the lack of randomized, controlled trials assessing its effectiveness, this medication seems to be working.

- Resistance to β-Lactam Antibiotics: Because enterococci have a low affinity for penicillin-binding proteins (PBP5 in E. faecium and PBP4 in E. faecal is), they are naturally resistant to β-lactam antibiotics [92]. The resistance varies according to the kind of β-lactams; for example, cephalosporin's have the lowest activity, carbapenems have a slightly lower activity, and penicillin has the maximum action against enterococci. When bacteria develop a particularly high level of resistance to β-lactam antibiotics compared to wild strains, another resistance mechanism linked to penicillin-binding proteins is occasionally seen. PBP5 surface protein overproduction is linked to resistance to β-lactam antibiotics in certain bacteria. One example is the overproduction of PBP5 by certain strains of E. hirae that are resistant to penicillin. Within E. hirae, the psr gene regulates the pbp5 gene[93]. When psr is rendered inactive by deletion or mutation, more copies of PBP5 are produced, which eventually causes all of the protein's molecules to be saturated. The creation of β-lactamases, which are enzymes that hydrolyse the β-lactam ring in antibiotic molecules, is a completely separate and less prevalent mechanism of resistance to β-lactams that some enterococci possess. The antibiotic that has been hydrolysed is inactive and does not prevent surface PBPs from performing their enzymatic activity. The β-lactamase expression gene is found on a plasmid and typically coexists with a gentamicin resistance gene. Small levels of B-lactamases are typically generated. Therefore, the MIC values for ampicillin and penicillin may be at a level that corresponds to bacteria that are susceptible to these antibiotics when the number of bacteria is low [94].
- Resistance to Inhibitors of the Third Step of Peptidoglycan Synthesis—Glycopeptides: The weakening of the connections between antibiotic molecules and cell wall receptors is the primary mechanism that gives bacteria resistance to glycopeptides. Outside of their cell membrane, enterococci that are susceptible or resistant to vancomycin have particular complexes made up of pentapeptides and peptidoglycans. Glycopeptide antibiotics bind to these target structures. The pentapeptides listed above are made up of tripeptide precursors that dipeptides bind to. Vancomycin-resistant enterococci (VRE) substitute D-serine or D-lactate for the terminal amino acid D-alanine, whereas strains susceptible to vancomycin have D-alanyl-D-alanine (D-Ala-D-Ala).The antibiotic is considerably weakened by the conformational changes brought about by the replacement of D-alanine for D-serine. There are less linkages with vancomycin if D-lactate is added in place of D-alanine. D-Ala-D-Ser dipeptide-containing strains exhibit resistance to low vancomycin doses and susceptibility to teicoplanin. Nevertheless, peptidoglycan precursors that contain D-Ala-D-Lac dipeptides exhibit a significant level of vancomycin resistance [95]. These structures participate in the creation of cell walls. Vancomycin stops cell wall formation by attaching to the pentapeptide molecule and blocking it. In the second scenario, cell wall production may occur even while vancomycin is present because the antibiotic's binding to the peptidoglycan precursor is restricted.

3. Escherichia coli

A common component of both humans' and animals' natural gut microbiota is Escherichia coli, or E. coli. In addition to commensals that frequently inhabit the intestines of birds and mammals, the E. coli species also includes strains that are extra intestinally pathogenic (ExPEC) and intestinally pathogenic (IPEC). Gastrointestinal tract infections are linked to IPEC bacteria. Enteropathogenic E. Coli (EPEC), enterotoxigenic E. Coli (ETEC), enterohaemorrhagic E. Coli (EHEC), enteroinvasive E. Coli (EIEC), enteroaggregative E. Coli (EAEC), adherent invasive E. Coli (AIEC), and diffusely adherent E. Coli (DAEC) are some of the pathotypes that can be identified among IPEC strains [96].ExPEC strains that cause infections in extraintestinal anatomic sites include: uropathogenic E. coli (UPEC), which causes urinary tract infections in humans and animals; neonatal meningitis-associated E. coli (NMEC); septicaemic E. coli (SePEC), which causes systemic infections in humans and animals; avian pathogenic E. coli (APEC), which causes avian colibacillosis; and endometrial pathogenic E. coli (EnPEC), a potentially emerging ExPEC lineage [97,98].

