Chapter

# Antibiotic Resistance among Iraqi Local *E. coli* Isolates

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## Abstract

*Escherichia coli* is a famous Gram-negative bacillary bacterium that belongs to Enterobacteriaceae. It is either micro-biota innocent for human or pathogenic with arrays of diseases. The pathogenic *E. coli* can be assigned to intestinal (InPEC) or extraintestinal (ExPEC) with disease ranging from watery diarrhea to pulmonary distress. The most prevalent form of InPEC is enteropathogenic *E. coli* (EPEC), while the most prevalent ExPEC is uropathogenic *E. coli* (UPEC). The other InPEC includes Shiga toxin–producing (STEC), enteroaggregative (EAEC), enterotoxigenic (ETEC), enteroinvasive (EIEC), diffusely adherent (DAEC) and adherent invasive *E. coli* (AIEC). ExPEC was implicated in cystitis, pyelonephritis, sepsis, respiratory tract infection, cervicovaginal infection (CVEC), meningitis (NMEC), otitis media, cholecystitis and wound infection. Antibiotic resistance is the challenging in world nowadays. Multidrug-resistant (MDR) *Escherichia coli* has become challenging with existing antibiotic options. *E. coli* pathogens have various virulence factors that determine their pathogenesis and antimicrobial resistance mechanisms. The rapid and ongoing spread of antimicrobial-resistant organisms threatens our ability to successfully treat a growing number of infectious diseases. It is well established that antibiotic use is a significant, and modifiable, driver of antibiotic resistance. The most commonly used antibiotic classes for InPEC and ExPEC were third-generation cephalosporin, carbapenem, fluoroquinolone and aminoglycosides. Actually, the most effective prescribed medication is one of the following: cefotaxime, ceftriaxone, ciprofloxacin, amikacin, gentamycin, levofloxacin and imipenem. Generally, according to our review for more than 100 local Iraqi studies among Iraqi provinces, the results revealed the resistance rate from highest to lowest as follows: cefotaxime (76.5%), ceftriaxone (75.9%), gentamycin (41.65%), ciprofloxacin (32.13%), amikacin (17.3%), levofloxacin (15%) and imipenem (5.14%). The resistance mechanisms may include genes encoding antibiotic-modifying enzymes like those of extended-spectrum beta-lactamases gene comprising: *blaCTX-M*, *blaTEM*, *blaSHV*, *blaOXA*, *blaPER*, *blaVIM*, *blaIMP*, *blaNDM* and *blaAMPc.* Efflux pumping includes AcrAB, while resistance to quinolone may be mediated by mutation among qnrA, qnrB, qnrD and qnrS. Resistance to aminoglycosides includes encoding to aminoglycoside-modifying enzymes like *aac(6)-Ib*, *aph(3)-I*, *aph(3)-IIa*, *aph(3)-Ib*, *ant(3)-I*, *aac(3)-II* and *aac(3)-IV*.

**Keywords:** InPEC, ExPEC, CVEC, NMEC, DEC, *blaCTX-M*, *blaTEM*, *blaSHV*

## 1. Introduction

*Escherichia coli* is prominent Gammaproteobacteria, Gram-negative bacilli live facultatively. It is the principal non-pathogenic facultative flora of the human intestine with harmless effect in healthy individuals. The virulent pathotypes of *E. coli* strains have the capability to cause a collection of intestinal and extraintestinal diseases, especially in immune-compromised persons [1]. Intestinal disease includes diarrhea or dysentery caused by six pathotypes, while extraintestinal diseases consists of vaginosis, urinary tract infections, respiratory tract infection, otitis media and meningitis [2, 3]. The enteropathogenic or diarrheagenic *E. coli* is an imperative cause of diarrhea in the newborn, immunocompromised and travelers. It can be assigned to one of the seven pathotypes: enteropathogenic (EPEC), Shiga toxin–producing (STEC), enteroaggregative (EAEC), enterotoxigenic (ETEC), enteroinvasive (EIEC), diffusely adherent (DAEC) and adherent invasive *E. coli* (AIEC) [4–6].

Uropathogenic *Escherichia coli* (UPEC) strains are the most significant causative agents of UTIs in humans. The total prevalence of UTIs caused by the UPEC strains is about 30–70% [7]. UPEC is the most common cause of community- and hospital-acquired urinary tract infections (UTIs). Isolates from uncomplicated community-acquired UTIs express a variety of virulence traits that promote the efficient colonization of the urinary tract. In contrast, nosocomial UTIs can be caused by *E. coli* strains that differ in their virulence traits from the community-acquired UTI isolates. UPEC virulence markers are used to distinguish these facultative extraintestinal pathogens, which belong to the intestinal flora of many healthy individuals, from intestinal pathogenic *E. coli* (IPEC) [8, 9].

