UMSHA Press

AJCMI
Avicenna Journal of Clinical Microbiology and Infection

Avicenna J Clin Microbiol Infect. 2026;13(1):49-59. doi:10.34172/ajcmi.3683

http://ajcmi.umsha.ac.ir

Review Article

Pathogenic *Escherichia coli* O-serogroups: A Link Between Virulence Gene, Immune Evasion, and Antimicrobial Resistance

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Article history:
Received: May 17, 2025
Revised: June 5, 2025
Accepted: June 8, 2025
ePublished: February 23, 2026

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Abstract

Background: *Escherichia coli* is a common intestinal commensal that includes pathogenic strains responsible for sepsis, gastrointestinal infections, and urinary tract infections (UTIs). Its diverse pathotypes, virulence factors, and O-serogroups contribute to its clinical significance. The emergence of multidrug-resistant (MDR) strains has complicated treatment strategies, representing a critical global health concern.

Methods: A literature search was conducted on PubMed, Scopus, and Google Scholar using the keywords *E. coli*, pathogenicity, O-serogroups, immune evasion, and antibiotic resistance to identify peer-reviewed English-language studies. Included were studies focusing on *E. coli* virulence, immune evasion, and MDR, while non-English studies, case reports, and editorials were excluded.

Results: Our analysis indicates that O-serogroups O25, O78, O145, and O157 are predominantly associated with MDR profiles, especially against β-lactams and aminoglycosides. This high prevalence of MDR in these serogroups significantly complicates clinical management, often leading to prolonged hospital stays, increased treatment failures, and higher rates of severe complications such as hemolytic uremic syndrome (HUS) in EHEC infections or recurrent UTIs in UPEC cases. For instance, resistance of O25 to β-lactams, observed in 92% of isolates for piperacillin, limits the efficacy of first-line therapies and necessitates the use of last-line antibiotics such as carbapenems, which may increase healthcare costs and the risk of further resistance development. The high resistance rates in these serogroups are attributed to O-antigen variability and the horizontal transfer of resistance determinants.

Conclusion: This study underscores the clinical significance of O-serogroup diversity in *E. coli* infections and its impact on therapeutic challenges. Understanding the distribution of virulence factors and resistance genes among key serogroups provides critical insights for developing effective management strategies for MDR *E. coli* infections. Future research should prioritize innovative therapeutic approaches targeting serogroup-specific resistance mechanisms.

Keywords: *Escherichia coli*, O-serogroups, Virulence factors, Immune evasion, Antibiotic resistance

Please cite this article as follows: Karimbakhsh M, Fatemi A, Abbasi M, Sojoudi Masuleh R, Khakpour N, Kazemi A, et al. Pathogenic *Escherichia coli* O-serogroups: a link between virulence gene, immune evasion, and antimicrobial resistance. Avicenna J Clin Microbiol Infect. 2026;13(1):49-59. doi:10.34172/ajcmi.3683

Introduction

Escherichia coli is an opportunistic pathogen commonly found in the human intestinal tract and is capable of causing infections such as urinary tract infections (UTIs), gastrointestinal diseases, and sepsis (1-4). Uropathogenic *E. coli* (UPEC), the leading cause of both uncomplicated and complicated UTIs, employs immune evasion strategies to persist in the urinary tract, contributing to recurrent infections and antimicrobial resistance. Over time, UPEC evolutionary adaptations have resulted in sophisticated

mechanisms that facilitate colonization of the urinary tract, enable invasion of host tissues, and promote survival within intracellular environments, resulting in high recurrence rates and multidrug resistance (MDR) in clinical isolates (4,5).

Escherichia coli employs various strategies, including capsule production and protein secretion, to evade complement-mediated immune responses, thereby enhancing its survival and contributing to severe outcomes like sepsis (6-8). UPEC also resists zinc-mediated innate immunity, enabling it to survive and multiply within the host, which facilitates its dissemination throughout the body (9). *E. coli* strains are classified based on their O-antigen. Pathogenic *E. coli* variants, such as enteroaggregative *E. coli* (EAEC), enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), and Shiga toxin-producing *E. coli* (STEC), cause gastrointestinal and systemic diseases, particularly in children, with some serogroups linked to hemolytic uremic syndrome (HUS) (10-14). However, the interplay between serogroup diversity, immune evasion mechanisms, and MDR remains poorly understood, limiting the development of effective interventions. While previous reviews have addressed *E. coli* pathotypes or resistance patterns separately, few have integrated O-serogroup diversity with immune evasion and MDR to provide a comprehensive molecular perspective.

