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Extended Spectrum Beta Lactamase Producing Extra-intestinal Pathogenic Escherichia coli (ESBL-ExPEC)

N. Lakshmidevi¹, Khadega Yahyah A. Al-hetar¹, G B Kavishankar¹,²

Abstract
Escherichia coli is a commensal bacterium but it can cause different infections for humans and animals after acquisition of virulence factor genes and with the time and by the random usage of antibiotics. It gains resistant to antibiotics that can be transmitted by E. coli to other pathogenic bacteria. Many measures and investigations should be taken as a kind of prevention and to reduce the damages that will be caused by E. coli.

Keywords: E. coli, ESBLs, Phylogenetic Groups, Resistance Genes, Virulence Factors.

INTRODUCTION

Escherichia coli is a normal inhabitant of the intestinal tract of humans and warm blooded animals. Most strains of E. coli are harmless commensals of mammals but others are capable of causing either intestinal or extra-intestinal disease⁶⁻⁸. Although usually harmless, various strains of E. coli have acquired genetic determinants (virulence genes) rendering them pathogenic for both humans and animals⁶. Extra-intestinal pathogenic E. coli (ExPEC) strains are clinically significant group of pathogens that cause a variety of clinical syndromes which include urinary tract infections, abdominal infections, nosocomial pneumonia, neonatal meningitis and sepsis⁶⁻⁸. Their cells produce diverse factors that allow them to overcome or subvert host defenses and to colonize, injure, and invade host cells or tissues. Investigation on the roles of these factors could lead to prevent or attenuate infections caused by the organisms that express them³⁶. Extra-intestinal infections due to E. coli cause tremendous morbidity, mortality and increased health care costs. The strains of E. coli that cause extra-intestinal infection are increasingly important endemic problem and underappreciated “killers”. Billions of health care dollars, millions of work days and hundreds of thousands of lives are lost each year to extra-intestinal infections caused due to E. coli. New treatments and prevention measures will be needed for improved outcomes and a diminished disease burden³⁸⁻⁶³.
Types of ExPEC infections
Urinary tract infection (UTI), sepsis, neonatal meningitis and bacteremia are the most studied extra-intestinal infection syndromes caused by E. coli. ExPEC infections can be grouped to many types related to the site of infection.

Urinary tract infections (UTI)
UTI is an infection involving the kidney, ureters, bladder or urethra. It can be divided into two categories namely: complicated and non-complicated infectious diseases. Complicated urinary tract infection occurs in patients with structural or functional abnormality of the genitourinary tract while non-complicated urinary tract infections usually occur in healthy tract with a normal structure and function and do not spread to other parts of body, the main pathogen being E. coli[83]. The ability of uropathogenic E. coli to cause UTI relates to virulence factors such as α-hemolysin together with pili mediated adherence to uroepithelial cells[20,84]. The infection is more common in women because of their relatively short urethras related to ascending infection to the bladder (cystitis) and occasionally to the kidneys[93].

Meningitis
The pathogenesis involves vaginal E. coli colonization of the infant via ruptured amniotic membranes or during childbirth, which penetrates epithelial and endoepithelial cells of the bladder and, invade the circulation and subsequently cross the blood-brain barrier[58] [58]. Failure of protective maternal immunoglobulin M (IgM) antibodies to cross the placenta and the special susceptibility of newborns plays an important role in infection. Most cases (75%) are caused by strains possessing the K1 capsular polysaccharide that contains sialic acid. The virulence factors involved are the same as with UTI (pili and α-hemolysin)[84]. Meningitis is a serious condition characterized by inflammation of the meninges or the membranes that surround the brain and spinal cord. This condition can be fatal and can leave survivors with long-term disabilities including deafness, blindness and brain damage[55].

