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Research paper

A Review on Antibiotic Resistance in Bacteria.

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Abstract

Antibiotics are now widely used in the treatment of infectious diseases. But the problem arise when the infectious agent become resistant to antibiotic drug therapy. Nowadays misuse of antibiotics in human, agriculture and veterinary medicine is the major reason for increased resistance. Resistance to antimicrobial agent's results in treatment failure,increased mortality and morbidity. Antimicrobial resistance is now a global problem because resistance can transfer through mobile genetic elements such as plasmids, transposons and integrons. Pathogenic species including staphylococci, *Streptococcus pneumonia* and *Mycobacterium tuberculosis* together with commensal enteric bacteria predispose the dual risk of emerging antibiotic resistance. Finally, control of antibiotic resistance bacteria depends on reduction of selection pressure and improved surveillance to detect their subsequent spread.

Keywords*: Antibiotic resistance, Dissemination, plasmids.*

1. Background

Since 1940s, antibiotics have been using as a powerful tool of modern medicine to defense infectious diseases and saving countless lives. But the extensive use of antimicrobials results in resistant pathogens in nature [1]. Over the years, the continued use of various antimicrobial agents has led microorganisms to develop resistance mechanisms against two or more drugs (multidrug resistance, MDR) [2,3], for example multidrug resistance has been observed in *Pseudomonas aeruginosa, Acinetobacter baumannii, E. coli,* and *Klebsiella pneumoniae* producing extended-spectrum *β*-lactamases (ESBL), vancomycin-resistant enterococci *Enterococcus faecium*(VRE), Methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), extensively drug-resistant (XDR) *Mycobacterium tuberculosis* [2,3], *Salmonella enteric* serovar Typhimurium, *Shigella dysenteriae, Haemophilus influenzae, Stenotrophomonas* spp., and *Burkholderia* spp. [3,4]. Today, the development of resistance to antimicrobial agents worldwide is responsible to make the treatment process complicated and the consequence is very severe [5,6,7,8]. When first line antibiotic fails to control infectious agent, second or third line drugs are alternative option which are generally much more cost-effective and toxic [9,10].

The problem of antibiotic resistance is more pronounced in developing countries [11,12,13]. In case of Cholera bacilli extensive resistance to furazolidone, co-trimoxazole and nalidixic acid has been observed in New Delhi (India) [14,15]. In almost all countries in the South East Asian (SEA) region, MRSA is solely responsible for hospital-associated infections [15,16]. The susceptibility pattern of *Neisseria gonorrhoeae* has been changed and resistance to penicillin and fluoroquinolones is more prevalent across the South East Asian region [15,17]. The European Centre for Disease Prevention and Control (ECDC) reported that antibiotic resistant bacteria is responsible for the death of 25,000 people annually [18,19].

In modern times, resistant organisms rapidly cross the boundaries of a country through travel and trade or by food chain [20,21,22]. Resistance due to chromosomal mutation is not frequent and confers resistance to structurally related compounds [23]. A range of research activities around the world have shown that use of antimicrobials is correlated with the selection of antimicrobial resistance [24]. Several antibiotics, notably tetracycline, have the ability to select bacteria having R plasmid mediated drug resistance [25,26]. It is well known that R plasmid can transferred to humans, either from animal or bacteria contaminated food products [27], from other human sources directly [28], or via contaminated water [29,30]. Inappropriate use of antibiotics accounts for 20% to 50 % of all antibiotics [31,32] and according to the Center for Disease Control and Prevention of USA,50 million of the 150 million prescriptions every year are unnecessary [10,33]. For preventing overuse and misuse of antibiotics in hospital, coordination among hospital personnel, infection control team and hospital pharmacist is mandatory [34,35].