This study synthesizes current findings on O-serogroup-specific resistance (e.g., O25, O78, O145, O157), immune evasion mechanisms, and their interplay to guide targeted diagnostics and therapies for MDR *E. coli* infections. Notably, *E. coli* serogroups O145 and O78 in avian pathogenic *E. coli* (APEC) have demonstrated an alarming rise in MDR, complicating treatment strategies (15). Given the importance of these factors in *E. coli* pathogenicity and antimicrobial resistance, this study sought to review and evaluate the most recent findings regarding *E. coli* interactions with both innate and adaptive immunity. By clarifying the complex relationship between *E. coli* and host immunity, this study aimed to inform future research and guide the development of effective treatment strategies. By integrating O-serogroup diversity, immune evasion mechanisms, and MDR patterns, this review provides a novel framework for understanding *E. coli* pathogenicity and informs innovative approaches to combat resistant infections.

Pathotypes, Serogroups, Virulence Factors, and Clinical Manifestations of *E. coli*

Escherichia coli pathotypes are classified based on their virulence factors, infection mechanisms, tissue tropism, and interactions with the host, resulting in a wide range of clinical outcomes. These pathotypes include: (i) EPEC, causing diarrhea by disrupting intestinal cell structure; (ii) ETEC, associated with watery diarrhea via toxin production; (iii) EAEC, causing persistent diarrhea through biofilm formation; (iv) STEC/Enterohemorrhagic *E. coli* (EHEC), leading to bloody diarrhea and HUS; (v) Enteroinvasive *E. coli* (EIEC), causing dysentery-like symptoms; (vi) Adherent-invasive *E. coli* (AIEC), associated with Crohn's disease; (vii) Diffusely adherent *E. coli* (DAEC), inducing diarrhea primarily in pediatric populations; (viii) UPEC, the main cause of UTIs; and (ix) Neonatal meningitis *E. coli* (NMEC), a key cause of neonatal meningitis (16-23).

EPEC, a major cause of diarrheal pathogens in infants, can lead to acute or chronic infections lasting more than two weeks, often with vomiting and fever in pediatric patients and abdominal discomfort in adults, potentially leading to life-threatening secretory diarrhea. Infection triggers inflammation and alters gut function, thereby contributing to disease severity (24-27). Cystitis, the most common manifestation of UPEC infections, presents with urinary frequency, dysuria, hematuria, and suprapubic pain (28). Furthermore, this pathotype may cause pyelonephritis, characterized by fever, flank pain, nausea, vomiting, and fatigue (29). EHEC infection typically begins with watery diarrhea, which may progress to hemorrhagic colitis (HC). In approximately 5%-15% of cases, particularly in children and the elderly, this can lead to HUS, characterized by non-immune hemolytic anemia, thrombocytopenia, and acute renal failure. Severe abdominal cramps are frequently observed, and patients may show altered consciousness, seizures, or other neurological symptoms associated with HUS (30-34). See Table 1 for an overview of *E. coli* pathotypes, serogroups, virulence factors, and their abbreviations.

Comparison of Antibiotic Resistance and O-serogroup in *E. coli* Isolates

Certain *E. coli* O-serogroups, such as O25 and O15, are associated with systemic infections (40,75). The O-antigen is a key biomarker for classifying *E. coli* strains, with over 181 O-antigen groups identified to date, including O25, O22, O21, O18, O16, O15, O8, and O1, which are often associated with UTIs. Their prevalence varies geographically, necessitating the collection of region-specific resistance data for effective UTI treatment strategies. Penicillins and cephalosporins exhibit high resistance rates globally. Notably, 94% of the studied *E. coli* strains exhibited MDR, with greater resistance rates reported in male and elderly patients. Serogroups O15, O8, and O25 showed resistance to at least one antibiotic, including imipenem. Imipenem resistance was detected in serogroups O2, O8, O15, and O25.