One of the important extraintestinal *E. coli* (ExPEC) infections is nosocomial ventilator-associated pneumonia (VAP) with the mortality rate reaching 13%. Until the early 2000s, the ExPEC was not considered as a major pathogen responsible for ventilator-assisted pneumonia that may be due to focusing on other bacteria like *Staphylococcus aureus*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* [10–12]. Many studies stated the high frequency of ExPEC among VAP even more than *Staphylococcus aureus* and *Pseudomonas aeruginosa*. In developing countries, both hospital- and community-acquired respiratory tract infections (RTIs) are linked with emerging MDR *E. coli* [13–15].

*Escherichia coli* is most commonly associated with bloodstream infections and death due to sepsis. Sepsis is a life-threatening clinical condition affecting more than 40 million worldwide with mortality rate more than 15%. The incidence of sepsis caused by Gram-negative bacteria, such as *Escherichia coli* (*E. coli*), has been steadily increasing since the late 1990s. It ranks as the leading cause of death in intensive care units. *E. coli* accounts for approximately 14.1% of early onset neonatal sepsis and it is the second most common pathogen, along with coagulase negative Staphylococcus, after group B Streptococcus (GBS)2 [16–18].

*Escherichia coli* (especially K1) is one of the most common causative pathogens of neonatal meningitis, but the presence of *E coli* in an immunocompetent adult, causing meningitis, is rare with an annual incidence of less than one case per year. The penetration of *E. coli* through the blood-brain barrier is a key step of the meningitis pathogenesis. Diabetes mellitus, alcoholism, cirrhosis, HIV infection and malignancies are some of the risk factors to develop *E coli* meningitis. A distant source is usually identified, either from the urinary or the digestive tract [19–22].

According to the World Health Organization, *Enterobacteriaceae*, including *Escherichia coli*, are among the critical priority antibiotic-resistant bacteria. Multidrug-resistant (MDR) *Escherichia coli* has been listed as a priority pathogen by the World Health Organization (WHO) due to emerging antimicrobial resistance (AMR) [23, 24].

## 2. *Escherichia coli* diseases and antibiotic resistance

*E. coli* causes a wide range of diseases that can be assigned to either intestinal caused by intestinal *E. coli* (InPEC) or extraintestinal caused by extraintestinal *E. coli* (ExPEC) [25]. The most important diseases are as follows:

### 2.1 ExPEC-associated cystitis and antibiotic resistance

Cystitis is a common and expensive condition that impacts humans of different age groups from the neonate till geriatric age group. It is a pathogenic inflammation of the lower urinary tract. Women are more commonly afflicted with UTIs, and they are caused by common pathogens such as *Escherichia coli* (86%) [26]. Uropathogenic *Escherichia coli* (UPEC) is significantly associated with cystitis via sets of virulence factors (adhesins, siderophores, toxins, capsule production and protease) that assist its colonization, invasion, and survival within the host urinary system [27, 28]. High recurrence rates and increasing antimicrobial resistance among UPEC threaten to greatly increase the economic burden of these UTIs [5]. The resistance rate of Iraqi local UPEC to different antibiotic classes is summarized in **Table 1**. The resistance genes are listed in **Table 2**.

The average resistance rate is as follows: cefotaxime (77%), ceftriaxone (70%), ciprofloxacin (45.47%), amikacin (23.42%), gentamycin (45.69%) and imipenem (6.06%). Resistance to beta-lactams was attributed to many mechanisms, and one of them is to the modifying enzymes especially *blaTEM*, *blaSHV*, *blaCTX-M*, *blaOXA*, *blaPER* and *blaVIM*, while resistance to ciprofloxacin was interpreted