Bacteremia
The presence of bacteria in the blood is called as bacteremia, septicemia, blood poisoning or bacteremia with sepsis. Bacteremia is an invasion of bacteria into the bloodstream. It may occur through wounds, infections, or by surgical procedure/injections. It represents the tenth major cause of death in developed countries. Among Gram-negative bacteria, E. coli represents the first cause of bacteremia, with more than 30% of incidence[30]. Septicemia is the presence of bacteria in the blood and is often associated with severe disease. Whereas, sepsis caused by toxin-producing bacteria is alternatively named as Systemic inflammatory response syndrome (SIRS). Isolates of E. coli that infect the bloodstream often possess virulence factors that enable the organisms to circumvent the normal clearance mechanisms and evade the host immune response. These include a range of adhesions (P, S and M), the siderophore aerobactin and haemolysin which are found in other ExPEC[55].

Phylogenetic grouping
Phylogenetic analysis of E. coli species have shown that, the majority of strains belong to four phylogenetic groups: A, B1, B2 and D related to the genetic markers chuA, yjaA and the DNA fragment, TspE4.C2(Fig.1)[15].

Figure 1. Clermont's dichotomous tree to determine the phylogenetic groups of E. coli

Commensal strains fall into groups A and B1, whereas, ExPEC belongs mainly to group B2. Diarrhoea genic strains fall into groups A, B1
and D3,8. Groups A and B1 are sister groups and group B2 is included in an ancestral branch.99 These phylo-groups apparently differ in their ecological niches, life-history and some characteristics, such as their ability to exploit different sugar sources, antibiotic-resistance profiles and growth rate.22


**Serotypes of E. coli.**

Depending on the surface antigens which include somatic (O), flagellum (H) and capsular (K), E. coli can be divided into serotypes, B2 O1:K1:H7/NMST95 that is frequently implicated in neonatal meningitis, urinary tract infections and septicemia in humans. These were detected in strains of animal and human origin from different dates and geographic sources.60 However, eight common serotypes (O1:K1:H1, O1:K1:H7, O2:K1:H7, O4:K5, O6:K2:H1, O6:H31 and O4 antigens are derived from phylogenetic group D2. Some strains in the colonic microbiota displayed “Uropathogenic” characteristics. This includes the “Uropathogenic O serotypes” (O1, O2, O4, O6, O7, O8, O16, O18, O25 and O75) and the capsular types K1 and K5.65 The K1 capsular antigen is typically associated with ExPEC strains that cause neonatal meningitis. Expression of this K1 capsule by so-called neonatal meningitis E. coli (NMEC) has been shown to protect these pathogens from both complement mediated killing and bacteriophages, also enhancing bacterial survival within brain microvascular endothelial cells and facilitating bacterial evasion of phagocytosis by professional phagocytes [98]. Escherichia coli serotyping can be done by traditional method using antisera but this technique is complex, costly, and time consuming. Moreover, cross-reactivity of antisera with multiple O antigens occurs frequently. In addition, transition from the smooth (S) to rough (R) form, which is the result of mutations in 1 or more of the multiple genes controlling O antigen synthesis, renders isolates unable to produce O antigen and, therefore, refractory to typing. A simple alternative molecular method for determination of the E. coli O type is based on allele-specific polymerase chain reaction amplification of 5V portion of the rfb locus. The method is described by Clermont, who detected the 12 principal O types (O1, O2, O4, O6, O7, O12, O15, O16, O18, O25, O75, and O157) found among bloodstream isolates of E. coli. Genes controlling O antigen synthesis are in a region of 4.2 to 20 kb, termed the rfb cluster, which is generally bordered by the gnd and galF genes (Fig. 2).
The number of genes in the rfb cluster varies from 6 to 19, and strains of different serotypes can show completely different gene sets and/or a different organization of conserved genes.