Despite increasing resistance, carbapenems (e.g., imipenem 5%, meropenem 3%) and aminoglycosides (e.g., amikacin 11%) remain among the most effective treatments for resistant UTI cases, consistent with global resistance patterns. Among the UPEC isolates, serogroups O8 and O25 were the most commonly isolated MDR strains, whereas serogroups O75 and O18 exhibited comparatively lower resistance levels (76). High resistance rates were observed for penicillins and cephalosporins,

Table 1. Pathotypes, Serogroups, Virulence Factors, and Clinical Manifestations of *E. coli*

Pathotype	Serogroup	Virulence Factor	Clinical Presentation	Reference(s)
UPEC	O1, O2, O4, O6, O7, O8, O15, O16, O19, O21, O75, O18, O22, O25, O83	*faeD, faeI, iroN, sigA, Pap, cnf1, afa, iuc, PapG, iha, usp, faeC, faeG, nlpI, sitA, terC, yfcV, ompT, irp2, gad, fdeC, vat, cva*	UTIs (Cystitis, Pyelonephritis)	(28,35,36)
EHEC (STEC)	O26, O45, O55, O91, O103, O104, O111, O113, O121, O128, O145, O146, O157	*Saa, sab, toxB, nleB, nleH, nleE, bleG, yad, yeh, csgA, fimA, bcsA, ehA, stx1, stx2*	Bloody diarrhea, HUS	(30,37-39)
EIEC	O28, O112, O152, O167	*ipaH, Sen, virF, invE,* Sat*, sigA, sepA, ial, ms06, ms07*	Dysentery-like symptoms	(40-43)
ETEC	O6, O7, O8, O9, O11, O15, O17, O20, O21, O25, O27, O29, O48, O56, O63, O64, O65, O71, O73, O77, O78, O149, O167	*CS22, tia, tibA, tibC, tufa, eltB, leoA, estP, yghJ, eatA, rpoS*	Gastrointestinal disorders in children from low- and middle-income countries, severe aqueous diarrhea exhibiting cholera-like symptoms, and etiological factors contributing to diarrheal diseases in both developing and industrialized nations	(40,44-49)
EAEC	O3, O7, O9, O15, O44, O51, O77, O86, O111, O126, O127, O144	*aar, aaiC, aap, aatA, aggA, aafA, ORF3, ORF4, capU, air, pet, pic, sat, astA, celB*	Persistent diarrhea	(40,44,45,50)
DAEC	N/A	*Iss, kpsMII, fyuA, iutA, aggR, est, astA, elt*	Watery diarrhea in children	(51-53)
NMEC	O1, O2, O6, O18, O75	*Mat, irp, iroN, traT, KpsMII, ompA, iss, cvaC, colv, sfa, fim, ehaB, cah, vat, ibeA, chuX, chuY*	Neonatal meningitis	(54-57)
EPEC	O39, O38, O103, O145, O157, O158, O111, O114, O119, O86	*Bfp, eae, tir, lifA, csgA, fimA, espA-D, MAP, nleA, nleF, cif*	Infantile diarrhea	(24-27,38,58,59)
MAEC	O5, O15, O48, O54, O132, O139, O149	*kpsCS, znuABC, ChiA, sfa, traT, papC*	Meningitis complications	(60-65)
APEC	O1, O2, O35, O78	*iucD, iucT, aerJ, fyuA, irp2, eitABCD, bfr, iroBCDEN*	Avian colibacillosis	(63,66-72)
SEPEC	O1, O2, O78	*Cnf, cdt, iss, cvaC, colv, KpsMII, KpsMI-neuA, traT, iroN, ibeA, B, C, crl, csg, pap, fim*	Sepsis symptoms	(54,73,74)

Note. E. coli: *Escherichia coli*; UPEC: Uropathogenic *E. coli*; UTI: Urinary tract infection; EHEC: Enterohemorrhagic *E. coli*; STEC: Shiga toxin-producing *E. coli;* HUS: Hemolytic uremic syndrome; EIEC: Enteroinvasive *E. coli*; ETEC: Enterotoxigenic *E. coli*; EAEC: Enteroaggregative *E. coli*; DAEC: Diffusely adherent *E. coli*; NMEC: Neonatal meningitis *E. coli*; MAEC: Meningitis-associated *E. coli;* APEC*:* Avian pathogenic *E. coli;* SEPEC: Sepsis-associated *E. coli;* N/A: Not found.

with resistance rates of 92% for piperacillin, 91% for ticarcillin, and 88% for amoxicillin-clavulanic acid, as illustrated in Figure 1. Fluoroquinolone resistance was also significant, with ciprofloxacin showing a resistance rate of 27%, while aminoglycosides (e.g., amikacin 11%) remained more effective (76,77).

