Review Article

Antibiotic Resistance in E*scherichia Coli*

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Article information:

Received: 2022-06-23
Accepted: 2023-06-09
Vol. 16, No. 1, Aug, 2023.

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Abstract

The treatment of bacterial illnesses is a complicated task because this micro-organism has the ability to develop a wide spectrum of antibiotic resistance and in different mechanisms. Antimicrobial drugs are typically categorized according to their primary mode of action, for example β-lactams and glycol-peptide agents may interfere with cell wall synthesis, while macrolides and tetracycline disturb bacterial protein synthesis, another group (fluoroquinolones and rifampin) can inhibit nucleic acid and genetic material synthesis, while inhibition of a metabolic pathway is a mechanism of trimethoprim-sulfamethoxazole agents, interference with the structure of bacterial membranes and function is a characteristics of polymyxins and daptomycin. Antibiotic resistance can develop in bacteria in a variety of ways. They may be naturally resistant to antimicrobial treatments, or they may be resistant due to genetic alterations or the transmission of a resistance allele from another species. The development of effluxing systems that prevent the medicine from accomplishing its aim intracellularly, adapting the medication's area of action, or providing a substitute biosynthetic activity that avoids the drug's effects could all be possible with a new resistant allele. By conjugation, transformation, or transduction, antimicrobial-inclined microorganisms can gain current genetic material from resistant bacteria, with transposons commonly assisting the inclusion of multiple resistance genes into the host's genome or plasmids. Antibacterial therapies provide selection stress, which allows new bacteria to emerge.

Keywords: bacteria, antibiotics resistance, Escherichia coli.

Introduction

What is the state of antibiotic resistance among bacteria?

The major ways by which bacteria resist antibiotics are enzymatic breakdown of antimicrobial agents, modifying the bacterial protein structure and thus disrupting antibacterial aims, or altering antimicrobial access to the cell by altering the microbial membrane permeability.

Antibiotic resistance either be mediated by the plasmid or maintained at the chromosomal levels, certain types of bacteria (e.g. *Mycobacterium tuberculosis* and *Streptococcus pneumoniae*) are human pathogens, while others (such as *E. coli*) can infect humans and other hosts such as cattle and flora, horses, poultry and fauna species. Because animals and the environment form the first-rate Antimicrobial resistance (AMR) reservoirs, pathogens may generate antibiotic and-or increased resistant tactics for pathogens as a result to the interplay of those ecologies which is recently became more critical. AMR-genes were found in soils that were no longer exposed to antimicrobials. The human hobby, on the other hand, is expanding and converting the environmental resistome. [1,2,3,4,5]

Antimicrobial Resistance **-alleles in gram-positive bacterium in wildlife:**

Clostridium difficile (*C. difficile*): It is one of the main causes of hospital acquired diarrhea and difficult to eradicate., however, it is also found in meat products and mammals of varying kinds (calves, ostriches, chickens, elephants). The fluoroquinolone resistance of this clone is linked to the substantial increase in *C. difficile* infections. Fluoroquinolones are broad-spectrum antimicrobials that are used to treat infections caused by bacteria in man and livestock. [4]

Quinolone-resistant determining regions (QRDR) in gyrase unit's genes, *gyrA*, was mutated in the majority of C. *difficile* Ripotype 027 (RT027) isolates, conferring fluoroquinolone resistance. Fluoroquinolone resistance develops in medical C. difficile strains as a result of changes in_*QRDR* for the both _*GyrA* with *GyrB* DNA gyrase components. They've also played a role in the establishment of the multidrug-resistant RT078 strain.

Resistance to cephalosporins is still unknown, and certain *C. difficile* isolated from mans and animal with high resistance to metronidazole-drug had discovered, with an unknown accurate way of the resistance

Because of the erythromycin-ribosomal-methylases (-erm) alleles of sophisticated *B.erm gene*-negative, Ribosomal methylation is the main major mechanism of antibiotic resistance in macrolide-lincosamide_streptogramin B (MLSB) institution in *C. difficile*. Strains resistant to both erythromycin and clindamycin, as well as those only resistant to erythromycin, have been discovered in C. difficile. In *C. difficile* separates, the *tet(M) gene* is the most common tetracycline resistance factor. (6)

Enterococcus faecium (E. faeceium):

Enterococcus faecium are commensal microorganisms found in the gastrointestinal tracts of mammals and other animals, as well as in the environment. They are resistant to cephalosporins and cotrimoxazole, and have a modest level of resistance to beta-lactams and aminoglycosides. (7)

