Review Article

Multidrug resistance in pathogenic *Escherichia coli*; a public health concern

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Abstract

Gram-negative bacteria mostly from *Enterobacteriaceae* family are multidrug resistance and contributing to the antibiotic resistance problems worldwide. *Enterobacteriaceae* resistance against antibiotics especially β-lactam type is progressively controlled by the organization of constantly expressed genes that code effective drug modifying enzymes. Strong and excessive selection pressure has deceptively been complemented by a transfer from “natural” resistance, such as membrane impermeability, and drug efflux, to the modern pattern of mobile gene pools that mostly decide the epidemiology of modern antibiotic resistance. *Escherichia coli* is recognized as a pathogen of fecal contamination, its presence in food shows the expected occurrence of other enteric pathogens. The current review focuses on drug-resistant *E. coli* that are harder to treat with common antibiotics, different ways of multi drug resistance in *E. coli* and the possible alternative therapeutic procedures for prevention and treatment of these bacteria.

Keywords: Antimicrobials; Community health; Nosocomial infections; Pathogenesis; Superbugs

Introduction

*Escherichia coli* are gram-negative bacillus, facultative anaerobe, and motile present singly or in pairs [1]. *Escherichia coli* is generally truncated to *E. coli* (coli is Latin for "of the colon") and has been discovered in 1885 by Theodor Escherish, a German pediatrician and bacteriologist [2]. It is able to initiate predominant infectious diseases such as intestinal and extra intestinal. Urinary tract infection (UTI) pneumonia, septicemia, wound infections and neonatal meningitis are include in Extra-intestinal infections [3, 4, 5].

*Escherichia coli* of clinical importance

It has five pathogenic types that are generally isolated from humans and animals anguish from diarrhea [6]. The enterotoxigenic *E. coli* (ETEC) causes traveler and infant diarrhea and is the significant cause of hemolytic uremic syndrome (HUS) [7]. The enteroinvasive *E. coli* (EIEC) that yields shigellosis-like infections in kids and adults. The enteropathogenic *E. coli* (EPEC) which is the leading source of infant diarrhea. These three types can cause food born diarrhea [8].The entero aggressive *E. coli* (EAEC) that cause diarrhea and gastroenteritis in infants and kids [9, 10]. The enterohemorrhagic *E. coli* (EHEC) that cause hemorrhagic colitis [11, 12, 13].

Four important types A, B1, B2, and D, are phylogenetic groups of *E. coli* strains, that are classified on the bases of simple and fast identification of DNA fragment TspE4C2
and (chuA and yjaA) genes [14]. Group A contains commensal strains, pathogenic extra-intestinal strains related to group B2 as compared to group D.

**Uropathogenic *Escherichia coli* (UPEC) and urinary tract infections**

It is a common bacteria that casing UTI infection [15]. It exists in the GIT as reservoir serve side for instigation of UTI [16]. Almost 85% of community-acquired UTIs and 50% of nosocomial UTIs caused by *E. coli*. The UPEC strain causing UTIs [17]. It is a notorious pathogen causing infections by adhering, invading and replicating in bladder epithelium [18]. When *E. coli* replicate, it causes inflammation, which enhanced bacterial existence and attack to the inner layers of the urothelium. Therefore, they persist in the cell and survive for an extended period and act as an origin of repeated UTIs. Acute cystitis well-known as bladder infection is a familiar type of UTI. Pyelonephritis is the septicity of the upper UTI or kidney and is generally more severe. However, they cause discomfort, a short course of antibiotics can treat the UTIs simply [19]. Due to the short urethra and closer to anus UTIs occurs frequently in women than men. Although, male prostate secret bactericide substances and Zn that are important to kill *E. coli* and prevent men from infection [20].