A History of antibiotics and development of antibiotic resistance

In 1929, Sir Alexander Fleming discovered the first antibiotic 'penicillin' [36]. Ernst Chain and Howard Florey in 1939 isolated penicillin [37] and during the Second World War used it to treat bacterial infections [38]. The new drug used clinically in 1940 and for these discoveries Fleming, Chain and Florey were awarded the Nobel Prize in 1945 [39]. In the late 1940s, new antibiotics were introduced [40], including streptomycin, chloramphenicol and tetracycline [10,41].

The golden age of antibiotic discovery was not long lasting and resistance has been observed to nearly all developed antibiotics (Table 1). After introduction of the drug penicillin in 1940s, resistant strains of staphylococci spp. was recognized in British civilian hospitals almost immediately [42,43]. Resistance to penicillin results in the development of a semisynthetic penicillin (methicillin) [44,45]. Similarly, streptomycin, chloramphenicol and tetracycline resistance was also reported in the late 1940s [46]. Streptomycin introduced in 1944s and resistant strains of

Mycobacterium tuberculosis were found to arise during patient treatment process in 1947 [47]. During a *Shigella* outbreak in Japan in 1953 *Shigella dysenteriae*was isolated which showed multiple drug resistant phenotypes, exhibiting resistance to chloramphenicol, tetracycline, streptomycin and the sulfonamides [10,46]. Vanomycin resistance began to appear in the mid-1980s and had increased more than 20 fold from 1989 to 1995 [48]. Several important multiple drug resistant organisms including MRSA, MRSE, VRSA, methicillin-resistant coagulase-negative *Staphylococci* (MRCNS), and penicillin-resistant *Streptococcus pneumonia*(PRSP) are known to be a serious problem in the treatment process [49,50]. Resistance to synthetic antibiotics trimethoprim and sulphonamides is caused by enzymes dihydropteroate synthetase (DHPS) and dihydropteroate reductase (DHFR) [51]. Resistance of *Shigella* species to nalidixic acid and ciprofloxacin observed in 1984 [52,53]. In hospital settings carbapenemase resistance mechanisms are found among *Escherichia coli* and *Klebsiella* isolates [54,55] and have also been isolated from farm animals [56,57].

Table 1: Emergence of resistance with the discovery of antibiotics.

Year of antibiotic discovery	Observed resistanc
Penicillin (1928)	Observed penicillinase in 1945
	Transferable penicillinase in *Gonococcus* in 1976
	Penicillin resistant *Enterococcus* in 1983
Sulfadrug, prontosil (1932)	Observed resistance in 1942
Streptomycin (1943)	Resistance to streptomycin observed in 1946
Tetracycline (1944)	Tetracycline resistance observed in 1950
Erythromycin (1948)	Resistance to erythromycin observed in 1955
Vancomycin (1953)	Vancomycin resistant Enterococcus (VRE) observed in 1987
	Vancomycin intermediate resistant *S. aureus* observed in 1996
Rifamycin (1957)	Resistant in 1962
Nalidixic acid (1962)	Observed resistance in 1966
Streptogramin B (1963)	Observed resistance in 1964
Cephalothin (1964)	Cephalothin (1st generation) resistance observed in 1966.
Gentamicin (1967)	Observed resistance in 1970
Cefotaxime (1981)	Cefotaxime resistance observed in 1983
3rd generation cephalosporin (1980)	Cephalosporin resistance observed in 1985.
Fluoroquinolone (1982)	Resistance to fluoroquinolone observed in 1985
Imipenem (1984)	Carbapenem resistant *Acinetobacter baumanii*observed in 1998
Daptomycin (1986)	Resistance observed in 1987
Linezolid (1955)	Linezolid resistant *S. aureus* and VRE observed in 2001
Bedaquiline (1997)	Resistant in 2006