| Antibiotic | No. of isolate/ study | Resistance % | Province | Reference |
|---|---|---|---|---|
| Cefotaxime | 246 | 85.13 | Babylon | [34, 40–43] |
| | 76 | 88.9 | Najaf | [30] |
| | 62 | 76.9 | Karbala | [44] |
| | 91 | 75.8 | Wasit | [36] |
| | 50 | 82.5 | Saladin | [45] |
| | 90 | 89.15 | Erbil | [46] |
| | 106 | 52 | Zakho | [47] |
| | 234 | 70 | Kirkuk | [48] |
| | 381 | 70.8 | Duhok | [49, 50] |
| | 50 | 78 | Sulemania | [51] |
| Ceftriaxone | 176 | 81.21 | Babylon | [34, 40, 41, 43] |
| | 62 | 100 | Karbala | [44] |
| | 81 | 75 | Missan | [31] |
| | 91 | 74.7 | Wasit | [36] |
| | 7 | 73.15 | Anbar | [33] |
| | 90 | 52 | Erbil | [46] |
| | 106 | 70 | Zakho | [47] |
| | 234 | 67 | Kirkuk | [48] |
| | 381 | 71.3 | Duhok | [49, 50] |
| | 50 | 34.5 | Sulemania | [51] |

| Antibiotic | No. of isolate/ study | Resistance % | Province | Reference |
|---|---|---|---|---|
| Ciprofloxacin | 258 | 41.73 | Babylon | [9, 34, 40, 41, 43, 52] |
| | 60 | 68.3 | Baghdad | [53] |
| | 50 | 72.5 | Saladin | [45] |
| | 14 | 25 | Tikrit | [54] |
| | 381 | 53.25 | Duhok | [49, 50] |
| | 113 | 24.8 | Anbar | [55] |
| | 50 | 52.6 | Sulemania | [51] |
| | 50 | 52.6 | Erbil | [39] |
| | 81 | 23.4 | Missan | [31] |
| | 91 | 40.6 | Wasit | [36] |
| Levofloxacin | 102 | 38.5 | Babylon | [42, 50] |
| | 14 | 0 | Tikrit | [54] |
| Amikacin | 322 | 25.1 | Babylon | [29, 34, 40, 41, 43, 51, 52] |
| | 62 | 24 | Sulemania | [44] |
| | 50 | 95 | Karbala | [45] |
| | 90 | 25.15 | Saladin | [46, 51] |
| | 14 | 5 | Erbil | [54] |
| | 234 | 5.9 | Tikrit | [48] |
| | 331 | 0.85 | Kirkuk | [48] |
| | 50 | 46 | Duhok | [49, 50] |
| | 113 | 9.8 | Anbar | [55] |
| | 81 | 11.1 | Missan | [31] |
| | 91 | 9.8 | Wasit | [36] |
| Gentamycin | 286 | 37.48 | Babylon | [29, 34, 40–43, 52] |
| | 106 | 74.35 | Sulemania | [30] |
| | 76 | 22.2 | Najaf | [45] |
| | 50 | 75 | Saladin | [46] |
| | 90 | 64.5 | Erbil | [54] |
| | 14 | 25 | Tikrit | [48] |
| | 381 | 51.2 | Duhok | [49, 50] |
| | 113 | 50 | Anbar | [55] |
| | 81 | 11.1 | Missan | [31] |
| | 91 | 46.1 | Wasit | [36] |
| Imipenem | 42 | 11.9 | Babylon | [41] |
| | 7 | 25 | Anbar | [33] |
| | 91 | 0 | Wasit | [36] |
| | 106 | 0 | Zakho | [47] |
| | 234 | 1.5 | Kirkuk | [48] |
| | 381 | 2.25 | Duhok | [49, 50] |
| | 113 | 4.5 | Anbar | [55] |
| | 50 | 4.7 | Sulemania | [51] |
| | 50 | 4.7 | Erbil | [54] |

**Table 1.**
*Distribution of antibiotic resistance among Iraqi local UPEC.*

| Antibiotic class | Genes | Province | Reference |
|---|---|---|---|
| Quinolones | *qnrA, qnrB, qnrD, qnrS* | Babylon | [9] |
| Beta-lactam | *blaTEM, blaCTX-M* | Sulemania | [29] |
| Beta-lactam | *blaTEM, blaCTX-M, blaSHV* | Najaf | [30–32] |
| Beta-lactam | *blaSHV* | Anbar | [33] |
| Beta-lactam | *blaTEM, blaCTX-M, blaSHV, blaOXA, AmpC* | Babylon | [34] |
| Beta-lactam | *blaCTX-M14, blaCTX-M15 blaCTX-M24, blaCTX-M27* | Duhok | [35] |
| Beta-lactams | *blaTEM, blaCTX-M, blaSHV blaOXA* | Wasit | [36] |
| Beta-lactams | *blaCTX-M* | Karbala | [37] |
| Beta-lactams | *blaTEM, blaPER, blaVIM and blaCTX-M-2, blaTEM,* | Baghdad | [38] |
| Aminoglycosides | *aac(6)-Ib, aph(3)-I, aph(3)-IIa aph(3)-Ib, ant(3)-I, aac(3)-II aac(3)-IV* | Najaf | [31, 39] |