**Pathogenesis and virulence factors**

A number of genes coding virulence factors for example adhesins, invasins, host cell surface-modifying factors, toxins, and secretion systems are elaborate in pathogenicity mechanisms of *E. coli*. Septicemia and UTI cases by extra-intestinal pathogenic *Escherichia coli* (ExPEC) carry pap, afa/draBC, kpsMTI, sfa/focDE, and iutA genes [21]. Iron acquisition mechanisms, adhesins, capsule, serum resistance, and toxins for example hemolysin and cytotoxic necrotizing factor type 1 and 2 are virulence factors present in ExPEC [22]. Medical devices prosthetic grafts and joints, urethral and intravascular catheters are involved in *E. coli* infection. Biofilm formation in *E. coli* by catheters create catheter-associated UTI (CAUTI) that is the most common hospital-acquired infections [23]. Genetic mobile elements present on a plasmid that is accountable for the virulence factors, colonization factors and toxin genes necessary for the pathogenesis.

**Fimbriae and other adhesins**

Pathogenesis of UPEC mostly contains type 1 pili that carry the FimH adhesin on the tip, it binds the bacterial receptors present on the surfaces of epithelial cells of the mammalian bladder that act in the pathogenesis of UTI [24].

**P fimbriae**

P fimbria was known as the first pathogenic factor of UPEC [25]. Eden and Hansson described that *E. coli* cause symptomatic pyelonephritis by attached to the epithelial cells. P fimbria is coded by the pap (pyelonephritis associated pili) operon, contain 11 genes [26]. 80% of pyelonephritogenic *E. coli* contain this virulence factor [27]. Pili play an important role in starting pyelonephritis [28]. Due to P fimbriae, infection severity enhanced [29]. These pili enhance the infection by permitting a solid binding to the vascular endothelium and helping weak binding to bladder epithelium [30].

**S and F1C fimbriae**

These fimbriae present in pyelonephritogenic *E. coli* that have the ability to identify sialic acid, except P antigens of human RBCs or mannosides [31]. Attachment by S pili are substantial and these are commonly related with *E. coli* causing sepsis, meningitis and upper UTI containing pyelonephritis and cystitis [32, 33, 34]. A number of ExPEC strain contain S fimbriae in which 50% of UPEC, 24% of neonatal meningitis-causing *Escherichia coli* (NMEC) and 9.2% of avian...
pathogenic Escherichia coli (APEC) strains are present [35].

**Dr/Afa Adhesins**

Mannose resistant P blood group-independent haemagglutinin, further named 075X, as it was present in serogroup 075 UPEC [36]. After that it was named Dr haemagglutinin, *E. coli* Dr adhesins are attached as a receptor with the Dr blood group antigen. Kidney Bowman’s capsule and the tubular membrane contain this antigen [37]. Dr adhesin family elements have ability bind to carcinoembryonic antigen (CD66e) [38].Elements from Dr adhesins family are involved in the upper urinary tract attachment and interstitial infection [39]. Due to a high hostile property of *E. coli*, its Dr adhesins causing a threat to the pregnant lady creating up-regulation of the decay-accelerating factor (DAF) receptor in pregnancy [40].

**Siderophore systems**

Bacterial growth required Iron. In *E. coli* DNA replication, transport of oxygen, electron and peroxides metabolism required iron for functions. Bacteria have the ability to find out iron when the iron is less in a host like a siderophore production. Siderophores are the ferric chelators, capture ferric iron from host sources. Aerobactin siderophore is important in *E. coli* for iron-chelating mechanism.

**Aerobactin**

In infection when the iron is low aerobactin play an important role by allowing bacterial growth, causing UTIs and other humans and animals infection. Infections related to *E. coli* aerobactin is important to causing pyelonephritis (73%) cystitis (49%) or bacteremia (58%) then other strain causes bacteriuria (38%), inner and outer aerobactin pathophysiology is important in the urinary tract [41]. In APEC and UPEC strains of *E. coli* have an aerobactin system that plays a vital role [42]. In infection of ExPEC, expression of iutA increase that encoding aerobactin receptor and enhance the infection [43].

**Toxins**

*E. coli* may produce numerous toxins. Extraintestinal pathogenic *E. coli* contain hemolysin and cytotoxic necrotizing factor both responsible for destruction in host cells.

