REVIEWS

Review
https://doi.org/10.36233/0372-9311-410

A modern view of diarrheagenic *Escherichia coli* — a causative agent of acute intestinal infections

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Abstract

Acute intestinal infections caused by *Escherichia coli* affect the gastrointestinal tract, leading to development of diarrheal syndrome, intoxication, and, in some cases, generalization of the pathological process. Diarrheagenic *E. coli* (DEC) strains differ from non-pathogenic (commensal) strains by the presence of specific virulence genes, pathogenesis characteristics, clinical and epidemiological manifestations of the diseases they cause. Based on the virulence determinants, 6 pathogenic DEC groups are distinguished: enteropathogenic, enterotoxigenic, enteroinvasive, shiga toxin-producing, enteroaggregative, diffusely adherent *E. coli* strains. The strains of each pathogenic group have distinct pathogenic mechanisms responsible for inflammatory processes in different compartments of the human intestine, which are clinically manifested as diarrheal syndrome. This paper presents a review of current scientific publications on epidemiology, pathogenesis, genetic properties, and antigenic characteristics of pathogenic *E. coli.* Although DEC biological properties have been extensively studied, many aspects require deeper insights to develop effective laboratory-based diagnostic techniques, treatment methods, epidemic control measures, and prevention strategies against *E. coli* infections.

Keywords: *review, diarrhea, acute intestinal infections, E. coli infections, diarrheagenic Escherichia coli, pathogenicity*

Funding source. This study was not supported by any external sources of funding.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

For citation: Makarova M.A. A modern view of diarrheagenic *Escherichia coli* — a causative agent of acute intestinal infections. *Journal of microbiology, epidemiology and immunobiology.* 2023;100(4):333–344.
DOI: https://doi.org/10.36233/0372-9311-410. EDN: https://www.elibrary.ru/rnmhnb

Научный обзор
https://doi.org/10.36233/0372-9311-410

Современное представление о диареегенных *Escherichia coli* — возбудителях острых кишечных инфекций

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Аннотация

Острые кишечные инфекции, обусловленные *Escherichia coli*, характеризуются поражением желудочно-кишечного тракта с развитием диарейного синдрома, интоксикации и в некоторых случаях генерализации патологического процесса. Диареегенные *E. coli* (DEC) отличаются от непатогенных (комменсальных)

DOI: https://doi.org/10.36233/0372-9311-410

штаммов наличием определённых генов вирулентности, особенностями патогенеза и клинико-эпидемиологическими проявлениями вызываемых ими заболеваний. В соответствии с детерминантами вирулентности выделяют 6 патогенных групп DEC: энтеропатогенные, энтеротоксигенные, энтероинвазивные, шигатоксин-продуцирующие, энтероагрегативные, диффузно-адгерентные. Штаммы каждой группы характеризуются конкретными патогенетическими механизмами, обеспечивающими развитие воспалительного процесса в разных отделах кишечника человека, клинически проявляющегося диарейным синдромом. В статье представлен обзор современной научной литературы по эпидемиологии, патогенезу, генетическим свойствам и антигенной характеристике патогенных *E. coli.* Несмотря на многолетнее и разностороннее изучение биологических свойств DEC*,* многие аспекты биологии этого вида требуют более углублённого анализа знаний, необходимых для разработки эффективных методов лабораторной диагностики, лечения, проведения противоэпидемических мероприятий и профилактики эшерихиозов.

Ключевые слова: *обзор, диарея, острые кишечные инфекции, эшерихиозы, диареегенные Escherichia coli, патогенность*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Для цитирования: Макарова М.А. Современное представление о диареегенных *Escherichia coli* — возбудителях острых кишечных инфекций. *Журнал микробиологии, эпидемиологии и иммунобиологии.* 2023;100(4): 333–344. DOI: https://doi.org/10.36233/0372-9311-410. EDN: https://www.elibrary.ru/rnmhnb

Introduction

According to the World Health Organization (WHO)[1] and the United Nations Children's Fund[2], there are about 2 billion cases of diarrheal disease worldwide every year, combining about 20 diseases of bacterial, viral, protozoal, or helminthic etiology; diarrheal diseases are the second (following pneumonia) leading cause of incidence and death in children younger than 5 years of age, mostly in developing countries (countries of Africa and Southeast Asia account for 78%). Approximately 1.9 million children die from diarrheal diseases each year, accounting for 18% of all deaths among children; over 5,000 children die daily from diarrheal diseases[3]. The studies conducted in Russia demonstrated a high proportion of infectious diseases in the overall incidence structure (36–49%) and the absence of any downward trend [4]. According to the World Bank's estimates, among 4 leading causes of global burden of diseases and injuries, three (diarrheal diseases, intestinal helminth infections, and tuberculosis) are infectious and parasitic diseases. Every year, in Russia, there are 35–40 million cases of infectious and parasitic diseases. In industrialized countries, diarrhea develops in 0.5–2.0 episodes per person a year. In the United States, more than 100 million cases of diarrhea are reported annually, accounting for nearly 25% of all hospitalizations. Affecting working-age population and children, diarrheal diseases have a significant social and economic impact [1–3]. In the past decades, despite advancements in medical and social technology, the global burden of infectious diarrhea has not decreased; on the contrary, it has increased due to high intensity tourism and migration of large groups of the population. Children under 5 years of age, adults over 60 of age, immunocompromised individuals, including individuals taking corticosteroids, receiving chemotherapy and radiation therapy, having organ or stem cell transplants, systemic diseases, living with acquired immunodeficiency syndrome, and alcohol abusers are at the highest risk of severe and life-threatening diarrhea. In 2013, WHO launched the integrated Global Action Plan for the Prevention and Control of Diarrhea. It is expected that its successful implementation will reduce diarrhea-related death rates to below 1.0 per 1,000 persons by 2025 [2].