**Table 2.**
*Antibiotic resistance genes among Iraqi local UPEC.*

due to the presence of *qnrA*, *qnrB*, *qnrD* and *qnrS* genes [9, 29–37]. Resistance to aminoglycosides among UPEC may be mediated by *aac(6)-Ib*, *aph(3)-I*, *aph(3)-IIa*, *aph(3)-Ib*, *ant(3)-I*, *aac(3)-II* and *aac(3)-IV* [31, 39].

### 2.2 ExPEC-associated sepsis and RTIs antibiotic resistance

Lower respiratory tract infections are a leading cause of morbidity and death worldwide. Optimizing the treatment of respiratory tract infections (RTIs) caused by multidrug-resistant (MDR) *Escherichia coli* has become challenging with existing antibiotic options. *E. coli* pathogens have various virulence factors that determine their pathogenesis and antimicrobial resistance (AMR) mechanisms [38]. The rapid and ongoing spread of antimicrobial-resistant organisms threatens our ability to successfully treat a growing number of infectious diseases. It is well established that antibiotic use is a significant, and modifiable, driver of antibiotic resistance [56, 57]. Physician visits for respiratory tract infections (RTI) commonly result in an antibiotic prescription, despite the fact that most upper RTIs are viral in nature. In these cases, antibiotics provide no benefit; thus, guidelines limit their recommended use to certain situations where the etiology is likely bacterial [58–60].

Over- and inappropriate prescribing of antibiotics is highly prevalent in the primary care setting, especially for upper respiratory tract infections (URTIs). In the outpatient setting, URTIs account for approximately 50–70% of total antibiotic prescriptions, even though most cases are of viral origin [61, 62]. The overuse of broad-spectrum antibiotics, such as third-generation cephalosporins, amoxicillin-clavulanate and fluoroquinolones, is strongly associated with the emergence of resistant strains, does not provide better clinical outcomes, and may lead to adverse events as well as unnecessary costs. Reducing unnecessary antibiotic prescriptions and the overuse of broad-spectrum agents may contain antimicrobial resistance and preserve the efficacy of existing antibiotics [63–65].

The Iraqi studies dealing with antibiotic resistance among sepsis-associated *E. coli* are summarized in **Table 3**. Most *E. coli* strains isolated from bloodstream

| Antibiotic | No. of isolate/study | Resistance % | Province | Reference |
|---|---|---|---|---|
| Cefotaxime | 7 | 92 | Najaf | [66] |
| | 19, 42, 2 | 94.8, 95.2, 100 | Duhok | [67–69] |
| | 9 | 41 | Karbala | [70] |
| | 41 | 51.1 | Baghdad | [71] |
| Ceftriaxone | 7 | 90 | Najaf | [66] |
| | 19, 42 | 94.8, 93 | Duhok | [67, 68] |
| | 9 | 29 | Karbala | [70] |
| Ciprofloxacin | 7 | 46 | Najaf | [66] |
| | 19 | 0.0 | Duhok | [67, 68] |
| Amikacin | 7 | 44 | Najaf | [66] |
| | 19, 42, 2 | 0.0, 35.7, 0.0 | Duhok | [67–69] |
| | 9 | 30 | Karbala | [70] |
| | 41 | 22 | Baghdad | [71] |
| Gentamycin | 7 | 46 | Najaf | [66] |
| | 19, 42, 2 | 78.5, 52.4, 40 | Duhok | [67–69] |
| | 9 | 38 | Karbala | [70] |
| | 41, 17 | 22, 29.4 | Baghdad | [71, 72] |
| Imipenem | 7 | 6 | Najaf | [66] |
| | 19, 42, 2 | 0.0, 9.5, 0.0 | Duhok | [67–69] |
| | 9 | 2 | Karbala | [70] |

**Table 3.**
*Distribution of antibiotic resistance among Iraqi local sepsis-associated* E. coli.

were resistant to most antimicrobials particularly β-lactam antibiotics and third-generation cephalosporins. It might be that long-term exposure to these antimicrobials by patients infected with bacteremia leads to horizontal transfer of plasmid-resistant antimicrobial genes between different strains of bacteria [66].