Earlier, clonal outbreaks of *E. coli* clinical infections included ‘Clonal Group A’ (CGA) in North America and O15:K52:H1 in multiple nations. In 2008, *E. coli* sequence type 131(ST131) was identified by utilizing multilocus sequence typing (MLST) of CTX-M-15 extended spectrum β-lactamase-producing *E. coli* from three continents. However, subsequent research has confirmed the worldwide prevalence of ST131, harbouring a broad range of virulence and resistance genes on a transferable plasmid.

**Virulence Factors:**

Most extra-intestinal infections including urinary tract infections (UTIs), sepsis and neonatal meningitis, are caused by distinctive “virulent clones” of *E. coli*. Such virulent clones exhibit diverse specialized virulence factors (VFs) that enable the organisms to overcome or subvert host defenses, injure or invade host cells and incite a noxious inflammatory host response, thereby producing disease. In several cases, pathogenicity has been correlated with the presence of genes encoding virulence factors organized on large blocks, called pathogenicity islands which can disseminate horizontally between distinct *E. coli* strains whether they are located on plasmids, bacteriophages, or even the bacterial chromosome.

Pathogenicity islands (PAIs) are large blocks of established or suspected virulence genes that are inserted into the *E. coli* genome (often at tRNA loci) and which may provide a mechanism for coordinate horizontal transfer of virulence genes between lineages within *E. coli* and even between species. By virulence factors, pathogenic *E. coli* interact with host molecules for colonization and usurping normal cell processes, including cytoskeletal dynamics and vesicle targeting for cellular structural, functional damage and host evasion. In the case of uropathogenic strains of *E. coli*, some virulence factors specifically promote the development of pyelonephritis, whereas others promote cystitis or asymptomatic bacteremia. The presence of two or more specific subset of virulence genes, including pyelonephritis associated pilli type C (papC), S-fimbrie (sfa/foc), afimbrial adhesions Dr adhesion types a,b,c (afa/draBC), aerobactin receptor (iutA) and kapsular polysaccharide (kpsMII), defines isolate as an ExPEC. Major virulence factors produced by *E. coli* include genes coding adhesions (pap, sfa/foc, afa/dra), iron-aquisition system (iutA),
haemolysins and capsules. The *E. coli* strains that are found to be associated with urinary tract infections (UTIs) (pyelonephritis, cystitis and asymptomatic bacteriuria) and with various enteric infections harbor *Afa/Dr* adhesins (*Afa/Dr* DAEC). *Dr* fimbriae were initially described as an O75X fimbria-like adhesin by Vaïsa nen-Rhen, who, after observing them in high incidence in uropathogenic *E. coli* serotype O75, proposed that they represent a clonal group. The *Dr* (O75X) adhesin was cloned from the clinical pyelonephritis strain *E. coli* IH11128 [64]. According to their carbohydrate binding specificity and capsular polysaccharides (kpsM) are antigenic proteins on the bacterial surface which are water soluble; commonly acidic that would otherwise provoke an immune response and thereby lead to the destruction of the bacteria. There are nearly 200 different polysaccharides produced by *E. coli*. *Escherichia coli* hemolysin (HlyA) produces large, clear zones of hemolysis around colonies on blood agar. The hemolysin is present in cell free filtrates and is the best characterized member of the RTX (repeat in toxin) toxin family. Its activity on polymorphonuclear granulocytes liberates leukotrienes, histamine along with ATP and is neutralized by specific antiserum. Cytolysin A or “silent hemolysin” (SheA) causes hemolysis when its gene, sheA (also known as *clyA* or *hlyE*), is present on high-copy-number plasmids; when certain regulator genes, *mprA* and *slyA*, are over-expressed or when the transcription of the chromosomal sheA is depressed (i.e., in *hsn* mutant *E. coli* strains). *Escherichia coli* also produce siderophores (iutA) that probably play an essential role in iron acquisition for the bacteria during or after colonization. The process of obtaining iron and other nutrients for bacterial growth may involve the lysis of host cells.