Acute intestinal infections (AIIs) caused by diarrheagenic *Escherichia coli* (DEC) affect the gastrointestinal tract, leading to development of diarrheal syndrome, intoxication and, in some cases, generalization of the pathological process (sepsis, meningitis, pyelonephritis, cholecystitis). DEC differ from non-pathogenic *E. coli* by the presence of specific virulence genes, pathogenesis characteristics, clinical and epidemiological symptoms of the diseases caused by them

[1] World Health Organization. Diarrhoeal disease. Key facts. Facts sheets, 2017.
URL: https://www.who.int/ru/news-room/fact-sheets

[2] The United Nations Children's Fund/World Health Organization. Diarrhoea: Why children are still dying and what can be done. 2009. URL: https://apps.who.int/iris/bitstream/handle/10665/44174/9789241598415_eng.pdf?sequ

[3] World Health Organization. Ending preventable child deaths from pneumonia and diarrhoea by 2025. The integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD). 2013. URL: https://www.who.int/maternal_child_adolescent/documents/global _action_plan_pneumonia_diarrhoea/en/

[4] Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing. On Sanitary and Epidemiological Wellbeing of the Population in the Russian Federation in 2019: National Report. Moscow; 2020. 299 p.

[3–5]. Based on the virulence determinants, DEC are classified into pathogenic groups (pathogroups). The specific nature of these determinants is manifested in the ability of each pathogroup to cause a disease with distinctive pathological syndromes. Currently, there are 6 commonly recognized DEC pathogroups:

- enteropathogenic *E. coli* (EPEC);
- enterotoxigenic *E. coli* (ETEC);
- enteroinvasive *E. coli* (EIEC);
- Shiga toxin-producing *E. coli* (STEC);
- enteroaggregative *E. coli* (EAEC);
- diffusely adherent *E. coli* (DAEC) [6–8].

In the opinion of some researchers, the assignment of DAEC to a separate pathogroup requires additional experimental evidence [9]. Strains of each DEC pathogroup have specific pathogenetic mechanisms involved in the development of inflammatory processes in different compartments of the human intestine, which are clinically manifested as diarrheal syndrome.

The active exchange of genetic information contributes to the natural occurrence of strains having sets of virulence genes that are specific for different pathotypes and pathogroups [7, 10]. A good example is *E. coli* O104:H4, which caused a major AII outbreak in Germany in 2011 and belongs to the "hybrid" group – enteroaggregative Shiga toxin-producing *E. coli* [11]. After the outbreak, multiple scientific publications have reported that this phenomenon is more common than previously thought. Therefore, the terms "hybrid" and "heterogeneous" *E. coli* are used to describe new combinations of virulence factors among classical *E. coli* pathotypes and DEC pathogroups [12–16].

Enteropathogenic *E. coli*

EPEC causes diseases in young children, mainly affecting the small intestine (coli infection, colienteritis). EPEC adhere tightly to the plasma membrane of epithelial cells and colonize the small intestine, destroying microvilli of enterocytes and the apical surface of epithelial cells. The loss of absorbent villi within the EPEC adhesion area leads to diarrhea due to electrolyte imbalance and malabsorption. EPEC differ from other DEC pathogroups by the presence of a pathogenicity island (the locus of enterocyte effacement), which encodes several important virulence factors, including the outer membrane protein – intimin (encoded by the *eae* gene), which is essential for the key mechanism of EPEC pathogenicity – "attachment and effacement" of enterocytes, as well as the EPEC adherence factor plasmid (pEAF) that encodes bundle-forming pili (Bfp), which promote bacterial adherence to intestinal epithelial cells. Depending on the presence or absence of pEAF, EPEC are classified into typical (tEPEC) and atypical (aEPEC). aEPEC do not have pEAF and, therefore, do not produce Bfp [6, 17].

In 1987, WHO recognized that EPEC comprised strains of 12 O serogroups (O26, O55, O86, O111, O114, O119, O125, O126, O127, O128, O142, and O158) [18]. Over the past 20 years, the list of EPEC serovars has increased significantly; currently, strains of 22 O serogroups and 60 serovars are associated with this pathogroup. **Table 1** presents classical and new O:H EPEC serovars.