The average resistance rate is as follows: cefotaxime (79%), ceftriaxone (76.7%), ciprofloxacin (23%), amikacin (21.95%), gentamycin (43.7%) and imipenem (3.5%). The third-generation cephalosporins were the most commonly prescribed antibiotics compiling 54.3% followed by quinolones 7.5% of all prescribed antibiotics. Cefotaxime and ceftriaxone seem to be the preferred prescribed antibiotic for both surgical and medical wards [32].

### 2.3 InPEC-associated diarrheagenic infection and antibiotic resistance

Diarrhea is one of the major causes of serious issues among children in the developing world. More than 4 million children die annually from diarrhea in developing world. Diarrheagenic *E. coli* (DEC) is the most common cause of bacterial diarrhea in children worldwide and responsible for about 600,000 deaths per year [73, 74]. Diarrheagenic *E. coli* infection manifests as watery or bloody diarrhea accompanied by mild-to-severe dehydration. Beta-lactamases are a big problem when produced by DEC rendering the infection hard to be treated or untreatable. The arising of resistance toward extended-spectrum cephalosporins is most often due to hydrolyzing them by extended-spectrum β-lactamases (ESBLs) or due to AmpC. AmpC β-lactamases can prompt resistance to cephalothin, cefoxitin, cefazolin, most

penicillins and beta-lactamase inhibitor-beta-lactam combinations. *Escherichia coli* isolates with CTX-M ESBLs are spreading multiresistance in the community and in hospitals [75, 76]. The resistance rate of Iraqi local diarrheagenic *E. coli* to different antibiotic classes is summarized in **Table 4**. The resistance genes are listed in **Table 5**.

The average resistance rate is as follows: cefotaxime (76.34%), ceftriaxone (79.87%), ciprofloxacin (26.3%), amikacin (31.21%), gentamycin (35.68%) and imipenem (8.18%).

The possible explanation to high level of resistance to this drug may be as a result of it being the most commonly available antibiotic used as a routine therapy among

| Antibiotic | No. of isolate/study | Resistance % | Province | Reference |
|---|---|---|---|---|
| Cefotaxime | 18 | 92 | Najaf | [66] |
| | 89, 39, 114 | 82.9, 89.7, 100 | Babylon | [76–78] |
| | 100, 145 | 71.4, 96.4 | Wasit | [79, 80] |
| | 51, 37 | 4, 54 | Baghdad | [81, 82] |
| | 30 | 96.7 | Tikrit | [83] |
| Ceftriaxone | 18 | 90 | Najaf | [66] |
| | 89, 39, 114 | 74.6, 79.5, 100 | Babylon | [76–78] |
| | 100 | 81 | Wasit | [79] |
| | 37 | 40.5 | Baghdad | [82] |
| | 163 | 76.66 | Basra | [84] |
| | 30 | 96.7 | Tikrit | [83] |
| Ciprofloxacin | 18 | 46 | Najaf | [66] |
| | 89, 39, 114 | 0.0, 15.8, 72.7 | Babylon | [76–78] |
| | 24, 51, 37 | 0.0, 8, 45.9 | Baghdad | [81, 82, 85] |
| | 145 | 25 | Wasit | [80] |
| | 30 | 23.3 | Tikrit | [83] |
| Amikacin | 18, 535 | 44, 0.0 | Najaf | [66, 86] |
| | 89, 39, 114 | 22.6, 12.8, 36.4 | Babylon | [76–78] |
| | 100, 145 | 7.1, 50 | Wasit | [79, 85] |
| | 24, 51, 37 | 16.6, 59, 67.5 | Baghdad | [81, 82, 85] |
| | 30 | 40 | Tikrit | [83] |
| Gentamycin | 18, 535 | 46, 9.1 | Najaf | [66, 86] |
| | 89, 39, 114 | 2.8, 51.3, 54.5 | Babylon | [76–78] |
| | 24, 51, 37 | 0.0, 16, 100 | Baghdad | [81, 82, 85] |
| | 145 | 57.14 | Wasit | [80] |
| | 30 | 20 | Tikrit | [83] |
| Imipenem | 18, 535 | 6, 0.0 | Najaf | [66, 86] |
| | 89, 114 | 9.5, 36.4 | Babylon | [76–78] |
| | 100, 145 | 0.0, 0.0 | Wasit | [79, 80] |
| | 37 | 13.5 | Baghdad | [82] |
| | 163 | 0.0 | Basra | [84] |