Several studies analyzed *E. coli* blood samples from patients aged over 60 years with bacteremia. A Japanese study (2015–2017) identified *E. coli* serotypes with high MDR prevalence, evaluating the antimicrobial susceptibility of 401 extraintestinal pathogenic *E. coli* (ExPEC) isolates against 21 antibiotics. UPEC serogroups O4 and O21 exhibited high resistance rates, whereas O75, O18, and O1 showed lower levels of resistance. O25B was the most prevalent MDR strain in bacteremic ExPEC cases, especially among elderly patients (76,78). Another study examined blood isolates collected during five retrospective observational studies conducted across Europe, North America, Asia-Pacific, and South America from 2011 to 2017. Analysis of resistance to last-line antibiotics revealed that colistin resistance was 0.7%, and carbapenem resistance ranged from 0.1% to 0.2%. Among these isolates, 31.6% were O25, and 42.9% were carbapenem-resistant, as depicted in Figure 2 (79). APEC O1 and O78 demonstrated susceptibility to

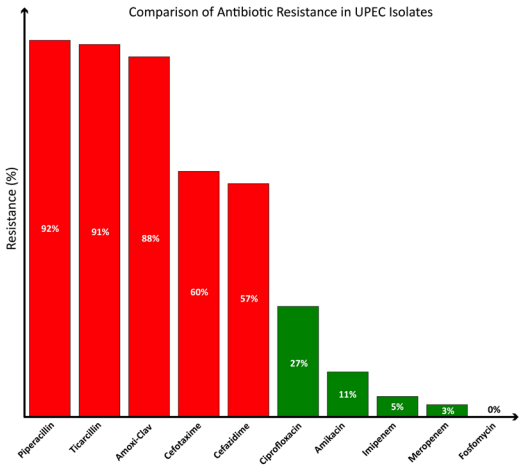

Figure 1. Comparison of Antibiotic Resistance in UPEC Isolates. Note. UPEC: Uropathogenic *E. coli*. The bar chart represents the percentage of resistance to various antibiotics among UPEC isolates. High resistance is observed for β-lactam antibiotics such as piperacillin (92%), ticarcillin (91%), and amoxicillin-clavulanate (88%), whereas fosfomycin shows no resistance (0%)

ciprofloxacin, azithromycin, and nalidixic acid (80), as seen in Table 2. Unlike UPEC, which showed high resistance to cephalosporins and fluoroquinolones, most APEC serogroups remain susceptible to fluoroquinolones,