**Hemolysin**

Extracellular pore-forming cytolysin is Hemolysin (HlyA) that was first recognized by its ability to lyse RBCs, that is the type of the Repeats in Toxin (RTX) bacterial toxins family [44, 45, 46]. Operon hlyCABD contains four genes responsible for hemolysin transfer, maturation, and synthesis [47, 48]. *E. coli* carry plasmid of hemolysin that varies in size, incompatibility groups and ability to conjugation [49, 50, 51]. When *E. coli* present in the low nutrients environment, their hemolysin plays an important role by destroying the host cell and gain nutrients for bacterial growth [52].

**Cytotoxic Necrotizing Factor (CNF)**

Caprioli and colleagues were first who described CNF1 toxin present in bacteria. It forms multinucleation in cells cultured that's why its named cytotoxic toxin, and necrotizing because it causes necrosis in rabbit skin [53]. The cnf1 gene code this toxin and it consist of 3042-bp in a single open reading frame [54]. CNF1 is present in the strain causing UTIs, containing prostatitis [55], and pyelonephritis [56]; bacteremia [57] and meningitis [58].

**Group 2 capsules**

The bacterial capsule is an essential virulence factor of virulent bacteria and causes invasive infections. It permits bacteria to avoid host immunological defenses, responsible for the infection mostly those sites that are sterile and hostile, including blood, lungs, kidney and meninges [59]. 80 different capsular polysaccharides are present in *E. coli* which contain linear polymers of repeating carbohydrate subunits, amino acid or a lipid element. In *E. coli* K1, K2, K3, K5, K12,
K13, K20 and K51 are common capsular antigen present in the fecal samples of patients with cystitis and pyelonephritis. 63% of women affected by pyelonephritis have K1 and K5 Capsular antigens, K1, 2, 3, 12, and 13 are distinguished in 70% girls affected from pyelonephritis. 79% of E. coli neonatal meningitis and neonatal sepsis samples contain K1 capsule [60]. Furthermore, K2 capsule is important in serum resistance and related in the pathogenesis of UTI [61].

Antimicrobial resistance
Bacteria can present diverse resistance phenotypes, where multi drug resistance is defined when bacteria can resist one drug in three or more antimicrobial groups [62]. Gram-negative multidrug resistant (MDR) bacteria mostly E. coli and K. pneumoniae is one of the major world problem [63]. Figure 1 shows mode of action of some common antibiotic groups.

Extended-spectrum β-lactamases (ESBL)
The term ESBL was used to explain β-lactamases with a broad spectrum of hydrolysis, in the structure of the enzymes, resulting from the change in one amino acid [64]. According to Ambler's classification, ESBLs belong to class A, in Bush’s classification present in group 2be functional group [65, 66]. Broad-spectrum cephalosporins (such as ceftazidime, cefotaxime, and ceftriaxone) are active against β-lactamases and clavulanic acid, tazobactam, and sulbactam inhibited β-lactamases [67]. TEM, SHV, and CTX-M are three main families of ESBLs present in Enterobacteriaceae.

β-lactamases TEM
The TEM (for Temoneira patient's name) according to the database of Lahey Clinic β-lactamase family is consist of more than 219 variants. TEM-1 that hydrolyzed ampicillin at a high rate than carbenicillin, cephalothin or oxacillin and low activity against extended-spectrum cephalosporin’s and clavulanic acid can inhibit it. TEM-2 was the first variant recognized, that have an identical hydrolytic profile to TEM-1 but it is not known an ESBL [68]. TEM-24, TEM-4, and TEM-52 are the utmost spreading TEM-type in Europe while TEM-52, TEM-106, and TEM-116 are commonly present in animals [69].

β-lactamases SHV
185 variants of the SHV (for Sulphydryl reagent Variable) family exist due to the internet site of the Lahey Clinic. SHV-1 β-lactamase is a natural enzyme that is chromosomally or plasmid-encoded, also have the ability to resist penicillin [70]. Both β-lactamases SHV-1 and SHV-11 are narrow-spectrum that contain point mutation, their origin is present in the K. pneumoniae chromosome [71]. It shows hydrolytic activity against ceftazidime, ceftriaxone, aztreonam, and cefotaxime [72].