Since the 1990s, due to the advances in the understanding of molecular aspects of the EPEC pathogenesis, researchers have been able to move beyond the serological groups, which do not always correlate with the disease, and to work out the definition based on pathogenicity. The Second International Symposium on EPEC adopted the following definition of the above DEC pathogroup: "EPEC are DEC that produce the characteristic A/E histopathology and do not produce Shiga-like toxins. tEPEC have a virulence plasmid known as the EAF (EPEC adherence factor) plasmid, which encodes Bfp pili mediating localized adherence to intestinal epithelial cells, while aEPEC do not have this plasmid. Most of the tEPEC strains belong to specific O:H serovars" [18–20].

Table 1. Serological variants of EPEC

O-antigen	H-antigen	Comments
O18	H7	
O20	H26; H34	
O25	H1	
O26	H$^-$; H11	O26: H$^-$ and O26:H11 may also be STEC
O44	H34	
O55	H$^-$; H6; H7	O55:H7, H10 and H$^-$ may also be STEC
O75	H$^-$	
O86	H$^-$; H8*; H27; H34	O86: H$^-$ may also be EAgEC
O88	H$^-$; H25	
O91	H7; H$^-$	
O103	H2*	
O111	H$^-$; H2; H7; H12	O111: H$^-$ may also be STEC
O114	H$^-$; H2; H10; H32	
O119	H$^-$; H2; H6	
O125	H–; H6; H21	O125 may also be EAgEC
O126	H$^-$; H2; H21; H27	
O127	H$^-$; H6; H9; H21; H40	
O128	H$^-$; H2; H7; H8; H12	O128:H2 may also be STEC
O142	H$^-$; H6; H34	
O145	H$^-$*; H 45*	
O157*	H8*; H10; H16*; H45	
O158	H$^-$; H23	

Note. *New serovar EPEC.

DOI: https://doi.org/10.36233/0372-9311-410

Epidemiological studies of tEPEC and aEPEC strains have demonstrated that tEPEC remains the leading cause of severe childhood diarrhea in developing countries. At the same time, aEPEC causes AII not only in children, but also in adults in industrialized countries. tEPEC strains are assigned to causative agents of anthroponotic infection, when a human is the only source of infection, and the contact transmission is the most frequent route of transmission in children's hospitals and healthcare facilities. aEPEC causes diarrheal diseases in children and adults; it is a causative agent of zoonotic infections, in which animals (frequently cattle) act as reservoirs of pathogens, which are mainly transmitted through animal origin foods. aEPEC strains pose a zoonotic risk to humans and support the concept that animals are a source of aEPEC infection in humans [6, 21, 22].

Enterotoxigenic *E. coli*

ETEC remains a leading cause of sporadic and cholera-like group diarrhea in children in tropical and subtropical developing countries; it is responsible for up to 40% of AIIs among bottle-fed infants. In economically developed countries, ETEC causes "traveler's diarrhea" in tourists visiting regions where ETEC infection is endemic. Among ETEC, there are strains that cause diarrhea in humans and domestic animals of various species. The key role here is played by unique colonization factors and receptors within the intestinal epithelium, i.e ETEC that are pathogenic to animals cannot colonize the human small intestine [23].

The major aspects of ETEC pathogenicity are adhesion leading to colonization of enterocytes and production of enterotoxins causing electrolyte imbalance in intestinal epithelial cells, leading to profuse diarrhea. ETEC adhere to epithelial cells of the human small intestine and colonize them using fimbrial factors of the CFA group (colonization factor antigens) encoded by *cfa,* genes, which can be located on chromosomes and on plasmids [8, 24]. Enterotoxins known as heat-labile (LT) and heat-stable (ST) differ in their properties and mechanisms of action. Both toxins are produced by approximately 5% of the ETEC population, while LT is produced by 25% and ST by 70% of ETEC [6]. By its structural and antigenic characteristics as well as by its mechanism of action, LT resembles a cholera toxin. It inactivates the regulatory protein that controls the activity of adenylate cyclase of the basolateral membrane of enterocytes, thus causing an increase in intracellular levels of cyclic adenosine monophosphate, stimulation of chloride secretion and inhibition of NaCl absorption resulting in profuse secretory diarrhea. There are two known variants of LT: LT1, which is produced by strains isolated from humans, and LT2 – the enterotoxin having similar structure and biological characteristics but produced by *E. coli* strains of animal origin. LT1 is encoded by the *eltI* gene located on plasmids; LT2 is encoded by the *eltII* gene located in chromosomes [7, 8, 24]. ST affects enterocytes, causing disruption of iron transport, electrolyte loss, reduction in sodium absorption, and, eventually, massive water release into the intestinal lumen. Two ST groups have been identified: STa (ST1) and STb (ST2). STa are further classified into STp ("porcine" ST, ST1a) and STh ("human" ST, ST1b) toxins having similar structures and mechanisms of action. The cellular guanylyl cyclase functions as a receptor for Sta; its activation increases cyclic guanosine monophosphate (cGMP) levels in enterocytes, leading to electrolyte loss and inhibition of NaCl absorption, thus causing massive secretion of fluid into the intestinal lumen. STb belongs to the group of membrane-damaging toxins. Currently, the receptor for STb has not been identified; unlike STa, STb does not increase cGMP levels, but it stimulates bicarbonate, prostaglandin E2, and serotonin secretion by enterocytes. STa and STb toxins are encoded by *estA* and *estB* genes located on plasmids. CFA-encoding genes are adjacent to enterotoxin-encoding genes; the simultaneous expression of *cfa* and *tox* genes provides ETEC virulence. Enterotoxins are pathogenetically inactive without colonization factors in the same way as CFA adhesins without toxins [23].