**Table 4.**
*Distribution of antibiotic resistance among Iraqi local diarrheagenic* E. coli.

| Antibiotic class | Genes | Province | Reference |
|---|---|---|---|
| Beta-lactams | *blaTEM*, *blaCTX-M*, *blaSHV*, *blaOXA*, *AmpC* | Najaf | [86] |

**Table 5.**
*Antibiotic resistance genes among Iraqi local diarrheagenic* E. coli.

gastrointestinal infections and people readily purchasing it across the counter for self-medication in last years. This could be a reflection of use and misuse of these antibiotics in the society. This finding is a result of the fact that outside the hospital environment the general population has easy access to various antibiotics from any pharmacy without prescription from a doctor [82].

### 2.4 ExPEC-associated vaginosis and antibiotic resistance

Bacterial vaginosis (BV) is the most common vaginal infections among women in reproductive age. It is a condition of vaginal flora imbalance, in which the typically plentiful $H_2O_2$-producing lactobacilli are scarce and other bacteria such as *E. coli* are abundant [87, 88]. Multi-drug resistant cervicovaginal *Escherichia coli* (CVEC) infections are a serious health problem. Bacteria use several strategies to avoid the effects of antimicrobial agents and have evolved a highly efficient means for clonal spread and for the dissemination of resistance traits [4]. Extended-spectrum β-lactamases (ESBLs) are capable of hydrolyzing broad-spectrum cephalosporins and monobactams. In addition, ESBL-producing organisms exhibit co-resistance to many other classes of antibiotics resulting in limitation of therapeutic options. Vaginal *E. coli* represents a real threat especially to neonates; however, little information is available regarding its antibiotic resistance [89, 90]. The resistance rate of Iraqi local cervicovaginal *E. coli* to different antibiotic classes is summarized in **Table 6**. The resistance genes are listed in **Table 7**.

The average resistance rate is as follows: cefotaxime (75%), ceftriaxone (47.5%), ciprofloxacin (29.4%), gentamycin (25.4%) and imipenem (7.8%).

### 2.5 ExPEC-associated otitis media, meningitis and cholecystitis infection and antibiotic resistance

Ear infection is a common clinical problem throughout the world and the major cause of preventable hearing loss in the developing world [92]. Its chronic form is a serious problem in all age groups with less chance of recovery. In certain cases,

| Antibiotic | No. of isolate/study | Resistance % | Province | Reference |
|---|---|---|---|---|
| Cefotaxime | 32 | 62.5 | Babylon | [88] |
| | 51 | 86.2 | Wasit | [91] |
| Ceftriaxone | 32 | 50 | Babylon | [88] |
| | 51 | 45 | Wasit | [91] |
| Ciprofloxacin | 51 | 29.4 | Wasit | [91] |
| Gentamycin | 51 | 25.4 | Wasit | [91] |
| Imipenem | 32 | 15.6 | Babylon | [88] |
| | 51 | 0.0 | Wasit | [91] |

**Table 6.**
*Distribution of antibiotic resistance among Iraqi local cervicovaginal* E. coli.

| Antibiotic class | Genes | Province | Reference |
|---|---|---|---|
| Beta-lactamases | *blaCTX-M*, *blaSHV*, *blaOXA* | Wasit | [91] |

**Table 7.**
*Antibiotic resistance genes among Iraqi local cervicovaginal* E. coli.

this condition can lead to serious life-threatening complications, such as hearing impairment, brain abscesses or meningitis, mostly in childhood and late in life [93]. *E. coli* is one of the major causative agents of ear infection. The burden and prevalence of ear infection are more intense in developing countries due to the poor living standard and hygienic conditions along with a lack of proper nutrition. Increased antimicrobial resistance is one of the greatest global public health challenges, which has been accelerated by overprescription of antibiotics worldwide. Infection with antibiotic-resistant bacteria may cause severe illness, increased mortality rates and an increased risk of complications and admission to hospital and longer stay. *E. coli* was the most prevalent multi-antibiotic-resistant pathogenic bacteria isolated from suspected patient ear discharges with otitis media [94–96].

Gram-negative bacillary meningitis continues to be an important cause of mortality and morbidity (15% and 50%, respectively) throughout the world despite advances in antimicrobial chemotherapy and supportive care [97]. *E. coli* is the most common Gram-negative bacillary organism causing meningitis. Recent reports of *E. coli* strains producing CTX-M-type or TEM-type extended-spectrum β-lactamases create a challenge. *E. coli* meningitis follows a high degree of bacteremia and invasion of the blood-brain barrier [21, 98].