β-lactamases CTX-M
CTX-M,m-type (Cefotaximase ) β-lactamases that consist of 157 elements, carry resistance to penicillins and cephalosporins, a number of variants show a high number of hydrolysis to cefotaxime than to ceftazidime [73]. The enzymes containing CTX-M-15, -16- 25, -27, -28, -29 and- 32 have an Asp240Gly substitution that increases the catalytic activity for ceftazidime [74].

Resistance to quinolones
The important way of resistance to quinolones is particular amino acid changes in the quinolones targets. The fluoroquinolone resistance occurs when a mutation occurs in genes that code the target antibiotics, the type II topoisomerases. The mutation in a serine 83 of gyrA is the most common mutation in Gram-negatives. The gyrA and gyrB are the subunits of DNA gyrase that are target genes, parC and parE are a subunit of DNA topoisoasemase IV. The important quinolone resistance determining the region (QRDR) is the small DNA sequence in which mutations occur [75]. Amino acid substitution is due to mutations.
in this place, which change the protein structure. That alters the fluoroquinolone-binding ability to the enzyme and create resistance [76]. A great mutation occurs within parC and gyrA genes among gram-negative bacteria [77].

**Figure 1.** Mode of action of some common antibiotics group
Aminoglycosides resistance
Resistance to aminoglycosides may be facilitated by many ways, mutation or methylation in the 16s RNA of 30s ribosomal subunit of binding site of aminoglycoside; change in the bacterial outer membrane, decrease the intracellular concentration of the antibiotic; active efflux systems activity increased; decrease transport of drug into the cell; and deactivation of aminoglycosides by enzymes [78, 79].

Distribution of antimicrobial resistance
Antimicrobial resistance distribution related to the increased industrial development and larger movement of people, the higher use of the antimicrobial substances in human and veterinary medicine, agriculture [80]. Furthermore, wastewaters from human and animal roots come in wastewater treatment plants (WWTPs) are the main source to spread resistant gene and bacteria. The associations between bacteria from different surroundings play a role in the spreading and selection of MDR microorganisms by horizontal gene transfer and play an important role in worldwide concern [81]. The graphical distribution of possible drug resistance are shown in (Figure 2).

Figure 2. Distribution of antimicrobial resistance adopted from Cantas et al., [82] with modifications
Antibiotic resistance from environmental and agricultural sites

Antimicrobials in animal farming and waste from hospitals and factories are possibly important drivers of resistance [83]. The environment is contaminated by human and animal sources, environmental and drinking water delivers may have great resistant of *E. coli* in all countries [84, 85]. In food and in food web human and animals antibiotic-resistant pathogens are same [86, 87], in homes pets can transfer same multi-resistant isolates to humans [88, 89]. Wild animals are frequently affected [90], seagulls are essential to spread resistance, relating in identified human pathogens [91, 92]. Table 1 shows the drug resistance, responsible genes and the source of *E. coli*.