Antimicrobial resistance to macrolides, tetracyclines, streptogramins, and glycopeptides has also been identified in medical and animal enterococcus isolates. Antimicrobials such as linezolids, daptomycins, and tigecyclin may administered to cure enterococcal diseases. Vancomycin-resistant enterococci (VRE) have become a severe medical challenging issue to their difficult management. Tn1546 variations with the glycopeptide resistance genes van A had also discovered among human and animal Enterococci. (8)

The proper activity of a 30:70 mixture of subtype streptogramins (quinupristins) alongside category (A) streptogramins (dalfopristins) against multiresistant *E_faecium* strains was proven. Quinupristins or dalfopristin-resistant E_faecium had discovered in human being with bird specimens in 1997, prior to its widespread medicinal use. When enterococci are utilized, the usage of virginamycin, astreptogramin approved for enhanced marketing in creatures has been associated to an increase in streptogramin resistance. (9)

Other antimicrobial resistant alleles found in humans and animals E_ faecium isolates include _aph(3') IIIA, tetracyclines *(_tet(M))*, and macrolides (*_erm(B)*). (9)

***Staphylococcus aureus* and related species**:

Staphylococcus aureus and similar species can be detected in the oropharynx epithelium, and the epidermis and many other body tissues, and are considered to be a typical and healthy element of the human flora.

Among the most frequent gained resistance values in staphylococci is methicillin resistance. This resistance is mostly owing to the gaining of the *_mecA* genetic factor, which encodes *PBP2a*, *a-lactam* low affinity penicillin binding proteins (PBP). Linezolid, the most common antibiotic in the oxazolidinone class, is used as a last-resort antibacterial for diseases initiated through VRE, MRSA, and penicillin resistance pneumococci's. Various methods have been identified in staphylococci that provide linezolid resistance, includes factor mutations in *23S rRNA genes*, in addition cellular proteins changes _L3, _L4, and _L22. (7,10,11,12,13)

Antimicrobial Resistance **-Genes in gram-negative bacteria from animals**

Acinetobacter baumannii: baumannii is a major nosocomial pathogens affecting immuno-compromised individuals with a variety of underlying conditions. In the lab, it has resistance to carbapenem and polymyxin. However, a newly mechanisms of colistins resistance facilitated through using of plasmids (*mcr*-genes) with different medications or may be medications resistant segregates is becoming increasingly widespread. (14,15,16)

Pseudomonas aeruginosa

It is a cause of public and sepsis diseases, particularly in immunodeficient and cystic fibrosis patients; it is inherently resistant to a variety range of antibiotic, such as benzylpenicillin, aminobenzylpenicillin, carboxypenicillin, first and second era cephalosporin, chloramphenicols, and tetracyclines. (16)

Despite the fact that the aminoglycosides, gentamicin and enrofloxacin had higher resistance rates, recent reviews have highlighted the rise of polymyxin-resistant P. aeruginosa. Despite the fact that no medical or ecological liens having *mcr-gene* had described, various ways of polymyxin resistance had fixed in P. aeruginosa, ensuring that P. aeruginosa with *mcr-1 plasmid* simplest owing slight alterations in colistin susceptibility (14,17,18,19,20,21,22).

Enterobacteriaceae: In the 1980s, a chromosome encompassing a transposon encoding the streptothricin-acetyltransferase enzyme facilitated by the emergence of streptothricin-resistant *E. coli*, arbitrated by a chromosome carried a transposons encoding for a streptothricins acetyltransferases (23)

Why antimicrobial resistance in *E. coli* is important?

Escherichia coli is a unique bacterium in the microbiological world since it not only causes serious illnesses in humans and animals, but it also contributes significantly to the autochthonous microbiota of various hosts. Possible transfer of virulent and/or resistant *E. coli* from animals to people via a variety of routes, including direct touch, contact with animal excretions, and the food chain, is a major source of worry. (23)

E. coli is also a key source of resistant strains, that also is to keep blaming for therapeutic failure in

both human and veterinary. Many resistance genes have been discovered in *E. coli* isolates during the last few decades, with most of these resistant strains gained via horizontal gene. [24] In the enterobacterial gene pool, *E. coli* serves as both a donor and a recipient of resistance genes, allowing it to receive resistance genes from those other bacteria while simultaneously passing on its own resistance genes to other bacteria. Antimicrobial resistance in *E. coli* is widely recognized as a major problem in humans and animals on a global scale, and it should be treated as a serious health issue. [25]