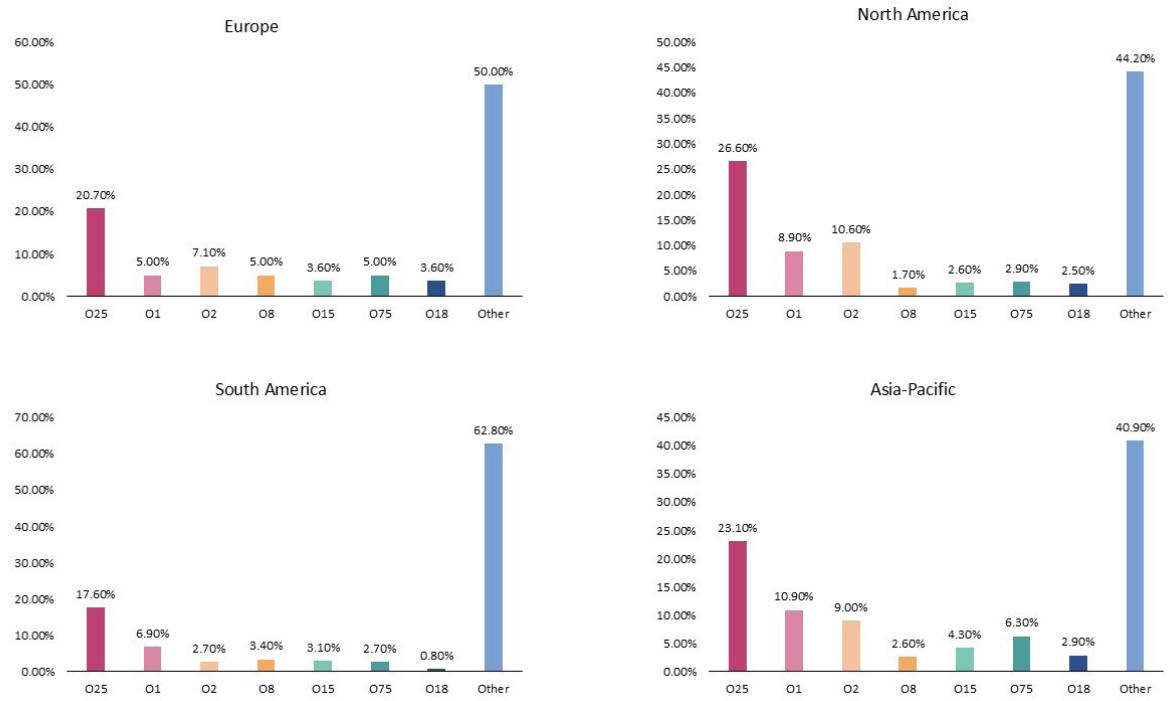

Figure 2. Geographic Distribution of *Escherichia coli* Serogroups. The bar charts depict the prevalence of different *E. coli* serogroups across Europe, North America, South America, and the Asia-Pacific region. Among the identified serogroups, O25 exhibited the highest frequency across all regions. Additionally, a substantial proportion of isolates were categorized as "Other", with the highest percentages observed in South America (62.8%) and Europe (50%)

except O7:H18, which displays extensive MDR.

Table 2 summarizes the resistance and susceptibility profiles of various *E. coli* O-serogroups to commonly used antibiotics. High resistance rates were observed for tetracycline, ampicillin, cefotaxime, and trimethoprim-sulfamethoxazole in many serogroups. In contrast, imipenem, meropenem, gentamicin, and amikacin generally maintained considerable susceptibility. These resistance patterns indicate the prevalence of MDR strains, which can significantly impact the therapeutic management of infections caused by these serogroups.

Immune System Evasion in E. coli

Escherichia coli employs diverse strategies to evade both innate and adaptive immune responses, enabling persistent infections and complicating clinical management (118,119).

Adaptive Immune Cell Functions

Adaptive immunity begins when T and B lymphocytes detect foreign antigens, leading to antibody production by B cells, cytotoxic responses by T cells, and immune regulation by helper T cells. Memory cells then provide long-term protection against recurrent infections (120). T cell activation occurs when T cell receptors (TCRs) interact with peptide-MHC complexes presented by antigen-presenting cells (APCs). CD8+cytotoxic T lymphocytes (CTLs) target intracellular pathogens through MHC class I, whereas CD4+helper T cells respond to extracellular pathogens via MHC class II. Additionally, memory CD8+T cells contribute to long-term immunity.

CTLs eliminate infected cells through the release of inflammatory cytokines, Fas-FasL-mediated apoptosis, and secretion of perforin and granzyme, whereas CD4+T cells differentiate into subtypes (e.g., Th1, Th17) to coordinate immune responses (121). Th1 cells promote CD8+T cell activation via Interleukin-2 (IL-2), while Th17 cells secrete IL-17, IL-22, and TNF-α to defend against extracellular bacterial infections. γδ T cells secrete pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and IL-17, which play a protective role against infection. Regulatory T cells (Tregs) help maintain immune homeostasis by suppressing excessive immune responses and facilitating inflammation resolution following infection (122).

Evasion of Innate Immune Responses

Innate immunity, including phagocytosis, complement activation, and antimicrobial peptides, serves as the first line of defense against *E. coli* (123). Pathogenic strains have developed various mechanisms to counteract these responses, thereby enhancing their survival within the host (118).

Complement System and Evasion

The complement system, a key component of innate immunity, lyses bacterial cells, enhances phagocytosis, and promotes inflammation (124). These pathways converge at the terminal stage, leading to the formation of the membrane attack complex, which disrupts bacterial cell membranes and induces osmotic lysis (125). *E. coli* evades

Table 2. Antibiotic Resistance and Susceptibility Patterns Among *E. coli* O-Serogroups