B Methicillin-Resistant *Staphylococcus aureus*

MRSA also called "methicillin-resistant *Staphylococcus aureus*", which are resistant to the action of methicillin [58,59,60] and related beta-lactam antibiotics. MRSA contain mecA gene that is present as the staphylococcal cassette chromosome mec (SCCmec) region (21-67 kb) in the chromosome [61,62,63]. Methicillin resistance was first observed in *Staphylococcus aureus* in the United Kingdom in 1961 [64,65]. Based on the source of acquiring disease, MRSA can be sub-categorized as Hospital-Associated MRSA (HA-MRSA) or Community-Associated MRSA (CA-MRSA) [66,67]. MRSA are most common in nursing homes and other long-term care facilities [68,69]. However, isolation of MRSA is no longer limited to hospital patients [70,71] and have been reported in diverse community people [72,73,74]. There have been several reports of VRSA (Vancomycin-Resistant *Staphylococcus aureus*) that are troublesome to control staph infections [63,75].

C Extended-Spectrum beta-lactamase (ESBL)

Gram-negative pathogens which are resistant to β-lactam antibiotics produce an enzyme β-lactamase [76,77,78]. Extended-spectrum beta-lactamases (ESBLs) are plasmid-associated beta lactamases [79] that can be divided into three groups: TEM, SHV, and CTX-M types [50,80]. ESBLs have the ability to hydrolyze penicillins, both narrow and extended-spectrum cephalosporins, oxyimino-cephalosporins (cefotaxime, ceftazidime), and monobactams (aztreonam) [81]. Strains resistant to quinolone are generally produces ESBL but their resistance depends on mutations in *gyr*A and *par*C genes [82]. ESBL producing isolates have been found throughout the Enterobacteriaeae, but predominantly *Klebsiella pneumoniae* and *E. coli* [50,51]. Beta lactamases encoding genes can transfer through plasmids and these plasmids also carry genes conferring resistance to several non-ß-Lactam antibiotics [76,83]. ESBLs are most often encountered in the hospital (intensive care) setting [77,84].

D Antibiotic resistance in Enterococci

Enterococcus spp., is considered as a major threat in intensive care units in the United States as they are the third leading cause of nosocomial infections [85,86]. Enterococcus spp. from poultry production and processing operations are frequently found to be resistant to multiple antibiotics such as tetracycline, macrolides, Streptogramin, lincosamides [86-90]. Vancomycin resistant enterococci (VRE) are usually found in "healthy" individuals in the community and in farm animals, but VRE still not common in hospitals [91-95].VRE associated infections are difficult to treat and there is another risk of transfer Van A gene cluster to Staphylococci spp. The increase in resistance associated with Enterococci has led to the ban of growth-promoting antimicrobials in the EU based on perceived risk [86,96].

2. Mechanism of resistance

When a new antibiotic is introduced, initial rate of resistance is normally low. However, increased use of antibiotics in present days is responsible for the development of resistant bacteria. The excessive use of antibiotics by mankind results in the excretion of large numbers of antibiotic resistant bacteria into the environment leading to colonization and infection to spread among individuals [89]. Antibiotic resistance mostly observed among gram-negative bacteria [97-99], specifically within the members of Enterobacteriaceae [99,100]. Bacterial resistance can be either categorized as intrinsic or acquired resistance [101]. Acquired resistance is mediated by plasmids (conjugation and transformation), transposons, integrons and bacteriophages (transduction), mutation of cellular genes, and a combination of these mechanisms [23, 102-104]. Several mechanisms have been discovered which bacteria employ to resist the killing effect of antibiotics such as by blocking of antibiotic entry, efflux mechanism, enzymatic inactivation of antibiotics, target site alteration, bypass mechanism etc [39,105-109]. Among these mechanisms, innate and acquired bacterial resistance can be conferred by efflux pumps and the genes encoding the pumps can be located on chromosomes or plasmids [110, 111,112]. Active efflux of antibiotics was first described in 1978 in *Escherichia coli* resistant to tetracycline [113,114,115]. Different antibiotic classes and mechanisms of resistance to these antibiotics with examples are given below (Table 2):

Table 2: Different classes of antibiotics and their resistance mechanisms.