Antimicrobial resistance is increasing among community-acquired *E. coli* isolates around the world, and worldwide travel is becoming a greater risk for colonization and infection. The focus has shifted to determining the cost and duration of colonization with resistant *E. coli* after a worldwide journey. Swabs were cultured to find *E. coli* resistant to gentamicin, ciprofloxacin, and/or third-generation cephalosporins. [25]

Someone who had been infected was far more likely to take medicines when travel; nonetheless, travel remained a danger independent of antibiotic use. Colonization with resistant *E. coli* was most common after a trip to Asia. Despite the fact that more than half of those carrying antibiotic-resistant *E. coli* after travel had no detectable resistant strands months prior, at least a quarter of those colonized at six months remained inhabited, implying that antibiotic-resistant *E. coli* invasion is common and may persist after a global journey. Medical practitioners should be aware of this risk, especially when dealing with patients with gram-negative sepsis. [24,25,26]

How the problem developed?

Both human and veterinary practices using antimicrobial agents at large scale for therapeutic purposes or preventive. Antimicrobial resistance genes can be fixed in bacteria as a result of widespread use of antimicrobials in animals, which can be zoonotic or effective in transmitting such genes to human-tailored pathogens or the human intestinal microbiota through direct contact, foods, or the surroundings. [27]

Misuse of antibiotics in food animals, as well as among scientists, has raised the danger of incurable diseases. Since of open mobility among nations, and also significant cattle trafficking across international borders, AMR is becoming a worldwide problem by way of nature. Furthermore, the onset of AMR is accompanied by a reduction within the discovery period. [27]

Antimicrobial drugs are mostly used for human being illnesses treatment and prevention in addition to the animals; nevertheless, they are still used in a few nations to promote growth in food animals. Its uncontrolled use in hospitals networks, and animals is the major causes of development of resistant bacteria. AMR also can transfer between animals to people, perhaps direct thru the transmission of the resistant microorganism or circuitously through the transmission of resistant strains from animal's microbes to the human's germs. [27,28].

Scientific explanation of the antibiotic resistance in *E. coli* and the mechanism of resistance? And How many antibiotics are *E. coli* resistant to

In *E. coli* and other gram-negative bacteria, the formation of beta lactamases, which are encoded in chromosomes or via plasmids, is the most common cause of beta lactam resistance [29]. Beta lactamases having a narrow spectrum are known as penicillinase and cephalosporinases. Extended spectrum lactamases (ESBLs) have a significantly broader spectrum and can hydrolyze a wide range of lactams. The majority of ESBLs are made up of the TEM enzymes SHV, OXA, and CTX-M).

E. coli have been detected in livestock and meat across Europe, Asia, Africa, the United States, and Spain, most likely as a result of the late 1990s use of the third-generation cephalosporin ceftiofur.[29] Blanc et al. discovered *CTX-M—14–*, *CMY—2–*, *SHV—2–*, and *TEM-52–* subtypes.[30] In Denmark, Jensen et al. discovered the firstly ESBL-producing *E. coli* from beef in 2004.[30] The *E. coli*-producing *TEM—52* was obtained from German meat imported from Germany.[30] ESBL-producing *E. coli* segregates were discovered in feces sections from fattening hens as part of a nationwide antimicrobial sensitivity surveillance program in Japan; CTX-M and CMY-2 producing *E. coli* strains were among them.[30]

CMY-2-encoding plasmid was noticed in *E. coli* recovered from people besides the pigs, demonstrating that the BLA (beta-lactamase genes) *CMY-2* gene has disseminated across the community. The ambitions in 33 of the 48 fecal samples analyzed were used to make this determination. In 20 samples, the volunteers have minimally single family member who had tested positive for ESBL--creation *E. coli* in the waste. [30]

Fluoroquinolone Resistance usually develops randomly as a result of point mutations in the Topoisomerases units *Gyra-*, *Gyrb-*, *Parc-*, or *Pare-*; low levels of surfaces porines appearance; or multiple Drug-Efflux pump hyper-expression. [30].

Ciprofloxacin-resistant *E. coli* isolated from poultry GIT (gastrointestinal tract), and can be

transmitted from vulnerable *E. coli* ancestors to people through the food system, resulting in a potentially fatal illness [31]. the inheritance of plasmid containing the (Quinolone Resistance genes (-*QNRA*, -*QNRS*, and -*QNRS* gene is responsible for Fluoroquinolone resistance by the *E. coli*. [31]

According to the Clinical and Laboratory Standards Institute [32], fluoroquinolone resistance expressed by *qnr* genes is reduced and can be listed as sensitive. *qnrB* was recently discovered in *E. coli* strains from pigs in Sweden and in an isolate of *E. coli* from a duck in China. *qnrS* was also discovered in pig and poultry isolates in China [33,34].