Cholecystitis is most often caused by gall stones. Gall stones are one of the most common disorders of the gastrointestinal tract. Bacterial infection accounts for 50–85% of the disease's onset. *Escherichia coli* was the main biliary pathogenic microorganism [99]. It is strongly associated with retrograde bacterial infection and is an inflammatory disease that can be fatal if inappropriately treated [100]. The resistance rate of Iraqi local *E. coli* isolated from otitis media, meningitis and cholecystitis to different antibiotic classes is summarized in **Table 8**. The resistance genes are listed in **Table 9**.

The average resistance rate is as follows: cefotaxime (72.57%), ceftriaxone (68.39%), ciprofloxacin (8.5%), gentamycin (42.46%) and imipenem (0%).

## 2.6 ExPEC-associated wound infection and antibiotic resistance

A wound can represent a simple or a severe disorder to an organ (such as the skin) or a tissue and can spread to other tissues and anatomical structures (e.g., subcutaneous tissue, muscles, tendons, nerves, vessels and even to the bone). Among all human body (HB) organs, the skin is without doubt the most exposed to impairment and injury, scratches and burns. By damaging the epithelium and connective structures, the HB's capability to provide protection from the outer environment is weakened [109]. An improper repair process can cause severe damage, like the loss of skin, initiation of an infection, with consequent harms to the subjacent tissues and even systemic ones. The most common and inevitable impediment to wound healing is the installation of an infection [110].

Skin and soft tissue infections (SSTIs) are one of the most common infections in patients of all age groups. The most common causative agents are *Staphylococcus aureus* and aerobic streptococci. However, several reports associating the *Escherichia coli* with SSTI have been published: *E. coli* was found to be the causative agent of neonatal omphalitis, cellulitis localized to lower or upper limbs, necrotizing fasciitis,

| Antibiotic | No. of isolate/study | Resistance % | Province | Reference |
|---|---|---|---|---|
| Cefotaxime | 93 | 100 | Anbar | [101] |
| | 22 | 76 | Najaf | [102] |
| | 2 | 100 | Baghdad | [103] |
| | 7 | 14.29 | Babylon | [104] |
| Ceftriaxone | 93 | 90.57 | Anbar | [101] |
| | 22 | 76 | Najaf | [102] |
| | 2 | 50 | Baghdad | [103] |
| | 7 | 57 | Babylon | [104] |
| Ciprofloxacin | 10 | 20 | Basra | [105] |
| | 93 | 98.11 | Anbar | [101] |
| | 22 | 76 | Najaf | [102] |
| | 5 | 0.0 | Tikrit | [106] |
| | 7 | 14.29 | Babylon | [104] |
| Levofloxacin | 22 | 62 | Najaf | [102] |
| Amikacin | 10 | 20 | Basra | [105] |
| | 22 | 14 | Najaf | [102] |
| | 2 | 0.0 | Baghdad | [103] |
| | 5 | 0.0 | Tikrit | [106] |
| Gentamycin | 10 | 20 | Basra | [105] |
| | 4 | 100 | Thi-Qar | [107] |
| | 22 | 44.8 | Najaf | [102] |
| | 2 | 50 | Baghdad | [103] |
| | 7 | 0.0 | Babylon | [104] |
| Imipenem | 22 | 0 | Najaf | [102] |

**Table 8.**
*Distribution of antibiotic resistance among Iraqi local* E. coli *associated with otitis media, meningitis and cholecystitis.*

| Antibiotic class | Genes | Province | Reference |
|---|---|---|---|
| Beta-lactamases | *acrAB* | Anbar | [101] |
| Quinolone | *gyrA*, *parC* | Anbar | [101] |
| Beta-lactamases | *blaCTX-M*, *blaSHV*, *blaOXA*, *blaTEM* | Najaf | [102] |
| Beta-lactamases | *blaCTX-M*, *blaSHV*, *blaOXA*, *blaTEM* | Al-Qadisiyah | [108] |

**Table 9.**
*Antibiotic resistance genes among Iraqi local* E. coli *associated with otitis media, meningitis and cholecystitis.*

surgical site infections, infections after burn injuries and others [111, 112]. Cellulitis due to *Escherichia coli* is rare and usually secondary to a cutaneous portal of entry. Skin and soft tissue infections (SSTIs) secondary to *E. coli* bacteremia have been reported exclusively in immunodeficient patients. The resistance rate of Iraqi local *E. coli* isolated from wound infection to different antibiotic classes is summarized in **Table 10**. The resistance genes are listed in **Table 11**.