ETEC are associated with a limited number of O groups and O:K:H serovars. **Table 2** presents the known and most common ETEC serovars causing AII in humans [6].

Enteroinvasive *E. coli*

EIEC infection is common in low-income countries and is very similar in its clinical presentation to bacillary dysentery [6, 23, 25]. The pathogenesis of EIEC infection is characterized by the ability of bacteria to invade the human colonic mucosa; their invasion is mediated by the expression of chromosomal and plasmid-borne genes. Following the penetration into colonic epithelial cells, EIEC replicate intracellularly and spread to adjacent cells, causing the inflammatory destruction of the intestinal epithelial barrier, thus provoking typical dysentery syndrome characterized by the presence of blood, mucus, and leukocytes in stools [8].

The taxonomic relatedness of EIEC and Shigella spp. and the similarity of their pathogenesis, virulence factors and genes present similar clinical manifestations of the disease. The infectious dose of EIEC is much higher than that of Shigella, and in some cases, the diseases caused by EIEC are milder [25, 26]. The main gene conferring the pathogenic phenotype of *Shigella* spp. and EIEC is the invasion plasmid antigen H coding gene (*ipaH*) located in the chromosome within a large F-type plasmid (pINV), which is responsible for pathogen replication and spread inside and outside epithelial cells and within the intestinal lumen. The pINV plasmid has been found only in *Shigella* spp. and EI-

EC; its loss is a very rare event, which determines an avirulent phenotype of the strain. Other virulence genes located on extrachromosomal plasmids play an auxiliary role in the interaction of the pathogen with the epithelium and can be unevenly distributed in *Shigella* spp. and EIEC strains; they encode proteins affecting the induction (*ial*) and transcriptional regulation (*invE*) of invasion genes. Tests limited to detection of genes located on extrachromosomal plasmids can produce false negative results, as strains may often lose these plasmids [8]. The biochemical characteristics were first described in 1967. Like Shigella, most EIEC strains are unable to decarboxylate lysine, lack the ability to ferment lactose, and are generally non-motile [6, 25, 27]. Being taxonomically related (the same genospecies), EIEC and Shigella spp. share several phenotypic and genotypic characteristics, making the differentiation between them challenging, especially in the presence of O-antigenic bonds (cross-reactions). This problem often leads to misinterpretation of the epidemiological information, causing difficulty with estimation of the actual burden of EIEC infections.

A limited number of serovars have been assigned to the EIEC pathogroup, namely O28ac:H$^-$, O29:H$^-$, O112ac:H$^-$, O115:H$^-$, O121:H$^-$, O124:H$^-$, O124:H7, O124:H30, O124:H32, O135:H$^-$, O136:H$^-$, O143:H$^-$, O144:H$^-$, O144:H25, O152:H$^-$, O159:H$^-$, O159:H2, O164:H$^-$, O167:H$^-$, O167:H4, O167:H5, O173:H$^-$, and recently O96:H19. Some of these EIEC-associated O antigens, such as O28, O112ac, O121, O124, O143, O144, O152, and O167, are identical to O antigens present in Shigella spp. [25, 27, 28].

EIEC-infected humans represent the principal source of infection. Although AIIs caused by EIEC occur worldwide, they are particularly common in low-income countries where poor hygienic and sanitary conditions contribute to their spread [6, 29]. In some Latin American and Asian countries (Chile, Brazil, Thailand, and India), EIEC are a common cause of AII [25]. In industrialized countries, outbreaks of EIEC are rare; EIEC infections are mostly reported as sporadic cases and are often travel-related, being associated with travelers returning from high-incidence countries. EIEC outbreaks were reported in Hungary (1959), the United States (1970), Czechoslovakia (1982), and Israel (1990). Recently, an increase in cases of EIEC infections has been observed in Europe. In 2012, an outbreak of colitis involving more than 100 individuals and caused by the new EIEC serovar O96:H19 was reported in Italy. In 2014, EIEC of this serovar were responsible for two outbreaks of *E. coli* infection in the United Kingdom [26, 29].