Antibiotic resistance in *E. coli* is a rapidly expanding problem due to the organism’s ability to mutate, acquire and transmit plasmids and other mobile genetic elements encoding resistance genes. There are many mechanisms that bacteria exhibit to protect themselves from antibiotics which include:

1. Target site alteration often results from spontaneous mutation of a bacterial gene on the chromosome and selection in the presence of the antibiotic. Examples include mutations in RNA polymerase and DNA gyrase, resulting in resistance to the rifamycins and quinolones, respectively.

2. Change in membrane permeability of bacterial cell which restrict antimicrobial agent to access target sites, as in Gram negative bacteria where outer membrane provides an effective barrier and first-line defense against antimicrobial agents. Whereas, Gram-positive organisms lack the outer membrane and hence lack the defence. This is perhaps one of the reasons for their high sensitivity to many antibiotics.

3. Efflux pumps are transmembrane transport proteins used physiologically in Gram positive and Gram-negative bacteria for exporting specific metabolites and xenobiotic toxic substances out of the cell and utilize proton motive force as an energy source. Tetracycline pumps are probably the best studied efflux system in both Gram-positive and Gram-negative bacteria.

4. Enzymatic inactivation or destruction of the drug. For example, bacterial β-lactamase...
evolved from β-lactam-binding enzymes interacts with β-lactam antibiotic and subsequently leads to disruption of the amide bond in four membered β-lactam rings, rendering the antibiotic inactive. β-Lactams are the most commonly used antibacterial agents for treating infectious diseases in humans, that include penicillins, cephalosporins, carbapenems, monobactams and β-lactams inhibitors. They are named so because of the β-lactam ring in their chemical structure. β-lactams exerts antimicrobial activity by inhibiting the synthesis of bacterial cell wall. Resistance to β-lactam antibiotics among gram negative bacteria is most frequently related to the production of the β-lactamase enzymes. The first report on mechanism for antibiotic resistance was published when Abraham and chain described an enzyme in E. coli that could hydrolyze penicillin. These enzymes according to the Ambler molecular classification have been divided into four major classes (A to D) depending on protein similarity. Extended spectrum β-lactamases (ESBL) are enzymes that are able to hydrolyze oxyimino cephalosprins, such as cefotaxime, ceftriaxone, ceftazidime and monobactams but not the cephemycins and carbapenems and are inhibited by "classical" β-lactam inhibitors such as clavulanic acid, sulbactam, and tazobactam. The resistance to EABLS is increasingly reported worldwide. β-Lactamase genes are located on bacterial chromosomes or on transferable elements such as plasmids, transposons or integrons, which play an important role in horizontal transmission of resistance genes. The first plasmid mediated beta lactamase namely TEM-1 was reported in 1965 in E. coli isolated from a patient named Temoneira in Athens and Greece, hence it was designated as TEM. Its location on plasmid facilitated the easy spread to other bacteria. There are over 90 TEM-type β-lactamases mainly found in E. coli and K. pneumonia in addition to other organisms. TEM-type β-lactamase enzymes have been isolated in different countries in Taiwan, Spain, Paris, Israel, Korea, Norway and USA. Bla-TEM was isolated from fecal collections together with many types of CTX-M in Hong Kong, Thailand and Malaysia. Escherichia coli strains are isolated from clinical infection since 