Considering resistance to aminoglycosides, the *aac* (3) -IV gene is the uniquely known to induce gentamicin and apramycin cross-resistance. *E. coli* with apramycin resistance linked to the -*aac* (3) --IV gene was identified for the first time in 1981 France farms animals. [35]

In 1986, *aac* (3) -IV was discovered in Enterobacteriaceae isolated from human patients for the first time [35]. Jensen et al. [36] discovered that apramycin use from the farm level increased the prevalence of aac (3) -IV-positive *E. coli* in sick pigs and healthy finisher pigs. The period of administration and the doses used had a significant impact on the incidence of apramycin/gentamicin cross-resistance in sick weaned piglets.

In the folic acid synthesis pathway, sulfonamides target dihydropteroate synthase [37]. Genes (*p., sul1, sul2*, and *sul3*) that encode alternative drug resistant versions of dihydropteroate synthase can encode sulfonamide resistance. *Sul1* and *sul2* have been found in *E. coli* isolated from animals and humans in a range of locations. (38,39). Despite the fact that sul3 was first detected in *E. coli* from a pig in Switzerland, it has since been identified in *E. coli* isolated both from the normal and sick humans in South America and Sweden. [38,39,40].

Sulfonamides are a type of antibacterial medication commonly prescribed *E. coli* infections, and sulfonamide resistance may contribute to poor quality of care in uncomplicated urinary tract infections. While, studies have found links seen between animal reservoir and human disease, the role of the infected animal in the establishment of antimicrobial-resistant *E. coli* urinary tract infection in humans is unknown. Sulfonamide-resistant *E. coli* specimens was evaluated with respect to tetracycline and streptomycin 80 percent of the time (502/627) and 74 percent of the time (462/627), respectively. [40]

According to literatures, streptomycin and ampicillin are the two most typically co-transferred resistance phenotypes among sulfonamide-resistant *E. coli* isolates from pigs, pig carcasses, and people. Loss of *sul2* (the most prevalent predictor of sulfonamide resistance) expression and sul2 genetic movement could allow for permanence in the context of treatment choice pressure, in additional to founder by the use of regularly utilized drugs. [40]

Chloramphenicol resistance was confirmed in a tiny percentage of *E. coli*, a medication approved for human clinical use in 1947. Within the United States, chloramphenicol is not always approved for usage in food animals. Different authors have discovered the persistence of chloramphenicol resistance in *E. coli* [40,48].

Florfenicol, a closely comparable drug, were supported by the United States in 1996 for the treatment of respiratory disorders in cattle. Nonenzymatic chloramphenicol tolerance is conferred via the flo allele, and preexisting bacteria may opt for emerging tolerance [46].

Only a few of the chloramphenicol-resistant genes are successful in mediating florfenicol resistance. Chloramphenicol-resistant strains, for example, no longer demonstrate florfenicol resistance since their resistance is solely reliant on the activity of chloramphenicol acetyltransferases. 35.6 percent of 104 chloramphenicol-resistant animal *E. coli* isolates were isolated before florfenicol licensure. [39]

Tetracycline resistance has been found in more than 90% of chloramphenicol-resistant *E. coli* samples. The findings also revealed an increasing tetracycline and *sul* resistance tendency in animal *E. coli* samples over time, in addition to the persistence of chloramphenicol. The chloramphenicol-resistance determinants that serve as a choice pressure will be described using founder of cell resistance determinants or unidentified substrate(s) [35,41].

Gentamicin resistance have unusual increase level in human *E. coli* samples, with resistance rates of more than 40%*E. coli* found in 2002. Since 1980, gentamicin resistance has grown in animal *E. coli* isolates. The rate of gentamicin resistance in avian (16.6 %) and cow (16 %) isolates is hardly higher than in pigs (14 %). In the poultry sector, gentamicin is frequently used.

When?