Shiga toxin-producing *E. coli*

STEC are common in all countries, being a major cause of foodborne diseases; they are characterized by a wide spectrum of clinical manifestations – from mild

Table 2. Serological variants of ETEC

O-antigen	(K):H-antigen
O6	H$^-$; K15:H16
O7	H$^-$; H18
O8	K47:NM, K25:H9; K40:H9; H10; K87:H19
O9	H$^-$; K9, K84:H2
O11	H27
O15	H11; H15; H45
O17	K23:H45; H18
O20	H$^-$; H30
O21	H21
O25	H$^-$; K7:H42; H16
O27	H7; H20; H27
O29	H?
O48	H26
O56	H$^-$
O63	H12; H30
O64	H$^-$
O65	H12
O71	H36
O73	H45
O77	H45
O78	H$^-$; K2:H1; H12
O85	H7
O86	H2
O88	H25
O105	H?
O114	H$^-$; H21
O115	H$^-$; H2; H40; H51
O119	H6
O126	H$^-$; H9; H12
O128	H7; H12; H19; H21
O133	H16
O138	K81
O139	H28
O141	H$^-$; H4
O147	H$^-$
O148	H28
O149	H4; H10; H19
O153	H10
O159	H$^-$; H2; H4; H5; H12; H20; H21; H34; H37
O166	H27
O167	H5
O?	H2; H10; H28; K39:H32

Note. H? — unknown H-antigen;O? — unknown O-antigen.

DOI: https://doi.org/10.36233/0372-9311-410

watery diarrhea to hemorrhagic colitis and hemolytic uremic syndrome (HUS) presenting a triad of symptoms: hemolytic anemia, thrombocytopenia, and acute renal failure. Small and large cattle, pigs, and more rarely other animals represent a natural reservoir of STEC. Active transmission factors include raw or undercooked meat products, raw milk, and secondarily contaminated foods. An infected person can be the potential source of infection, posing a risk to others [21, 30, 31].

The ability to produce one or more Shiga toxin (Stx) family cytotoxins constitutes the main virulence factor of STEC strains; toxin-encoding genes are located in the genome of the Stx-converting temperate bacteriophage. Stxs are classified into two types, Stx1 and Stx2. Stx1 is structurally and antigenically identical to the toxin produced by *S. dysenteriae* I (90% homology), while Stx2 has less than 60% homology. *E. coli* strains can produce either Stx1 or Stx2 and/or both toxins at the same time. Strains possessing Stx2 are more virulent than strains harboring Stx1 [7, 8]. It has been found that infections caused by Stx2-producing strains progress to HUS 6.8 times as frequent as infections caused by strains producing Stx1 or both Stx1 and Stx2 [30].

STEC having additional virulence factors (intimin and enterohemolysin) associated with severe infection in humans are known as enterohemorrhagic *E. coli* (EHEC). Compared to STEC, the pathogenic hallmark of EHEC is their tight adherence to intestinal epithelial cells, similar to the EPEC pattern, the key role in which belongs to the outer membrane protein – intimin encoded by the *eae* gene located in the pathogenicity island known as a locus of enterocyte effacement [8, 30].

E. coli serovar O157:H7 was first recognized as a pathogen during outbreaks of hemorrhagic colitis and HUS in the early 1980s. It is still an important STEC serovar associated with numerous outbreaks and sporadic cases of hemorrhagic colitis and HUS worldwide [32–36]. More than 100 STEC serovars are associated with human infections (**Table 3**).

Multiple international epidemiological studies have shown that the most common *E. coli* serovars responsible for human diseases include O26:H11, O45:H2, O103:H2, O111:H8, O121:H19, O145:H28, which are known as "The Big Six Non-O157 STEC" [32, 35].

The average incidence of HUS caused by STEC is estimated to be 2.1 cases per 100,000, while among children under 5 years of age it is 6.1 cases per 100,000. According to the European Centre for Disease Prevention and Control, HUS caused by O157:H7 *E. coli* develops in up to 7% of cases of sporadic diseases and in 20% of cases during outbreaks[5]. Prospective studies conducted in the United States showed that STEC infections in children under 5 years of age progressed to HUS in 12.9% of cases, among 5 to 10-year-old children — in 6.8% of cases, and among children over

Table 3. Serological variants of STEC

O-antigen	H-antigen	O-antigen	H-antigen
O1	H⁻; H20	O98	H⁻; H25
O2	H⁻; H5; H7; H29; H39	O101	H19
O4	H⁻; H10	O103	H⁻; H2
O5	H⁻; H16	O111	H⁻; H2; H8; H11; H30; H34
O6	H1; H3; H34	O112ab	H2
O7	H4	O113	H⁻; H2; H4; H7; H21
O8	H19	O114	H48
O15	H⁻; H27	O115	H8; H10; H18
O18	H⁻; H7; H11	O116	H⁻; H21
O22	H8; H16	O117	H4
O25	H⁻	O118	H⁻; H12; H16; H30
O26	H⁻; H11; H32	O121	H⁻; H7; H19
O38	H21	O125	H⁻; H8
O39	H4	O126	H⁻; H8; H27
O40	H8	O128	H⁻; H2; H8; H12; H25; H35
O43	H2	O132	H⁻
O45	H2	O136	H12; H16
O46	H31; H38	O139	H19
O48	H21	O145	H⁻; H8; H16; H25
O49	H⁻;	O146	H8; H21
O50	H⁻; H7	O153	H⁻; H21; H25
O55	H7; H10	O156	H⁻; H7; H25
O65	H16	O157	H⁻; H7
O69	H11	O163	H2; H19
O74	H?	O165	H⁻; H19; H25
O76	H19; H25	O171	H2
O80	H⁻	O172	H⁻
O82	H8	OX3	H21
O84	H⁻; H2	O?	H2; H4; H7; H8; H10; H12; H16; H19; H21; H25; H32
O91	H⁻; H10; H14; H21	OR	H⁻; H2; H25

Note. O? — unknown O-antigen.