2000. SHV-type ESBL refers to sulfhydryl variable active site is common in K. pneumoniae and E. coli as sub-type SHV. The native SHV-1 enzyme was first described in 1972. It is typically a plasmid-encoded enzyme in E. coli that confer resistance to many types of penicillin and is not classified as ESBL as TEM-1 and TEM-2. The plasmid-encoded β-lactamases capable of hydrolyzing extended-spectrum cephalosporins, SHV-2 was isolated from K. ozaenae from Germany in 1983 which efficiently hydrolyzed cefotaxime and to a lesser extent ceftazidime. The resistance to ESBLs has been reported by Rasheed and it is found that, dissemination of the resistance to extended spectrum cephalosporin including ceftazidime was by SHV-8 and SHV-1 enzyme which they isolated from E. coli that was susceptible to these antibiotics under selective pressure of treatment with various cephalosporins. There are over 35 SHV-type β-lactamases. The SHV-5 enzymes with TEM-1 were isolated from episodes of bacteremia in Taiwan. SHV-12 was isolated in 2003 from K. pneumoniae in Taiwan. SHV-12 and SHV-5 were isolated from E. coli isolates in Israel, while SHV-5 was isolated from patients in University Malaya Medical Centre during the period from 1998 to 2000 in Malaysia and in 2001. Many types of SHV β-lactamase are isolated from clinical infections in Norway and China. New SHV sub types including SHV-71, and SHV-75 were reported for the first time in Thailand. The CTX-M enzymes reflect the potent hydrolytic activity of these β-lactamases against cefotaxime and may hydrolyze ceftazidime and cefepime. In Japan, during 1986, non TEM and non SHV isolate which are designated as FEC-1 was isolated from cefotaxime resistant E. coli. In 1989, cefotaxime-resistant clinical E. coli strains which neither produced TEM nor SHV was isolated, so a new β-lactam designated as CTX-M-1 was reported. Enterobacteriaceae species have been considered as a natural producer of Ambler class A ESBLs like Klyvera species which are the original source for CTX-M types. The name of CTX-M enzymes refers to their ability to hydrolyze cefotaxime. The CTX-M family shows approximately 40% similarities to TEM and SHV β-lactamases at the amino acid level. Since the mid-2000s, CTX-M β-lactamases had been identified in different members of Enterobacteriaceae especially in E. coli and have become the most widespread and common type.
of ESBL\textsuperscript{74}. *CTX-M*, depending on their amino acid sequence similarities is subclassified into five groups: (i) *CTX-M-1* group includes six plasmid-mediated enzymes (*CTX-M-1, CTX-M-3, CTX-M-10, CTX-M-12, CTX-M-15, CTX-M-22, CTX-M-23, CTX-M-28 and F13-1), (ii) *CTX-M-2* group includes eight plasmid mediated *CTX-M* enzymes (*CTX-M-2, CTX-M-4, CTX-M-4L, CTX-M-5, CTX-M-6, CTX-M-7, CTX-M-20, and Toho-1), (iii) *CTX-M-8* group includes one plasmid mediated member, (iv) *CTX-M-9* group includes nine plasmid mediated enzymes (*CTX-M-9, CTX-M-13, CTX-M-14, CTX-M-16, CTX-M-17, CTX-M-19, CTX-M-21, CTX-M-27, CTX-M-24) and (v) *CTX-M-25* group includes the *CTX-M-25* and *CTX-M-26* enzymes\textsuperscript{8}. In Europe, the reports on *CTX-M* were rare until the late 1990s, although there were large outbreaks of *Salmonella typhimurium* with *CTX-M-4* and *CTX-M-5* enzymes in Latvia\textsuperscript{9}, Russia and Belarus in the mid-1990s\textsuperscript{90}. In France, many types of *CTX-M* enzymes including *CTX-M-1*, *CTX-M-3*, and *CTX-M-14* were detected in six clinical isolates from 1999 to 2000\textsuperscript{17}. While, *CTX-M-15* was the predominant enzyme among \β-lactamase producing clinical isolates in addition to *CTX-M-14* from four different hospitals in