O-Serogroup	Resistant Antibiotics (%)	Susceptible Antibiotics (%)	Reference
O1	Tetracycline (100), Amoxicillin (100), Co-amoxiclav (84), Cefazolin (87), Cefotaxime (60), Ceftazidime (57), Cotrimoxazole (78), Ciprofloxacin (70)	Fosfomycin (100), Imipenem (97), Meropenem (97)	(77)
O2	Imipenem (5), Cefotaxime (less than 2), Meropenem (1.3)	Tetracyclines (94.12), Ampicillin (83.01), Nalidixic acid (98.7)	(76,81,82)
O4	Piperacillin (92), Tetracycline, Kanamycin, Neomycin, Streptomycin, Erythromycin	Imipenem, Amikacin, Rifampicin, Fosfomycin, Colistin, Gentamicin	(76,83,84)
O7	Ampicillin, Cefotaxime, Imipenem, Amikacin, Tetracycline, Kanamycin, Neomycin, Cephalothin, Streptomycin, Erythromycin	Ciprofloxacin (100), Azithromycin (100), Nalidixic acid (100), Levofloxacin (56.7)	(85-89)
O8	Piperacillin (92), Ampicillin (47.46), Streptomycin (44.07), Tetracycline (42.37), Cefotaxime, Ceftazidime	Amikacin (98.31), Imipenem (5), Doxycycline (96.61), Ofloxacin (94.92)	(90,91)
O15	Nalidixic acid (98.7), Ampicillin (97.3), Amoxicillin-Clavulanate (96), Fluoroquinolones (92), Cefotaxime (High resistance noted in UPEC)	Piperacillin-Tazobactam (13.3), Nitrofurantoin (5.3), Meropenem (1.3), Imipenem (susceptible in UPEC strains)	(91,82)
O18	Piperacillin (92 in UPEC strains), Oxytetracycline (73.75), Tetracycline (71.25), Erythromycin (65), Enrofloxacin (7.5), Florfenicol (7.5), Norfloxacin (2.5)	Imipenem (87.7), Gentamicin (86), Cefepime (83.7), Colistin (19/3217 in ExPEC strains)	(76,92-94)
O21	Piperacillin (92), Cefotaxime (100), Amoxicillin/Clavulanic Acid (46), Nalidixic acid (33.7), Ampicillin (27.7), Tetracycline (100)	Imipenem (95), Meropenem (83), Nitrofurantoin (82.7), Gentamicin (86)	(76, 95, 96)
O22	Ampicillin, Tetracycline (up to 100), Nalidixic acid (up to 99), Enrofloxacin (82), Trimethoprim-sulfamethoxazole (82)	Amikacin (100), Gentamicin (64)	(76,94,97)
O25	Ampicillin (83.7), Piperacillin (53.8), Fluoroquinolones (55.5-60.6), Trimethoprim/Sulfamethoxazole (56.4), Cefotaxime (100 in ESBL strains)	Imipenem (80-92), Amikacin, Gentamicin (84-100), Ciprofloxacin (51.25 in ESBL strains)	(91, 97-101)
O26	Erythromycin (100), Gentamicin (98), Streptomycin (82), Kanamycin (76), Ampicillin (72), Dihydrostreptomycin (54.5), Oxytetracycline (45.5)	Ampicillin (65), Enrofloxacin, Spectinomycin, Neomycin	(102-105)
O35	Tetracycline (100), Ampicillin (89), Nalidixic acid (99), and trimethoprim-sulfamethoxazole (82), Streptomycin, Erythromycin, Neomycin	Amikacin (100), Gentamicin (64), and Colistin (100 resistance), Chloramphenicol (87)	(89, 94,97,106)
O46/O134	Kanamycin and Cephalexin (100)	Ampicillin (65), Nitrofurantoin, Meropenem	(82,105, 107)
O75	Piperacillin (92), Ampicillin (27.7), Tetracycline (100), Nalidixic acid (99)	Imipenem (95), Gentamicin (86), Meropenem (83)	(76,94,95)
O78	Ampicillin (100), Oxytetracycline (94.12), Trimethoprim-sulfamethoxazole (78.5), Ampicillin-sulbactam (78.4), Ceftazidime (75.5), Cefepime (74), Ceftriaxone (65.3), Ciprofloxacin (47.8), Gentamicin (29), Levofloxacin (28.8) Cefazolin (17.5), Meropenem (9.5), Tobramycin (9), Amikacin (5)	Gentamicin (98), Chloramphenicol (87), Colistin sulfate (100)	(81,95,108)
O83	Tetracycline (up to 100), Ampicillin (up to 89), trimethoprim-sulfamethoxazole (up to 82), Piperacillin (92)	Ciprofloxacin (94.64), Gentamicin (91.07), Imipenem (95), Amikacin	(76,95,109)
O86	Ampicillin, Tetracycline, Nalidixic acid, and Cefuroxime (100), Trimethoprim-Sulfamethoxazole (78.5), Ampicillin-Sulbactam (78.4), Ceftazidime (75.5), Cefepime (74), Ceftriaxone (65.3), Ciprofloxacin (47.8), Gentamicin (29), levofloxacin (28.8) Cefazolin (17.5), Meropenem (9.5), Tobramycin (9), Amikacin (5)	Ofloxacin, Ciprofloxacin, and Gentamicin	(110,111)
O145	Erythromycin (100), Gentamicin (98), Tetracycline (90), Oxytetracycline (100), Ampicillin (72), Streptomycin (82), Kanamycin (76), Ceftiofur (90.6), Cefotaxime (50.4), Nalidixic Acid (37), Trimethoprim-Sulfamethoxazole (42.1)	Ampicillin (35)	(102,104,112)
O157	Tetracycline (100), Oxytetracycline (100), Ampicillin (100), Chloramphenicol (94.7-97.6), Erythromycin (89.5-40), Gentamicin (56), Cephalothin (42), Cefuroxime (56), Ceftazidime (35)	Ciprofloxacin, Norfloxacin, Ofloxacin (100), Cefuroxime (100 in some studies)	(113-117)