[5] European Centre for Disease Prevention and Control. Shiga toxin/verocytotoxin-producing Escherichia coli (STEC/VTEC) infection. Annual epidemiological Report for 2018. URL: https://www.ecdc.europa.eu/sites/default/ files/ documents /shiga-toxin-verocytototoxin-escherichia-coli-annual-epidemiological-report2018.pdf

10 years of age — in 8% of cases[6]. In 2015, the non-O157 and O157 STEC infection incidence rates were 1.65 and 0.95 cases per 100,000. In 2018, the European Union/European Economic Area reported a significant increase in STEC-associated AII cases, which ranked third among zoonotic infections, being surpassed only by campylobacteriosis and salmonellosis [21].

Enteroaggregative *E. coli*

EAEC is a "new" pathogroup of DEC causing AII among children and adults in all countries; the highest incidence rates are reported among children under 5 years of age [6, 14, 37–40]. The meta-analysis of epidemiological research literature showed a statistically significant association of EAEC with acute, persistent, and chronic diarrhea, with diarrhea in HIV-infected patients and traveler's diarrhea. The symptoms of infections caused by EAEC include watery diarrhea often accompanied by pathological impurities such as mucus and blood, tenesmus, nausea, vomiting, low-grade fever. Depending on the immune status and genetic susceptibility, some patients may develop persistent diarrhea lasting more than 14 days. Genetic susceptibility associated with EAEC diarrhea was first identified in North American travelers to Mexico. Single nucleotide polymorphisms detected in IL-8 gene promoters and promoter regions of the genes encoding lactoferrin, CD14, and osteoprotegerin were recognized as indicators of susceptibility to chronic diarrhea caused by EAEC [6, 14, 41–43].

Studies conducted in Latin America, Asia, Africa, and former socialist countries of Eastern Europe have shown that EAEC is the most common bacterial cause of diarrhea in children [44]. The results obtained in the United States, Europe, and Israel also demonstrate that EAEC is a frequent cause of diarrheal diseases in children [6, 45]. In the United States, incidence rates of *E. coli* infections caused by EAEC in young children surpass those of campylobacteriosis and salmonellosis [14, 39]. Researchers agree that EAEC are the leading bacterial pathogens among hospitalized children with acute diarrhea both in less developed and in industrialized countries [40]. There is evidence that AIIs caused by EAEC are more common among adult population in industrialized countries compared to developing countries. In the United States, EAEC was the most common cause of diarrhea in emergency and outpatient clinics among adult patients [46]. In Japan, the AII outbreaks caused by EAEC involved older children (> 5 years) and adults. In Africa, cases of EAEC diarrhea were observed among adult population of Mali, Nigeria, and Ghana [47]. Large-scale epidemiological studies conducted in many countries have shown that the diarrhea incidence is approximately 3.2 episodes per child, and up to 20% of them were associated with persistent diarrhea (> 14 days). After EAEC was recognized as the cause of chronic persistent diarrhea in Indian children, its etiological role in chronic diarrhea in children in many other countries, including Europe and America, has become unquestionable [14, 43]. Currently available data on the epidemiology of EAEC infection are inconsistent due to a large variation in pathogen detection methods, patients' age and socioeconomic status. In developing countries, EAEC is the main cause of persistent diarrhea among children with decreased physical and mental development associated with malnutrition [14, 39, 40]. In recent years, sporadic cases of EAEC diarrhea among children and adults in economically developed countries as well as group cases of infections and foodborne outbreaks in Europe, Japan, Mexico, and India have been frequently reported [6, 12, 40, 43]. In Germany, since 1997, EAEC has been the third most frequently isolated bacterial pathogen in young children with diarrhea (2%), after *Salmonella* spp. (13.4%) and STEC (3.1%). Asymptomatic carriage of EAEC is frequently detected in individuals with low socioeconomic status in developing countries. The persistence of EAEC may induce chronic intestinal inflammation, even in the absence of diarrhea, reducing the absorptive function of the intestine and leading to alimentary dystrophy and growth retardation. Considering the high number of asymptomatic EAEC-carrying children, this pathogroup of DEC has a significant impact on public health as a cause of impaired physical and cognitive development [14]. According to WHO, an estimated 32% of children under 5 years of age, who live in impoverished areas, are stunted. Unfortunately, growth deficits that occur in early life are not fully reversible and these permanent deficits are a marker of a steady loss of human potential. Stunting has been observed not only in children from poor developing countries, but also in those living in impoverished slums in middle-income countries [6, 14, 40, 43, 44, 46].

Despite ample evidence that EAEC are common DEC in Russia, they are less extensively studied and are less known compared to EPEC, EIEC, and ETEC.