Antimicrobial class	Mechanism of resistance	Examples
Beta-lactams	Enzymatic destruction	Resistance of *Enterobacteriaceae* to penicllins, cephalosporins, and aztreonam.
	Altered target	Resistance of *staphylococci* to methicillin and Oxacillin.
	Decreased uptake into cell	Resistance of *Enterobacter aerogenes*, *Klebsiella pneumonia*.
Tetracycline	Active efflux from the cell	Resistance of Enterobacteriaceae to tetracycline.
Chloramphenicol	Reduced uptake into cell	Resistance of *Pseudomonas putida* to chloramphenicol.
Glycopeptides	Altered target	Resistance of enterococci to vancomycin.
Aminoglyosides	Enzymatic modification	Resistance of many Gram-positive and Gram negative bacteria to aminoglycosides.
	Decreased uptake into cell	Resistance of a variety of Gram-negative bacteria to aminoglycosides
	Altered target	Resistance of *Mycobacteriumsp.* to streptomycin.
Quinolones	Decreased uptake into cell	Resistance of Gram negative and *Staphylococci* (efflux mechanism only) to various quinolones.
	Altered target	Gram negative and Gram positive resistance to various quinolones.

2.1. Acquisition and Dissemination of antimicrobial resistance

Bacteria contain genetic material which can transfer to other related species using a range of genetic processes [116] such as bacterial conjugation, transformation, transduction and transfer through more efficient means such as using transfer vehicles-plasmids, transposons and integrons [6,39]. Antibiotic resistance to many antibiotics have been directly acquired through plasmids [117-124]. Mobile genetic elements such as plasmids and transposons accumulate several resistance genes which results in multiple drug resistance [2]. Transposons spread efficiently and are transferred by conjugation, transformation or transduction [2]. In heterogeneous communities the rate of plasmid transfer is very high because plasmid can cross species and genus barrier [125]. As a result resistance persists in microorganisms that are not exposed to antibiotics [126].

Horizontal gene transfer among bacteria led to the rapid dissemination and acquisition of antibiotic resistance [127,128]. It is known that the organisms which possess integrase are capable of acquiring antibiotic resistance genes [129]. Hospitals were generally considered to be the major source of antibiotic resistant bacteria and resistance genes due to selective pressure, but it is becoming clear that other reservoirs of resistance genes could exist [130].

2.2. Activities that lead to antimicrobial resistance

Misuse of antibiotics in agriculture and veterinary practice

The use of antibiotics as feed additives to promote animal growth and to prevent infections [131-136] contributes to the emergence of antibiotic-resistant pathogens and reduces the effectiveness of the antibiotic to treat human infections [137-140]. Low level exposure of antibiotics through feed additives over long periods results in enrichment of resistant bacterial populations [141-144]. In veterinary, use of antibiotics has been resulted in the development of high frequency resistant gut flora [145-146]. Different clonal types of methicillin-resistant Staphylococcus is responsible for transmission in human which is acquired from livestock, such as ST398 in the Netherlands, CC93 in Denmark, and ST 130 in Europe [147-150]. Industrial agriculture in developed countries is considered to be the most important reservoir for antimicrobial resistant *Salmonella* spp., *Campylobacter* spp., MRSA, *E. coli* and enterococcal infections [151,152].

3. Inappropriate use

The level of antibiotic consumption is directly correlated with the level of antibiotic-resistant infections [153]. Inappropriate use of antimicrobials results in the selection of resistant microorganisms [154,155]. Many people; especially the poor, largely rely on informal healthcare providers [156-158] and they are not qualified enough to offer quality health service for the community [159]. Systematic drug sensitivity reports against microorganisms from countries like Bangladesh are sparse [156, 160]. Hospital restrictions are limited in terms of antibiotic usage for prophylaxis is the main reason for inappropriate therapy [161]. Self-medication is one of the major reasons of antibiotic resistance in low- and middle-income countries where antibiotics are easily obtained without prescription from the pharmacies [162]. Lack of practice in combination therapy favors selection of resistance in certain infections [163,164].