Note. *E. coli: Escherichia coli;* UPEC: Uropathogenic *E. coli*. APEC: Avian Pathogenic *E. coli;* ESBL: Extended-spectrum beta-lactamase.

complement-mediated destruction by exploiting host regulators such as Factor H (FH) and C4b-binding protein (C4bp) (126, 127). Capsules, complement-inactivating proteases, and outer membrane proteins enhance bacterial virulence (128). In ExPEC, the K1 capsule binds FH to inhibit the alternative pathway, while K2 and K54 capsules confer serum resistance (127). EspP cleaves C3, C3b, and C5, while *Pic* protease cleaves C3, C4, and C2 (129, 130). The *StcE* protease produced by *E. coli* O157:H7 binds to the C1-inhibitor (C1-INH) to inhibit classical pathway activation (131, 132). The *Prc* protease enhances serum resistance in *ExPEC* (133), while *OmpA* and *NlpI* recruit C4bp to block the classical pathway (134). During STEC-HUS, Shiga toxins (*Stxs*) exacerbate immune evasion by disrupting FH function (118). These strategies collectively enhance *E. coli*'s resilience against complement-mediated

killing and complicate therapeutic outcomes.

Avoidance of Phagocytosis

Escherichia coli strains, particularly UPEC and APEC, produce surface structures such as capsules and polysaccharide layers that inhibit phagocytic uptake by neutrophils and macrophages (118).

Bacterial Evasion Mechanisms of Adaptive Immunity

Escherichia coli evades adaptive immunity by disrupting T cell activation through impairment of the immunological synapse (IS) between T cells and APCs. It further disables APCs by downregulating MHC class II expression, interfering with antigen processing, and degrading co-stimulatory ligands (119). In EPEC and EHEC, the locus of enterocyte effacement (LEE) encodes 41 genes, including five Type III Secretion System (T3SS) effectors (Tir, Map, EspF, EspH, and EspZ), which modulate host cell functions. For example, EspZ inhibits apoptosis, and its secretion along with other effectors is critical during the early stages of infection (123). Additionally, Z3495, a LysR-type transcriptional regulator, enhances LEE gene expression and promotes bacterial adherence to epithelial surfaces (132). *E. coli* employs sophisticated strategies to subvert adaptive immunity, mainly by disrupting T cell activation and antigen presentation. Notably, Tir in EHEC acts as a receptor for the bacterial adhesin intimin, triggering actin polymerization and forming attaching and effacing (A/E) lesions. Additionally, Tir suppresses host immunity by recruiting Src Homology Phosphatase-1 (SHP-1) via a tyrosine-based inhibitory motif (ITIM)-dependent phosphorylation mechanism. This leads to TGF-β Activated Kinase 1 (TAK1) dephosphorylation and subsequent downregulation of pro-inflammatory responses (133,134). This T3SS-mediated pathogenesis, including the A/E lesion formation and immune suppression, is illustrated in Figure 3. This suppression of inflammatory responses by Tir exacerbates EHEC infections, contributing to severe outcomes such as HC and HUS. It delays immune clearance, allowing prolonged bacterial persistence in the host (135). Moreover, T3SS-mediated delivery of effectors such as EspF and EspH disrupts epithelial integrity, thereby increasing the risk of systemic dissemination and complications like sepsis, particularly in vulnerable populations (136).