Today, it is generally recognized that EAEC infections are anthroponotic, and the human is a reservoir and source of infection, though research is not over [14]. There is no evidence that animals can represent a reservoir and source of EAEC [39].

EAEC was first described in 1987 by J. Kaper et al. in the study examining patterns of adherence of

[6] Centers for Disease Control and Prevention (CDC). Guidance for Public Health laboratories on the isolation and characterization of Shiga toxin-producing Escherichia coli (STEC) from clinical specimens. 2012. 62 p. URL: https://www.aphl.org/AboutAPHL/publications/Documents/FS_2012April_Guidance-for-PHLs-Isolation-and-Characterization-of-Shiga-Toxin-Producing-Escherichia-coli-STEC-from-Clinical.pdf; World Health Organization, Food Agriculture Organization of the United Nation. Shiga toxin-producing Escherichia coli (STEC) and food: attribution, characterization, and monitoring: report. 2018. URL: https://apps.who.int/iris/handle/10665/272871

DOI: https://doi.org/10.36233/0372-9311-410

E. coli strains, which were collected from Chilean children with diarrhea, to Hep-2 cells in culture [7]. The strains demonstrated a distinctive "stacked-brick" pattern of aggregative adherence to epithelial Hep-2 cells. The in vitro detection of aggregative adherence remains the gold standard in detection of EAEC; however, such tests require special equipment and are time-consuming. Moreover, EAEC can be found in strains of other DEC pathogroups, such as aEPEC [7, 46].

Therefore, following the present-day definition, EAEC are diarrheagenic *E. coli* that are characterized by aggregative adherence to Hep-2 cells and do not have main genetic markers associated with other DEC pathogroups (EPEC, ETEC, EHEC, EIEC). EAEC differ from other classical DEC pathogroups by wide variability of antigenic properties and genetic markers of virulence [6, 12, 14]. At the same time, none of the described virulence factors was unambiguously associated with the virulence of EAEC, and the genes encoding them lack uniform representation in all isolated strains [39]. Results of in vitro, in vivo, and ex vivo tests convincingly demonstrate that EAEC can adhere to jejunal, ileal, and colonic epithelium, forming a strong biofilm, followed by cytotoxic and proinflammatory effects.

The pathogenesis of the disease includes three stages:

- abundant adherence to the intestinal mucosa;
- production of cytotoxins and enterotoxins;
- induction of mucosal inflammation [41, 47].

For the first stage, the presence of fimbrial and afimbrial adhesins is essential. Several colonization factors have been identified in EAEC strains. Adherence is characterized by increased secretion of mucus, which leads to the formation of a strong biofilm where EAEC are embedded. At the next stage, EAEC produce a cytotoxic effect on the intestinal mucosa due to the secretion of toxins, causing microvillus vesiculation and extrusion of epithelial cells. EAEC-induced inflammation results from abundant colonization of the intestinal mucosa [39]. The most extensively studied EAEC adhesins are aggregative adherence fimbriae (AAF), which mediate cell aggregation and biofilm formation [8, 46]. Depending on the cytotoxic or enterotoxic effect, in vitro EAEC can produce various toxins that are encoded by one chromosomal locus. *Shigella* enterotoxin 1 (ShET1) is a toxin that is present in *Shigella flexneri 2a* strains; it causes accumulation of fluid in ileal loops and promotes development of secretory diarrhea typical of infections caused by EAEC and *Shigella*. Enteroaggregative E. coli heat-stable toxin 1 (EAST-1) is a 38-amino acid homolog of the ETEC STa toxin; it activates adenylate cyclase, causing elevated cGMP levels and promoting development of watery diarrhea. The gene encoding EAST1 (astA) is found in approximately 40% of EAEC and among strains of other pathogroups: 100% of STEC O157:H7, 41% of ETEC, 22% of EPEC and in 38% of *E. coli* strains isolated from patients without AII symptoms [14, 41]. EAST1 can be found in commensal *E. coli* strains. Two proteins, Pet and Pic, are serine protease autotransporters of *Enterobacteriaceae* (SPATE). Pet is a cytotoxin that modifies the cytoskeleton of enterocytes, leading to cell rounding and detachment; Pic is a multitask protein that mediates hemagglutination, mucus cleavage and hypersecretion, intestinal colonization, cleavage of surface glycoproteins. SPATEs are immunogenic proteins, as evidenced by the presence of antibodies against Pet and Pic in sera of children recovering from diarrhea caused by EAEC. EAEC-secreted anti-aggregation protein – dispersin that is encoded by the aap gene binds to lipopolysaccharide, neutralizing the negative charge of the bacterial surface, leading to AAF projection and, consequently, to dispersion along the intestinal mucosa. Dispersin can be present in strains of other DEC pathogroups and commensal *E. coli* [46].