From 2007 and 2016, twenty-six studies were done in different Iranian regions to determine the prevalence of cefepime-resistant *E. coli*. [49,50] The number of instances in the study ranged from 13 to 504. In 53.42 60 % of patients, cefepime_resistant_*E. coli* was discovered. The lowest and greatest sample sizes were found in Mazandaran and East Azerbaijan, correspondingly. Out from the ten years studied, 2016 had the greatest incidence rate,

marked increase in antibiotic resistance in recent decades. The highest rate of occurrence was 61.95 % in 2016, while the lowest was ?% percent in 2007. [49] In Iran, the incidence of cefepime-resistant *E. coli* ranged about 15.32 percent up to 100 percent [49,51,52]. Cefepime-resistant. *coli* is found in diverse places worldwide. It is anticipated to harm 10.3% of individuals in the United States, 8.8% of people in European countries, 6.0% of people in Argentin, and 12% of people in Indian state [53,54]. In Southeast Asian countries, cefepime_resistant_*E. coli* is uncommon, with a frequency of 0 in Taiwan and 13.5 percent in China [55,56]. Iran have the maximum rate a rate than its neighbors. The rate of *E. coli* resistant to cefepime was 12% in Saudi Arabia, 0% in Egypt, and 13% in Turkey [57,58]. This gap in prevalence could be attributable to drug abuse or a lack of access to drugs. The unavailability of novel antibiotics in some nations' treatment protocols, and a lack of appropriate monitoring and assessment mechanisms. [58]

Cefepime-resistant. *coli* was recognized in 1% of population in Brazil (59). Cefepime_resistant_*E. coli* were described as frequent in about 8.3% of Ghana's population and 64.5% in Bamako [60]. Iranian peoples owing a far higher level of cefepime resistance in this bacterium than the world average and the lot of nations. Iran's high incidence rate is attributable to excess antibiotic use, an absence of a comprehensive range of services organization to screen AMR, and an absence of effective rules to prevent and regulate antimicrobial resistance, as long as aforementioned causes. When our results are matched to other studies, it indicates that Cefepime-resistant *E. coli* is rampant in the state.[59] A study done in Mazandaran with a number of respondents of 24 cases and a prevalence estimate of 100% [52] had the greatest frequency. Cefepime_resistant_*E. coli* was discovered on 15.32 % of cefepime_resistant_*E. coli* patients on a study including 137 cases in Kerman. The overall incidence percentage in Iran was found to be approximately 53%.

Variations in medical diagnostic circumstances, indiscriminate drug usage, and clinical interruptions can all be attributed for the observed disparities and increased incidence of cefepime resistant *E. coli* in different parts of Iran. Without the need for a doubt, resistant bacterial variants grow more widespread in specific regions before migrating across the country. To avoid the spread of cefepime-resistant *E. coli* in the nation, persons must be trained, raising attention must be raised, and the procedure of prescribing medicines and its proper use must be monitored.[60]

The antimicrobial residues in food of animal origin and the public health importance

Customers have voiced fears about medicine remains in their meals having a negative impact on health. Excessive levels of animal pollutants in animal tissues have a serious impact on health. The maximal amount of antibiotic residues allowed in animal tissues at the time of slaughter is referred to as tolerances. The tolerances are in place to make sure that any residual tablets are not harmful if ingested. The present evidence for specific health hazards linked with specific pharmacological instructions of medication, as well as the dangers related to drug residues in meat and dairy that exceed the set-up threshold, is discussed in this paper. [60] The primary focus is on the potential for adverse public health effects as a result of acute exposure to unlawful residues. Long-term consequences are also examined, as well as fresh research on the impact of residues on gut flora. The bulk of veterinary medication residues in foods are so low in concentration that they rarely provide a long-term or continuous health concern to consumers. The advantage of food safety at a reduced price.

Future thoughts

In recent years, the number of multi drug resistance microorganisms has raised at an astonishing speed, posing major health dangers. The spread of resistant illnesses caused by those germs has resulted in death and morbidity, so finding solutions to bacterial resistance is critical. So, here's a few of our opinions on antibacterial drug conversion and biofilm development, as well as a number of therapies, including generating new antibacterial generation, combination therapy, natural antibacterial compounds, and micro particles technologies.

Conclusion

Antimicrobial resistance in bacterial pathogens is a major issue, with high rates of morbidity and mortality. Gram-positive and Gram-negative bacteria that are multi drug resistance are hard to treat and may be uncurable with standard treatments. The current lack of effective therapies, as well as the failure of successful prevention measures and the lack of new antibiotics, all contribute to the obstacles of microbial infection and associated illnesses, requiring the advancement of novel possible treatments and new antibacterial treatments. Multi-drug resistance is aided by biofilms, which can make environmental management challenging. The work of the antibiotics resistance tracking news Taskforce is an important step in laying the groundwork for advancing the field for both clinicians and researchers, and ultimately for patients.

Acknowledgements!!

This study was supported by department of medical microbiology department college of medicine university of karbala.

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