Paris\textsuperscript{10}. In Italy, various types of *CTX-M* were investigated in a single hospital among Enterobacteriaceae\textsuperscript{68}. However, the proportion of *CTX-M* rose from 0% in 1998 to 58% in 2004 in Austria\textsuperscript{19}. Three types of multidrug resistant *E. coli* isolates were responsible for urinary tract infections or colonization belong to phylogenetic group B2 with *TEM-1* and *CTX-M-15* isolation in a French Geriatric hospital\textsuperscript{23}, while *CTX-M-15* was the predominant in four hospitals\textsuperscript{47}. Furthermore, ESBL producing *E. coli* that causes peritonitis still sensitive to some of antibiotics such as cefipime and imipenem\textsuperscript{97}. However, *CTX-M-9* enzymes were isolated from *K. oxytoca* in UK before 2000\textsuperscript{4}. In Norway, *CTX-M-15* and *CTX-M-9* were found to be the dominant ESBL producing *E. coli* during 2003\textsuperscript{96}. Whereas, *CTX-M-15* producing *E. coli* was considered as an epidemic type in community and hospital infections\textsuperscript{99}. As in Portugal, *CTX-M-15* was common between 2004 and 2006\textsuperscript{59}. However, *CTX-M-1* producing *E. coli* strains have been reported in western Austria in 2006\textsuperscript{78}. The most widespread and prevalent type of *CTX-M* enzyme among human clinical isolates of *E. coli* is *CTX-M-15*. The *CTX-M-15* producing *E. coli* often belongs to the international uropathogenic sequence type named *ST131* and to a lesser extent *ST38, ST405*, and *ST648*\textsuperscript{76}. The international dissemination of *ST 131* have in part contributed to the worldwide emergence of *CTX-M-15* producing *E. coli* *ST131* with *CTXC-M-β-lactamases when compared to other ESBL-producing *E. coli* was more likely to be resistant to antibiotics, for producing the aminoglycoside modifying enzyme aac(6')-ib-cr, and cause community-acquired infections including uropsis\textsuperscript{75}. A recent study from Canada reported the molecular epidemiology of ESBL-producing *E. coli* causing bacteremia over an 11-year period (2000-2010) showed that *ST131* was the most common and antimicrobial resistant sequence type and the influx of a single pulsotype of *ST131* was responsible for a significant increase of ESBL-producing *E. coli* especially since 2007\textsuperscript{70}. Johnson\textsuperscript{40}, studied 199 trimethoprim-sulfamethaxazole resistant and fluoroqunolone resistant *E. coli* isolated from urines in Canada during 2002-2004 and identified *ST131* in 23% of isolates and nearly all were fluoroqunolone resistant (i.e., 99%) but, notably, remained susceptible to the cephalosprins. However, 2% of *ST131* in that study were resistant to the cephalosprins\textsuperscript{39}. Another study by Johnson et al.\textsuperscript{40} has done on 127 ExPEC *E. coli* from 2007 SENTRY and meropenem yearly susceptibility test information collection (MYSTIC) surveillance programs across the United States. This study showed that 45% of strains belonged to *ST131*, but interestingly this sequence type included 52% of isolates that showed resistance to ≥ 3 antimicrobial classes. *ST131* has significant higher virulence score than other ExPEC and certain virulence factors such as uropathogenic specific protein (usp); outer membrane protein (*ompT*); secreted autotransporter toxin (*sat*); aerobatic receptor (*iutA*); and pathogenicity island marker (*malX*) were associated with this sequence type. This study showed that *ST131* had distinctive virulence and resistance profiles and concluded that the combination of antimicrobial resistance and virulence may be responsible for epidemiological success of this sequence type.