- Resistance to β-Lactams: Bacteria can produce β-lactamases constitutively or by induction. Constitutive enzymes are continuously produced by cells and are a fixed characteristic of the bacterial strain or species, independent of the presence of antibiotics in the environment. Natural resistance to an antibiotic that it has affinity for can be caused by constitutive β-lactamase, if it is produced in sufficient quantities. Bacteria must be activated by β-lactam antibiotics found in the environment in order to produce induced β-lactamases. Temporary resistance is determined by the synthesis of these enzymes, which continues until the activator is eliminated from the environment. Permanent resistance to the antibiotic can result from mutations that happen during induction, causing the bacteria to continue producing the induced β-lactamase even after the inductor is removed [99]. The primary cause of E. coli resistance to β-lactams is the generation of extended spectrum β-lactamases (ESBL), which hydrolyse penicillin's, cephalosporin's (apart from cephamycin), and monobactams but cannot hydrolyse carbapenems. B-lactamase inhibitors, such as clavulanic acid, sulbactam, and tazobactam, inhibit the activity of these enzymes [100]. The presence of B-lactamases in the periplasmic space, which are typically encoded by large plasmids (such as IncF, IncI1, IncN, IncHI1, and IncHI2 [101], allows for their unchecked and quick proliferation.

- Resistance to Tetracycline's: Efflux pumps, which are responsible for pumping the antibiotic out of the cytoplasm, are most frequently involved in the mechanism of tetracycline resistance. The genes tet(A), tet(B), tet(C), tet(D), tet(E), tet(G), tet(J), tet(L), and tet(Y) encode efflux systems that determine resistance to tetracycline's in E. coli. Proteins that serve to shield the ribosome are another way that organisms fight tetracycline's. They restrict the binding of tetracycline's to the ribosome by attaching to it. This category of proteins in E. coli is encoded by the tet(M) and tet(W) genes. Furthermore, E. coli has been found to have the tet(X) gene, which codes for oxidoreductase, which inactivates first- and second-generation tetracycline's [102].Tet(A), Tet(B), and indirectly Tet(C) are the most often identified genes encoding efflux systems [103,104]. It should be mentioned that tet genes have not always been found in bacteria that have undergone testing for their presence. For instance, Jahantigh et al. [105] verified the existence of isolates carrying two or three tet genes concurrently (43.3% and 13.3%, respectively), in addition to strains containing a single tet gene, primarily tet(A), as well as tet(B), tet(C), and tet(D).

4. Staphylococcus spp

The most prevalent bacteria in humans and animals that cause clinical infections of the skin and mucosae, including pyoderma, otitis, soft tissue infections, and surgical wound infections, including Staphylococcus aureus cased bacteraemia (SAB), are Staphylococcus species. The fact that Staphylococcus bacteria are resistant to several antimicrobial treatments contributes to their increased significance in the pathophysiology of mammals and birds [106]. Although staphylococci are susceptible to penicillin's, semi-synthetic penicillin's like oxacillin, nafcillin, and cloxacillin are employed in treatment since strains of the bacteria have become resistant to natural penicillin's. Specifically used to combat infections produced by methicillin-resistant Staphylococcus species, vancomycin is the second important antibiotic. The so-called alternative to vancomycin, however, exhibits good activity against resistant staphylococci, such as trimethoprim-sulfamethoxazole, ceftaroline, daptomycin, fosfomycin, linezolid, oritavancin/dalbavancin, telavancin, or omadacycline, given the possible risk of vancomycin resistance occurrence (there are already vancomycin-resistant strains of Staphylococcus species worldwide, including in Poland) [107,108]. Despite the hazards associated with vancomycin therapy, particularly renal impairment, it remains the gold standard for treating resistant staphylococcal infections and is also referred to as the last-resort antibiotic. Treatment for Staphylococcus species infections in animals, particularly livestock, is correlated with the type of illness. For instance, cephapirin, pirlimycin, and ceftiofur are the most often used medications in North America for the treatment of bovine mastitis in dairy cows [109]. In nations that are members of the European Union, pigs and poultry are more likely than cattle and sheep to be treated with antibiotics. Tetracycline's and penicillin's are the most often prescribed antimicrobial medicines for livestock skin diseases. However, fluoroquinolones, aminoglycosides, and macrolides are also used by veterinarians. B-lactam antibiotics, particularly penicillin's, are most frequently used for therapeutic reasons to treat bovine mastitis, calves' pneumonia, cows' metritis, and pigs' erysipelas [110,111].