| Antibiotic | No. of isolate/study | Resistance % | Province | Reference |
|---|---|---|---|---|
| Cefotaximes | 7 | 85 | Karbala | [113] |
| | 165 | 100 | Baghdad | [101] |
| | 2 | 90 | Anbar | [114] |
| | 9 | 33.33 | Karbala | [115] |
| | 4 | 100 | Baghdad | [116] |
| | 16 | 88.09 | Baghdad | [117] |
| | 51 | 74.5 | Najaf | [118] |
| Ceftriaxone | 7 | 77 | Karbala | [113] |
| | 165 | 90.57 | Baghdad | [101] |
| | 2 | 90 | Anbar | [114] |
| | 4 | 100 | Baghdad | [116] |
| | 7 | 100 | Erbil | [119] |
| | 19 | 83.8 | Erbil | [120] |
| | 15 | 75 | Erbil | [121] |
| | 51 | 68.6 | Najaf | [118] |
| Ciprofloxacin | 7 | 42 | Karbala | [113] |
| | 165 | 98.11 | Baghdad | [101] |
| | 2 | 20 | Anbar | [114] |
| | 9 | 100 | Karbala | [115] |
| | 4 | 50 | Baghdad | [116] |
| | 7 | 85.8 | Erbil | [119] |
| | 16 | 73.8 | Baghdad | [117] |
| | 19 | 54.4 | Erbil | [120] |
| | 15 | 16.66 | Erbil | [121] |
| | 51 | 35.2 | Najaf | [118] |
| | 28 | 85.7 | Diyala | [122] |
| Levofloxacin | 2 | 20 | Anbar | [114] |
| | 4 | 0.0 | Baghdad | [116] |
| | 7 | 85.8 | Erbil | [119] |
| | 16 | 73.8 | Baghdad | [117] |
| | 15 | 17.7 | Erbil | [121] |
| Amikacin | 2 | 20 | Anbar | [114] |
| | 9 | 22.22 | Karbala | [115] |
| | 4 | 75 | Baghdad | [116] |
| | 7 | 14.2 | Erbil | [119] |
| | 19 | 1.9 | Erbil | [120] |
| | 15 | 18.33 | Erbil | [121] |
| | 51 | 39.2 | Najaf | [118] |

| Antibiotic | No. of isolate/study | Resistance % | Province | Reference |
|---|---|---|---|---|
| Gentamycin | 7 | 55 | Karbala | [113] |
| | 2 | 90 | Anbar | [114] |
| | 9 | 66.67 | Karbala | [115] |
| | 7 | 57.1 | Erbil | [119] |
| | 16 | 35.71 | Baghdad | [117] |
| | 19 | 40.6 | Erbil | [120] |
| | 15 | 25 | Erbil | [121] |
| | 51 | 78.4 | Najaf | [118] |
| | 28 | 64.3 | Diyala | [122] |
| Imipenem | 2 | 10 | Anbar | [114] |
| | 9 | 22.2 | Karbala | [115] |
| | 4 | 0.0 | Baghdad | [116] |
| | 7 | 0.0 | Erbil | [119] |
| | 16 | 4.76 | Baghdad | [117] |
| | 19 | 1.25 | Erbil | [120] |
| | 15 | 5 | Erbil | [121] |
| | 51 | 0.0 | Najaf | [118] |

**Table 10.**
*Distribution of antibiotic resistance among Iraqi local* E. coli *associated with wound infections.*

| Antibiotic class | Genes | Province | Reference |
|---|---|---|---|
| Beta-lactamases | *blaNDM-1* | Baghdad | [123] |
| Carbapenem | *blaIMP* | Baghdad | [124] |
| Beta-lactamases | *blaNDM-1* | Basra | [125] |
| Beta-lactamases | *blaCTX-M* | Erbil | [121] |
| Beta-lactamases | *blaTEM*, *blaSHV*, *blaOXA51* | Babylon | [126] |

**Table 11.**
*Antibiotic resistance genes among Iraqi local* E. coli *associated with wound infections.*

The average resistance rate is as follows: cefotaximes (81.56%), ceftriaxone (85.62%), ciprofloxacin (60.15%), levofloxacin (39.54%), amikacin (27.26%), gentamycin (56.97%) and imipenem (5.4%).

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