Figure 3 illustrates T3SS-mediated delivery of virulence factors (e.g., Tir, EspF), which facilitate the formation of A/E lesions and suppress host immune responses. Shiga toxins (STX1, STX2) contribute to the development of HUS and HC by damaging renal endothelial cells.

Antigenic Variation

Escherichia coli uses antigenic variation to evade immune recognition by altering surface molecules. It shifts antigen expression via a single locus containing multiple silent gene copies (137). The O-antigen of Lipopolysaccharide exhibits extensive structural diversity in its sugar composition. As

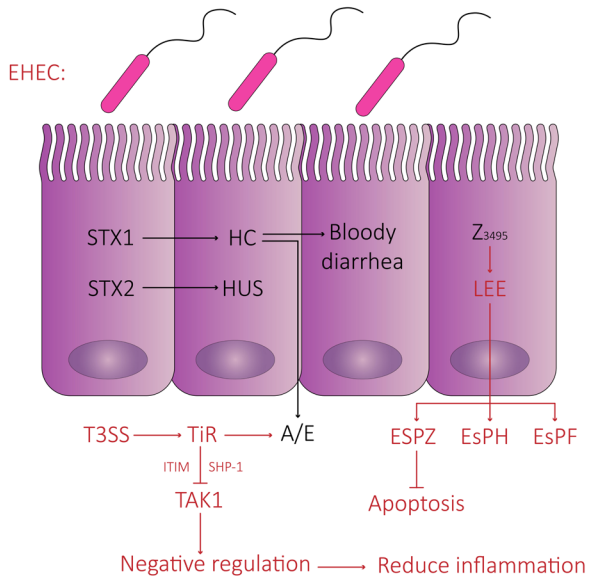

Figure 3. Schematic Representation of EHEC Pathogenesis. *Note.* EHEC: Enterohemorrhagic *E. coli*

a surface-exposed molecule, it is highly immunogenic. In *E. coli*, O-antigen synthesis relies on genes at the *galF-gnd* locus, with homologous recombination driving antigenic variation (138,139).

Conclusion

This review integrates molecular perspectives on *E. coli* pathogenesis, emphasizing the pivotal contributions of O-serogroup variability, MDR, and immune evasion strategies in determining infection severity. The high prevalence of MDR in serogroups such as O25, O78, O145, and O157, with resistance rates up to 95% for β-lactams, exacerbates treatment failures, prolongs hospitalization, and increases the risk of severe complications such as HUS and recurrent UTIs (137). Similarly, immune evasion mechanisms, including T3SS-mediated immune suppression through Tir and antigenic variation, hinder immune clearance and promote persistent infections and systemic complications such as sepsis in vulnerable patients (138). These findings highlight the significant clinical challenges, as MDR and immune-evading *E. coli* strains often resist both conventional antibiotic treatments and innate immune responses.

To address these issues, operational strategies for infection control are essential. Hospitals should implement rapid diagnostic techniques to identify high-risk MDR pathogens, enabling targeted antibiotic stewardship and reducing inappropriate therapy (140). The integration of advanced surveillance systems with rigorous hygiene measures can curb the nosocomial transmission of APEC and UPEC strains, especially in intensive care units. Sustainable solutions require continued research into innovative therapeutic strategies such as targeting effectors like Tir or EspF with small-molecule inhibitors to enhance immune clearance and reduce the incidence of HUS (137). These strategies, grounded in molecular

insights, offer a promising roadmap for improving clinical outcomes and addressing the growing threat of MDR *E. coli* infections.

Acknowledgements

The author would like to thank the faculty of Mazandaran University of Medical Sciences for their academic support.

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Competing Interests

Authors declare no conflict of interests.

Consent for Publication

Not applicable.

Data Availability Statement

Not applicable. No new datasets were generated or analyzed in this review.

Ethical Approval

Not applicable. This review article does not involve any human participants, human data, or human tissue.

Funding

No funding or sponsorship was received for this study or the publication of this article.

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