### Table 1 Multidrug resistance in *E. coli* with antibiotic resistance genes from different sources

<table>
<thead>
<tr>
<th>Strain</th>
<th>Resistance</th>
<th>Resistance genes</th>
<th>Source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>CEZ, CTF, KM, GM</td>
<td>bla&lt;sub&gt;TEM&lt;/sub&gt;, bla&lt;sub&gt;CMY&lt;/sub&gt;, strA, strB, aacC2, aphA1, aphA1-IAB, tetB, tetC, dhfrXIII</td>
<td>Beef cattle farms</td>
<td>[93]</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>CEZ, CTF, GM, BCM, CP, ERFXIV</td>
<td>bla&lt;sub&gt;TEM&lt;/sub&gt;, strA, strB, aacC2, aphA1, aphA1-IAB, tetB, catI, dhfrVII</td>
<td>Beef cattle farms</td>
<td>[93]</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>KM, CL, CP, ERFX</td>
<td>bla&lt;sub&gt;TEM&lt;/sub&gt;, strA, strB, aphA1-IAB, tetB, catI, fhoR, dhfrVI</td>
<td>Beef cattle farms</td>
<td>[93]</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Cip, Amp, Kan, Na, Str, Rif, Chl, Smx, Tet, Tmp</td>
<td>bla&lt;sub&gt;TEM&lt;/sub&gt;, dfrA1, aphA1, aphA2, sul2, aadA1, tetB</td>
<td>Animal source food</td>
<td>[94]</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Nal, chl, Amp, Str, Rif, Kan, Tet, Tmp Smx</td>
<td>bla&lt;sub&gt;TEM&lt;/sub&gt;, dfrA1, aphA2, aadA1, tetB, sul2</td>
<td>Animal source food</td>
<td>[94]</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Amp, Cip, Amcd, Na, Kan, Str, Tet, Rif, Chl, Tmp Smx</td>
<td>bla&lt;sub&gt;TEM&lt;/sub&gt;1b, sul2, dfrA1, aphA2, aadA1, tetA</td>
<td>Animal source food</td>
<td>[94]</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Amp, Nal, Amcd, Kan, Str, Rif, Chl, Tet, Smx</td>
<td>bla&lt;sub&gt;TEM&lt;/sub&gt;1b, aphA2, tetB, sul2</td>
<td>Animal source food</td>
<td>[94]</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>A, Ac, Amx, At, Caz, Ctx, Cip, Ctr, Co, G, Ofx, T.S</td>
<td></td>
<td>ESBL Producers</td>
<td>Raw meat</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>A, Amx, C, At, Ac, Ctx, Caz, Cip, Ctr, Co, Mpr, Ofx, Ctr, T</td>
<td></td>
<td>ESBL Producers</td>
<td>Vegetables salad</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>A, At, Amx, Ctr, Ctx, Caz, C, Ctr, Co, Cip, G, Ofx, T</td>
<td></td>
<td>ESBL Producers</td>
<td>Raw chicken, egg surface</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Amp, Cfm, Cro, Ctx</td>
<td>bla&lt;sub&gt;ACT&lt;/sub&gt;-M-15, qnrS</td>
<td>Water</td>
<td>[96]</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Amp, Cro, Cip, NA, Sxt, Te, Ctx, Cfm, Nor, E, K</td>
<td>bla&lt;sub&gt;ACT&lt;/sub&gt;-M-15, bla&lt;sub&gt;OXA&lt;/sub&gt;-1, bla&lt;sub&gt;OXA&lt;/sub&gt;-47</td>
<td>Water</td>
<td>[96]</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Amp, Cro, Cip, NA, Te, E, Mel, Sxt, Atm, Ctx, Cfm, Nor,</td>
<td>bla&lt;sub&gt;ACT&lt;/sub&gt;-M-15, bla&lt;sub&gt;TEM&lt;/sub&gt;</td>
<td>Water</td>
<td>[96]</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Amp, Nor, Cip, Cro, NA, Cfm Te, E, Atm, Caz, Ctx, Sxt, K, C</td>
<td>bla&lt;sub&gt;ACT&lt;/sub&gt;-M-15, bla&lt;sub&gt;TEM&lt;/sub&gt;, bla&lt;sub&gt;OXA&lt;/sub&gt;-1, bla&lt;sub&gt;OXA&lt;/sub&gt;-47</td>
<td>Water</td>
<td>[96]</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Amp, Nor, Cro, Sxt, NA, Te, C, Cfm, K, Atm, Caz, Cn, Ctx, Cip, E, Tzp</td>
<td>bla&lt;sub&gt;ACT&lt;/sub&gt;-M-15,bla&lt;sub&gt;TEM&lt;/sub&gt;, bla&lt;sub&gt;OXA&lt;/sub&gt;-1, bla&lt;sub&gt;OXA&lt;/sub&gt;-47, qnrB</td>
<td>Water</td>
<td>[96]</td>
</tr>
</tbody>
</table>
Possible treatment alternatives for multidrug resistance bacteria
Due to MDR bacteria risk for the occurrence of untreatable infections has become a main problem in the world [97, 98]. Nitrofurantoin, ampicillin, fluoroquinolones, sulphamethoxazole/trimethoprim and Third-generation cephalosporins (3GC) are first-line drugs that have shown low susceptibility in UPECs [99]. It is necessary to develop strong and new therapeutic approaches to eliminate infections by E. coli. Certain new approaches for the treatment of bacteria are given below [100].