- Resistance to Tetracycline's: One of the staphylococci's resistance mechanisms to tetracycline's is a reduction in their intracellular concentration brought on by a particular removal mechanism (efflux), which is linked to the existence of the genes tetK and tetL, which encode membrane transporters [112]. Small plasmids encode inducible resistance to tetracycline's, while chromosomal determinants tet(M) and tet(O) encode constitutive resistance, which is solely linked to active ribosome protection against tetracycline binding and is not connected to an efflux pump [113]. Another mechanism of resistance to fluoroquinolones and the trimethoprim/sulfamethoxazole combination is the active removal of the antibiotic from the cell.
- Resistance to β-Lactams: The primary mechanisms of resistance to β-lactam antibiotics include the production of penicillin-binding protein PBP2a, also known as PBP20, which has a low affinity for β-lactam antibiotics and causes resistance to all β-lactam antibiotics currently used in treatment, as well as the ability to produce β-lactamase, which results in resistance to natural penicillin's, amino-, and ureidopenicillins [114]. Methicillin-resistant Staphylococcus aureus strains acquired in hospitals caused the first epidemics in the late 1970s and early 1980s. In order to stop β-lactam antibiotics from attaching to the site of action, these bacteria develop a modified penicillin-binding protein (PBP2a), which renders drugs with a β-lactam ring useless. The chromosome's mecA or mecC gene, which is a component of the staphylococcal cassette chromosome mec (SCCmec) area, determines resistance to β-lactam drugs. The production of a modified protein that prevents binding by penicillin's, cephalosporin's (except from the most recent generation, ceftaroline), carbapenems, or monobactams is the responsibility of both mecA and mecC. In several European nations, bacteria isolated from humans and agricultural animals, as well as from pets and wild animals, have been shown to contain mecC, a novel homologue of mecA (mecALGA251). It has been established that the primary source of mecC strains Is cattle populations [114]. Remarkably, there have been very few reports of the MECC gene in avian species. Methicillin-resistant coagulase-negative staphylococci (MRCNS) are thought to account for 80–90% of isolates linked to hospital-acquired infections in humans. It has been suggested that S. epidermidis could serve as a gene bank for S. aureus, a more dangerous species. Furthermore, findings from other authors show that MRCNS are isolated from food more frequently than S. aureus that is resistant to methicillin [115].

Factors Contributing to Antibiotic Resistance in Bacteria

When bacteria develop defences against the effects of drugs, antibiotic resistance results. Numerous biological, environmental, and human variables accelerate this. The main contributing elements are listed below, along with a detailed explanation of each.