3.1. Antibiotic resistance in genetically modified crops

Antibiotic-resistance genes acts as "markers" in genetically modified crops in order to detect the genes of interest [165]. The resistance genes are not removed from the final product and could be acquired by microbes in the environment [166]. The gene associated with antibiotic resistance may transfer to unrelated microorganisms such as *Aspergillus niger* [167,168].

3.2. Antimicrobial resistance in the environment

In both clinical and agricultural settings, an increase in the prevalence of drug resistant microbes and resistance genes has been linked to the selective pressure of antibiotic use [169]. The environmental "resistome" acts as a reservoir of antimicrobial resistance genes [170-172]. Studies on environmental microbiology shows that antibiotic resistance gene determinant (ARGD have been found in diverse environmental samples, such as soil [171,173], oceanic cold seep sediments [174] and also in pristine environment [172,175]. Opportunistic pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Burkholderia* spp., and *Stenotrophomonas* spp. in the soil contain several antibiotic resistance genes and have the capacity to acquire new resistance genes [176]. Soil acts as a reservoir for β-lactamase genes and can transferred to pathogens [171]. Broad-host-range plasmids play a significant role in this process [77] that should be avoided from entering medically important pathogenic bacteria [178]. Enterococcus spp. resistant to various types of antibiotics observed in coastal water of Iran and may transfer resistant genes to other bacteria [179]. A global increase in the transfer of new resistance determinants after the introduction of the blaOXA genesirrespective of their geographical distribution, such as the Klebsiella pneumoniae carbapenemase (KPC) type enzymes, Verona integron-encoded metallo-β-lactamase (VIM), Imipenemase Metallo-β-lactamase (IMP) and New Delhi metallo-β-lactamase (NDM), and the OXA-48 type of enzymes [180, 181].

The depletion or removal of selection pressure in the environment does not always ensure the reduction of resistant microbes. In the USA, no decline in the levels of ciprofloxacin resistance has been observed following the ban of fluoroquinolones in chickens.[182,183].

3.3. Combating antimicrobial resistance

Although antibiotic resistance is unavoidable, it is necessary to take necessary steps to control antibiotic resistance. With increasing resistance researchers are trying to develop antibiotics that could confer improved activity and less toxicity.[113]. These approaches include tapping the novel antimicrobial agent from marine environment other than soil [184,185], isolation of antimicrobial peptides and compounds from animals and plants [186]. Phage therapy,an approach that has been extensively researched and used as a therapeutic agent in United States.[187-190]. Currently, most of the bacteria resistant to antibiotics possess efflux pumps, many of which are multidrug pumps that recognize a number of different antibacterial classes and other compounds.[191]. So efflux pump inhibitor that can be used in combination with current antimicrobials may be an innovative way to control antibiotic resistance problem [108,192]. To prolong the useful life of antibiotics cycling is another choice which can reduce selection pressure.[177,193]. The essential features and appropriate resources for an optimal infection control program have been identified.[194] which focused on nosocomial infections, education on appropriate use of antibiotics and development of regulatory guidelines in isolation practices, hand hygiene and equipment sterilization.

4. Conclusion

Antibiotic resistance is now a global threat because of the increasing resistance to most commonly used antibiotics. But, it is not possible to stop the use of antibiotics or to prevent the development of resistance. To overcome the situation or to minimize the problem of antibiotic resistance it is necessary to restrict overuse of antibiotics in agriculture and veterinary medicine, introduce better diagnosis, prevent self-medication and development of new antibiotics. Bacteria use different innate and biochemical resistance mechanisms and it is important to identify the location of resistance genes in a chromosome and their expression to develop control steps.

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6. Conflict of interest

The author declares that there is no conflict of interest.

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