Anti adhesion agents, phytochemicals and nanoparticles
In UPEC pathogenesis Type 1 pili carry FimH adhesin present on the tip, act as important virulence factors and good target side for treatment. By stoping development of pili can assistance in the treatment of E. coli [101]. Plants are being progressively discovered as the potential therapeutic agent because it has the ability to kill the microorganism by a different mechanism and decrease the chance of resistance against it. Saponin, indole-3-carbinol, salicylic acid, 7-hydroxycoumarin (7-HC) are phytochemicals that have antibiofilm and inhibitory activity against the E. coli and Staphylococcus aureus [102]. The E. coli O157: H7 biofilm formation inhibit by use of Ginkgolic acid and Ginkgo biloba extract by downregulating curli and prophage genes [103]. Citrus fruits contain a b-sitosterol glucoside that repressed O157: H7 motility and formation of biofilm [104]. Phenolic acids can repressed biofilm formation and bacterial motility [105]. The antibiofilm activity of phenolic-rich maple syrup extract (PRMSE) use against virulence bacteria such as E. coli, it has ability to suppressed MDR genes and genes related to biofilm formation, motility and adhesion [106].

Nanoparticles are stable and containing great bioavailability, it can easily transfer to kill microbes. Silver nanoparticles are flexible, stable and have the ability to stop the infection and formation of biofilm by E. coli. Due to the great surface to volume ratio and small size silver nanoparticles can be integrated into medical instruments and wound dressings. Toxicity of silver containing thiol group that reduces several enzymes which stop the replication of DNA and protein translation. Silver nanoparticles have been formed from the aqueous extract of Calotropis Procera flower and have effective ability against ETEC biofilm and reduce colonization in the small intestine [107]. In many years the incidence of antimicrobial resistance increased among foodborne pathogens [108, 109]. The regular and unessential use of antimicrobials for agriculture and treatment purpose for animals and human are involved to spread resistant bacteria. Treatment of these bacteria with common antibiotics are very difficult [110]. Pathogenic strains of E. coli primary target people with low immunity [8]. The bacterial sensitivity profile reveals that Carbapenems, Aminoglycoside, Pipercillin-Tazobactam, Ciprofloxacin, Nitrofurantoin, third-generation Cephalosporins, Levofloxacin and Azithromycin are highly effective and Cotrimoxazole and Nalidixic acid were least effective against the E. coli. An E. coli isolated from broilers showed 100% resistance against cephradine [111]. It is suggested that for proper treatment and prevention of bacterial resistance, the doctor should prescribe antibiotic after having the results of culture sensitivity [112].

Conclusion
E. coli is constantly present in the environment, due to its stability and low bioavailability it creates the problem in the world. Incorporating nanoparticles or coating on a specific surface of a natural compound
can improve efficacy. Medical instrument and wound dressings coating with silver nanoparticles were operative to treat E. coli biofilm. Antimicrobial nanospray JUC was sprayed on catheter was seen very effective to restrict E. coli biofilm formation. It is concluded that Gram-negative bacilli (Enterobacteracea) were responsible for UTI and most strains were MDR. The E. coli is the most common isolated bacteria from UTI and the most active antimicrobial agents were tobramycin, ciprofloxacin, and amikacin against Gram-negative bacilli. New strategies and good food safety treatment are required to stop the contamination of food ingredients and to decrease the drug resistance. Emerging a novel and natural antibiotic with a diverse mode of action is essential for the treatment of such MDR bacteria.

Authors’ contributions
Conceived and designed the experiments: A Akbar & M Shafee, Performed the experiments: F Liaqat & W Naeem, Analyzed the data: W Naeem, Contributed materials/analysis/tools: W Naeem & GI Khan, Wrote the paper: W Naeem & A Akbar.

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