1. Overuse and Misuse of Antibiotics in Humans: Antibiotics are frequently overprescribed for viral diseases, such as the flu or the common cold. Some bacteria can survive and become resistant because to incomplete courses or improper dosing. In certain nations, self-medication and unprescription access to antibiotics exacerbate this issue.
   Impact: Selective pressure allows resistant strains to multiply and spread.[116]
2. Use of Antibiotics in Livestock and Agriculture: In healthy animals, antibiotics are used to prevent disease and promote growth in addition to treating infections. Large bacterial populations are exposed to sub therapeutic antibiotic dosages as a result, which encourages resistance.
   Impact: Resistant bacteria can spread to humans through the food chain, water, and direct contact.[117]
3. Poor Infection Prevention and Control in Healthcare Settings: In hospitals, resistant bacteria proliferate as a result of poor hand hygiene, sterilization, and isolation of diseased patients. The situation is made worse by overcrowded facilities and the reuse of equipment.
   Impact: Nosocomial (hospital-acquired) infections with multidrug-resistant organisms (e.g., MRSA, VRE) are increasing.[118]
4. Inadequate Sanitation and Hygiene in Communities: The spread of resistant bacteria in the environment is facilitated by inadequate waste management and water quality. Natural water supplies are contaminated by antibiotics and resistance genes found in human and animal waste.
   Impact: Environmental reservoirs act as breeding grounds for resistance genes (resistome).[119]
5. Lack of New Antibiotics and Limited Innovation: Because antibiotics are less profitable than medications for chronic illnesses, pharmaceutical companies invest less in them. There aren't many new antibiotics being developed, and resistance to more recent drugs appears fast.
   Impact: Treatment options for multidrug-resistant (MDR) infections are diminishing.[120]
6. Global Travel and Trade: Traveling abroad allows resistant strains to proliferate quickly across national boundaries. International transmission is facilitated by the international trade in food and livestock goods.
   Impact: Resistance genes and organisms spread from endemic to non-endemic regions.[121]
7. Environmental Contamination with Antibiotics and Resistant Genes: Antibiotic residues are released into adjacent water bodies by pharmaceutical production facilities. Environmental bacteria develop resistance as a result of this.
   Impact: Antibiotic resistance genes can transfer from environmental bacteria to human pathogens via horizontal gene transfer.[122]
8. Horizontal Gene Transfer (HGT): Through conjugation, transduction, or transformation, bacteria exchange resistance genes. Resistance genes are transferable between animals and settings.
   Impact: Once a resistance gene evolves, it can rapidly disseminate across microbial populations.[123]

Fig. 2: Factors Responsible

Detection of Antibiotic Resistance in Bacteria

Detecting antibiotic resistance is crucial for appropriate treatment and surveillance of resistant pathogens. Detection methods are broadly classified into phenotypic, genotypic, and automated/molecular techniques

1. **Phenotypic Methods:** These detect actual resistance traits expressed by bacteria, usually by testing their growth in the presence of antibiotics.

a. Disk Diffusion Method (Kirby-Bauer Test):
   Principle: Measures the zone of inhibition around antibiotic-impregnated disks placed on agar inoculated with the test bacteria.
   Interpretation: Zone diameters are compared with CLSI or EUCAST standards to categorize as susceptible, intermediate, or resistant.
   Advantages: Inexpensive, easy to perform, Widely used in routine labs
   Limitations: Not suitable for slow-growing or anaerobic bacteria, Semi-quantitative [124]

b. Broth Dilution Method (MIC Determination)
   Principle: Serial dilutions of antibiotics in broth to find the Minimum Inhibitory Concentration (MIC) that prevents visible growth. Can be micro dilution (in 96-well plates) or macro dilution (in tubes).
   Advantages: Quantitative, Accurate MIC values guide therapy
   Limitations: Labor-intensive, Requires standardized inoculum

c. E-test (Epsilometer Test)

Principle: Uses a strip with a gradient of antibiotic concentration. MIC is read where bacterial growth intersects the strip.
Advantages: Combines ease of disk diffusion with MIC determination
Limitations: Expensive compared to disk diffusion

d. Modified Hodge Test / Carba NP Test
Used for detection of carbapenemase-producing organisms (e.g., KPC, NDM). Carba NP test detects enzyme hydrolysis of carbapenem using colour change.

2. **Genotypic Methods:** These detect specific resistance genes or mutations associated with antibiotic resistance.

a. Polymerase Chain Reaction (PCR): Detects known resistance genes (e.g., mecA, blaKPC, vanA). Real-time PCR (qPCR) allows quantification.
Advantages: Rapid and specific, Detects resistance even before expression
Limitations: Only detects known genes, Cannot measure actual expression levels or phenotypic resistance [125]

b. DNA Microarrays: Detect multiple resistance genes simultaneously using hybridization. Useful in surveillance and epidemiology.
Limitations: High cost, Requires advanced lab facilities

c. Whole Genome Sequencing (WGS): Provides complete data on all resistance genes, plasmids, and mutations. Useful for outbreak investigations, tracking resistance evolution.[126]

3. **Automated Systems:** These integrate identification and resistance testing using computerized platforms.
Examples: VITEK 2 (bioMérieux), Phoenix (BD), MicroScan (Beckman Coulter)
Features: Rapid results (within hours), MIC and susceptibility profiles, Linked to lab information systems

4. **Advanced Molecular Techniques**

a. Loop-Mediated Isothermal Amplification (LAMP): Detects specific resistance genes using isothermal DNA amplification. Faster and simpler than PCR.

b. CRISPR-based Detection: Uses Cas enzymes to identify resistance sequences. Still in research stage but shows promise for rapid diagnostics.