**The relationship between phylogenetic group, virulence factors and antibiotic resistance:**

Most virulence factors are concentrated predominantly either within group B2 or jointly
within groups B2 and D, but certain factors are concentrated significantly in group D and not in group B2, while others are distributed across the population without a significant concentration in either group B2 or group D. There are significant prevalence differences for individual virulence factors among CTX-M producers and non-producers; however, aggregate virulence factor scores are similar\(^7^3\). Ten VFs are less prevalent in the ESBL isolates than the susceptible *E. coli*, while *iutA* and *traT* are more prevalent in ESBL isolates. Moreover, the CTX-M producing isolates had significantly fewer VFs than TEM-producing isolates\(^9^0\). Distribution of virulence factors differs among ESBL *E. coli* producing different types of β-lactamases. Most ESBL *E. coli* belong to phylogenetic group D especially that are producing CTX-M-14. Whereas, CTX-M-15 producing *E. coli* belong to group B2 with the differences in virulence factors between the strains\(^7^2\). Phylogenetic group B2 that carries a high level of virulence factors are mostly the most frequent ExPEC causing many types of bacteremia, while groups A and B1 strains are almost exclusively infected compromised host\(^6^9\). Most of *E. coli* pathotype ExPEC are isolated from aquatic systems and belong to group B2 and D with a high level of virulence factors and resistance genes\(^2^4\). Among ExPEC isolates, majority of ESBL negative strains of *E. coli* produce multiple virulence factors; whereas, most of the ESBL producers do not produce multiple virulence factors. A rise in the number of virulence factors is associated with decrease in the rate of ESBL production [90]. However, CTX-M-15 producing *E. coli* belongs to virulent phylogenetic groups mainly B2, while CTX-M-9 belongs to virulent group D\(^4^1\). Studies have shown that virulence factors increase antibiotic resistance in resistant strains and increase sensitivity in susceptible strains\(^3\). *Escherichia coli* strains isolated from human and animal waste water are mostly A, B1 and D phylogenetic groups and it usually harbors the same virulence factors (less virulence) with high antimicrobial resistance. However, group B2 isolated from human waste water contains large number of virulence factors, but susceptible to antibiotics. The emergence of resistance among human *E. coli* is most related to the usage of antibiotics in food animal productions \([8^6]\). Studying the virulence factors and understanding its association with antibiotic resistance can help in the management of infections and also shed lights on new vaccine candidates. A study by Picard\(^7^2\) reported that most of commensal *E. coli* belong to phylogenetic groups A and B1 which are devoid of virulence factors; whereas, pathogenic *E. coli* belongs to phylogenetic groups B2 and D which contain high level of virulence factors. The pathogenetic group B2 and D which carry large members of virulence factors are susceptible to antibiotics. The resistance to antibiotics is associated with decreased virulence\(^3^5\). The relationship between virulence and antimicrobial resistance varies based on particular resistance phenotype; for ciprofloxacin resistance, the relationship is strongly influenced by phylogenetic background\(^1^6\). Distribution of β-lactamases differs among phylogenetic groups, SHV-type and to a lesser extent TEM-type producing *E. coli* that exhibits numerous virulence factors; whereas, CTX-M producing *E. coli* belongs to group D, exhibits low virulence factors and are resistant to fluoroquinolone\(^1^0\). Fluoroquinolone resistant *E. coli* which often shows resistance to other antibiotics such as ampicillin, tetracycline, chloramphenicol, sulfamethoxazole and gentamicin belong to phylogenetic groups; A, B1 and D\(^4^5\). The distribution of virulence factors affects the susceptibility to antibiotics. The resistant *E. coli* strains which belong to B2 group harbor fewer virulence factors than the susceptible strains of the same phylogenetic group\(^7^1\). Several studies have demonstrated that the presence of some virulence factors increases the resistance in resistant strains and susceptibility in susceptible strains\(^3\). However, distribution of resistance genes among phylogenetic group depends on the type of CTX-M genes, most ESBL *E. coli* that belong to group D especially those producing CTX-M-14 while CTX-M-15 producing *E. coli* belong to group B2. The distribution of virulence factors also varies between the strains\(^7^3\). The CTX-M producing *E. coli* belongs to phylogenetic group B2 and harbors more virulence factors\(^5^2\). A CTX-M-15 producing *E. coli* belongs to virulent phylogenetic group mainly B2, while CTX-M-9 producing *E. coli* belongs to virulent group D\(^4^1\). Studying the relationship between phylogenetic groups and virulence factors, resistance genes is important in the efficient management of the infection.
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