5. **Phenotypic Confirmatory Tests for Specific Resistance Types**

Resistance Types	***Confirmatory Tests***
ESBL (e.g., in E. coli)	Double-disk synergy test
Carbapenemase (e.g., K. pneumoniae)	Carba NP, mCIM
MRSA	Cefoxitin disk, mecA PCR
VRE	Vancomycin screen agar, vanA/vanB PCR

Table no.2 : Confirmatory Tests

Antibacterial resistance worldwide

Antimicrobial resistance is a worldwide issue that varies geographically. In both industrialized and developing nations, acquired bacterial resistance is prevalent in isolates from patients with community-acquired infections and from seemingly healthy yet carrier persons, especially in areas where the high prevalence of infectious diseases drives the need for antibiotics. A number of infections are becoming more resistant, especially to first-line, low-cost broad-spectrum antibiotics,[127,128] and the emergence and spread of resistant strains have happened rather quickly after the introduction of new medications, such as fluoroquinolones. Outbreaks can lead to significant fatality rates as resistance grows. For instance, acute respiratory tract infections kill 3.5 million children annually, and the most common pathogens linked to pneumonia, especially in preschool-aged children,[129,130] are Haemophilus influenzae and Streptococcus pneumoniae. Since its initial discovery in Australia and Papua New Guinea in the 1960s, penicillin-resistant pneumococci have spread throughout the world. In a study on pneumococci carriage in Malawian children, it was discovered that 22% and 23% of the isolates of clinical and carriage pneumococci were penicillin resistant.[131,132] In the undeveloped world, where an estimated 16 million cases of typhoid occur year and 700,000 people die,[133] the disease is also prevalent. Unfortunately, Salmonella typhi, which is resistant to many drugs, first appeared in 1987 and has since expanded throughout sub-Saharan Africa, south-east Asia, and the Indian subcontinent. Additionally, in vitro resistance to the commonly available antibiotics was 76% and 79% (ampicillin), 72% (co-trimoxazole), 71% (trimethoprim-sul-famethoxazole), and 55% (gentamicin) in two different studies on non-typhoidal salmonellae (NTS) bacteraemia in Malawian children. Additionally, an increasing resistance (20%) to chloramphenicol was noted.[134,135,136]

The evolution of antibiotic resistance has not spared isolates from burn patients; in fact, immunocompromised burn patients who receive several medicines are effectively breeding grounds for antibiotic-resistant bacteria that can appear quickly. For instance, even after just one session of treatment, sensitive Enterobacter is known to develop resistance to third-generation cephalosporin's. 20% of all bacterial isolates in a recent investigation on the bacteriology of burns at the QECH, Blantyre's Burns Unit showed general broad-spectrum resistance (≤100%) to panels of antibiotics utilized.[137,138,139] The rise of multidrug-resistant tuberculosis, which is spreading quickly and has the potential to go out of control, is even more concerning. As a catalyst, the HIV/AIDS pandemic has exacerbated the effects of tuberculosis and may have contributed to a progressive rise of antituberculosis drug resistance.

In Russia, Estonia and other hotspots, which are spread over more than 100 countries worldwide, multidrug-resistant tuberculosis (MDR-TB) is at an all-time high. MDR-TB has extended to Western Europe and North America, not the peri-urban slums of the third world, according to a study commissioned by the philanthropist George Soros Open Society Institute. Traditionally, TB and MDR-TB have been seen as a plague of the poor. In the new millennium, MDR-TB is the biggest threat to public health unless it is controlled.[140]

There are four approaches to accomplish these goals.

1. A reduction in the forces of selection The biggest selected pressure is seen in two fields: agriculture and medicine. It is clear that in order to prevent the development and spread of resistant bacteria, selective pressures that favour and sustain the existence of

resistant mutants over sensitive strains must be reduced.[138] While auditing antibiotic use, limiting antibiotic choice, developing prescription guidelines, and emphasizing ongoing medical and public education can help reduce the misuse of antibiotics by patients, health care professionals, and unskilled practitioners, a concerted international effort is needed to reduce the use of antibiotics outside of human medicine and simultaneously improve the rational use of antibiotics in medicine. A restriction on the selling of pharmaceuticals over-the-counter is likewise desirable, but in developing nations, where medical facilities are woefully inadequate, this may be challenging to implement.[141,142]

2. Implementing effective infection control In order for an antibiotic-resistant infection to propagate, it must be carried, communicated, or otherwise transferred to other patients once it has infected one. Additional patients in order for the infection to proliferate. The vector that promotes the spread is frequently an untrained or negligent healthcare professional. Therefore, the prevention of multi-drug resistant infections requires hand washing, basic control, disinfection of ambient surfaces, and, where necessary, patient isolation or quarantining.[138]
3. A rise in research endeavours The world is not keeping up with bacteria's capacity to adapt to and resist antibacterial, despite recent developments in microbiology, biochemistry, and drug discovery and development. Since the 1960s, no new classes of antibiotics have been developed, which is thought to be contributing to the increase in bacterial resistance.. For instance, the development of antibiotics has accelerated since the 1940s, but no novel clinically beneficial structures were found after 1961, and practically all medications introduced since the 1960s are modifications of pre-existing antibiotics that bacteria have "evolved" to resist. As a result, bacteria that had "learned" to withstand one member of a class of chemical drugs needed no additional education to overcome subsequent alterations. In order to relieve pressure on the current ones and, in the process, lessen antibiotic resistance in bacteria, it is necessary to step up research efforts in the field of antibacterial.[143]
4. Monitoring for antibiotic resistance: Any successful antimicrobial strategy must be supported by an effective surveillance system that can identify, track, and document the establishment of any antibiotic resistance locally, nationally, and internationally. Following the establishment of the link between use and resistance, surveillance data can be used as "information for action" to support initiatives aimed at reducing unnecessary prescriptions and extending the useful life of currently available antibiotics. To ascertain the degree to which varying national prescribing practices correspond to varying resistance rates, international collaboration on resistance surveillance is therefore crucial. In order to address the problem, the World Health Organization is already setting up surveillance networks. To get the intended effect, both developed and developing nations must work together.[144,145,146]

Problem of Control

Lack of funding makes it difficult to implement most antimicrobial resistance strategies, particularly in developing nations where, according to World Bank data, health spending in 1990 averaged $41.00 per person, while in the developed world it was $1500.00 per person. The result of such egregious underfunding in underdeveloped nations is a persistent and chronic shortage of drugs, which puts ongoing strain on medical institutions. The successful application of measures to prevent drug resistance in underdeveloped nations is frequently hampered by a lack of political will to address health issues head-on and by misaligned priorities, even in cases where funding is available. Perennial military wars in Asia and sub-Saharan Africa further exacerbate the situation by frequently causing a breakdown in sanitation and health services, which accelerates the spread of resistant pathogens.[147,148] For instance, resistance to multiple first-line antibiotics in clinical isolates of Shigella dysenteriae and Vibrio cholera contributed to increased mortality during outbreaks of cholera and bacillary dysentery among Rwandan refugees.[149] Political corruption and egregious financial mismanagement have left many people living in extreme poverty, even in developing nations that are not at war. As a result, people with communicable diseases who cannot afford medical care may spread the disease to others. This is due to the fact that poverty always unavoidably disrupts patient compliance, which causes antibiotic resistance to develop during both short-term treatment of acute infections and long-term treatment of chronic infections e.g. tuberculosis [150]

Consequences of failure to control antibacterial Resistance

Currently, infections brought on by resistant microorganisms do not improve with therapy, which raises the risk of death, morbidity, and chronic illness. Treatment must be changed to "second line" drugs, which are typically more costly and less accessible to most people, when illnesses develop resistance to first-line antimicrobials. This effectively renders many infections incurable. One example is tuberculosis, which is one of the most common illnesses and one of the main causes of death for people worldwide. 3.5 million people die from tuberculosis each year, and deadly strains of drug-resistant tuberculosis have already been found in over 100 countries and are still spreading. The epidemic has taken a terrifying new turn and is expected to become, among other things, a public health disaster of the new millennium. By the year 2000, the annual global incidence was predicted to rise to 10.2 million.[151]

Impact of HIV epidemic

According to papers in this journal, severe invasive bacterial illness in Malawian adults and children is highly linked to HIV infection.[152,153,154] Although the precise magnitude of the impact is still unknown, the HIV epidemic is probably going to have a significant influence on the development of antibiotic resistance. Compared to HIV-uninfected individuals, adults and children with HIV are more likely to require more frequent hospital stays and get more courses of antibiotics, both of which are risk factors for the development of antibiotic resistance. Additionally, they are vulnerable to disease recurrence after receiving the proper antibiotic treatment. Additionally, there is growing evidence that people with HIV have greater and longer-lasting carriage rates of common bacterial infections than people without HIV. These elements could help to explain why HIV-positive adults and children are more likely to contract resistant organisms [155,156]

Future Directions to Combat Antibiotic Resistance in Bacteria

1. Development of New Antibiotics: Investment in research to discover new classes of antibiotics. Reviving older antibiotics with new formulations or combinations
2. Alternative Therapies

- Phage Therapy: Bacteria-specific viruses as targeted treatment.
- Antimicrobial Peptides: Natural immune molecules.
- CRISPR-Cas9: Gene-editing tools to destroy resistant genes.

3. Antibiotic Stewardship Programs: Promote rational use of antibiotics in healthcare. Avoid misuse and over prescription.
4. Rapid Diagnostic Tools: Point-of-care tests to identify pathogens and resistance. Reduces empirical and broad-spectrum use.
5. Improved Surveillance Systems: Strengthen local and global data collection (e.g., GLASS by WHO). Early detection of outbreaks and resistance patterns.
6. Public Awareness and Education: Inform public and healthcare professionals about resistance. School-based and media campaigns.
7. Stronger Regulations: Restrict OTC sale of antibiotics. Monitor and regulate antibiotic use in livestock.
8. Vaccination and Infection Prevention: Broaden vaccine coverage (e.g., pneumococcal, typhoid). Promote hygiene, sanitation, and clean water access.
9. Global Collaboration: International partnerships for data sharing and unified policies. WHO, CDC, FAO, and others working.

Fig. 3: Future Directions to Combat Antibiotic Resistance in Bacteria

CONCLUSION:

The development of antibiotic resistance in bacteria is one of the most significant issues facing modern medicine. The prevalence of multi-drug resistant foodborne infections in developing nations, primarily in Asia and Africa, is a particularly alarming phenomena. In many cases, the ratio is as high as 100%. Furthermore, it has been documented that the development of drug resistance in numerous bacterial species is facilitated by the transfer of resistance genes between species via the resistance mechanism. Such a transfer, along with plasmid transfer by conjugation, has been verified in multiple investigations in Enterococcus species, Staphylococcus species, Streptococcus species, and Listeria species. This suggests a substantial worldwide danger of multi-drug resistance in bacteria. In order to regulate the rate at which medication resistance spreads among bacteria worldwide, it is necessary to keep an eye on these bacteria's resistance. The prevalence of various bacterial species in farm animals and their resistance to antibiotics varies by region, animal species, and housing arrangement. It is also linked to the degree of economic growth in a particular region of the world. Multidrug resistance in bacteria spreads so quickly and easily that it constitutes a global threat to both humans and animals. This necessitates the use of strategies for bacterial control other than antibiotics in addition to thorough drug resistance detection. Consequently, there is a great need to discover new methods for controlling bacterial infections. As a result, a number of novel treatments have been investigated that employ bacteriophages, antimicrobial peptides, and combinations of two or more antibiotics. However, since the alimentary tract is the site of the majority of infections, precautions like better sanitation, safe food and water supplies, prompt detection and treatment, and the creation of next-generation vaccines are required to lower the risk of infection.

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