Recently, it was suggested that EAEC should be divided into subgroups: typical (tEAEC) and atypical (aEAEC). This classification is based on the presence or absence of the aggR gene that encodes a transcriptional activator of the expression of both chromosomal and plasmid-encoded virulence factors, including AAF and dispersin [39, 46]. It was assumed that tEAEC strains have higher pathogenic potential [40, 48]. Several researchers reported outbreaks of diarrhea caused by aEAEC [6, 14]. Atypical EAEC are commonly isolated from children with AII; in some cases, they are detected more frequently than tEAEC [39].

Multiplex PCR tests designed for detection of multiple genes (aggR, *aaf*, aap, aatA, pic, pet, and astA) encoding adhesins, cytotoxins, enterotoxins, and secreted proteins were used for detection of EAEC strains [40, 47]. Although several protein components such as dispersin, Pic, ShET1, EAST-1, and Pet are involved in the virulence of EAEC, none of them is present in all strains; therefore, it was suggested that triplex PCR should be used for detection of 3 genes (aggR, aatA, and aaiA), as it provides simplified and fast detection of EAEC, including tEAEC and aEAEC [14]. As suggested by some researchers, the combination of virulence genes may depend on a geographical region [40, 48]; therefore, international microbiological surveillance of EAEC could lead to the achievement of a proper diagnostic algorithm [39].

The large number of R-type strains among EAEC presents a challenge for serotyping, resulting in multiple non-typable strains [14, 40, 48]. Nevertheless, currently, strains of 11 serological groups (and serovariants) of EAEC have been identified: O3:H2; O7:H$^-$; O15:H18; O44:H18; O51:H11; O77:H18; O86:H$^-$; O86:H2; O111:H21; O126:H27; O127:H2; O144:H49; ONT:H21; ONT:H33; however, the list for the DEOC pathogroup is not final.

In recent years, EAEC has been reported as a causative agent of extraintestinal infections: urinary tract

infections (cystitis, pyelonephritis) and biliary tract infections (cholangitis, cholecystitis). EAEC virulence markers have been detected in UPEC strains isolated from urine [16, 49]. The presence of UPEC markers was also detected in collections of EAEC strains [50]. These findings have demonstrated that some EAEC strains can cause urinary tract infections. Recently, EAEC has been reported as a causative agent of urosepsis and meningitis [13].

Diffusely adherent (attaching) *E. coli*

The DAEC pathogroup includes diverse strains producing numerous fimbrial and afimbrial adhesins, which mediate specific diffuse adherence to HeLa or Hep-2 epithelial cells [8, 9]. Some researchers believe that the role of DAEC in AEI requires additional epidemiological studies due to the difficulties associated with its classification and identification [51].

DAEC is detected not only in humans, but also in animals (cattle, poultry, and pigs). Clinical symptoms of the disease include diarrheal syndrome, abdominal pain, dehydration, and fever. There are no "unique" clinical symptoms specific for AII caused by DAEC. In economically developed countries, in children with diarrhea, the DAEC prevalence is lower than the prevalence of other DEC pathogroups. In developing countries, the DAEC prevalence accounts for up to 18% of the overall prevalence of DEC [51].

For a long time, the pathogenicity and epidemiological significance of DAEC have been the subject of debate, and are still controversial. Some researchers associate DAEC strains with diarrhea in children and adults, while others argue that DAEC can be present in the human intestine in all age groups without clinical symptoms of AII. Acute diarrhea caused by DAEC presents a relatively new problem of public health significance [8, 9].

Adhesins of the Afa/Dr family, which are responsible for the diffuse adherence phenotype, are the main virulence factors in the DAEC pathogenesis. It has been found that the daaC gene, which recognizes a conserved region of Afa/Dr operons, was more frequently detected in strains isolated from patients with diarrhea than in the control group of healthy individuals [51]. However, in some studies, DAEC strains expressing Afa/Dr were isolated with equal frequency from patients with diarrhea and from healthy individuals of the control group, thus leading to the assumption that additional virulence factors may be involved in the pathogenesis: adhesins identical to UPEC adhesins, such as AfaE-I, AfaE-II, AfaE-III, AfaE-V, and F1845 associated with diarrheal DAEC strains; secreted autotransporter toxin belonging to the SPATE family [9, 48]. A wide variety of genes encoding adhesins makes it difficult to identify infections caused by DAEC, thus contributing to the exclusion of these pathogens from the routine diagnosis of gastrointestinal and urinary tract infections.

Conclusion

The study of AII pathogens is one of the top-priority areas in medical microbiology. *E. coli* has been long associated with diarrheal syndrome, being also considered a representative of the intestinal microbiota. The invention of PCR and high-throughput next-generation sequencing has changed the ideas about the role of *E. coli* as a causative agent of diarrheal diseases and as a resident of the intestinal microbiota; the scientific interest in this bacterium has not only increased, but also has extended into new avenues of research. While the studies laying the foundation for differentiation of *E. coli* and associated diseases were based on the phenotypic method of serotyping by O and H antigens, today, the priority attention is given to molecular and genetic characteristics of specific *E. coli* strain, to pathogenicity and resistance genes, to sequence types, etc.

To a large extent, the interest in *E. coli* can be explained by a high proportion of incidence of *E. coli* infections in the overall structure of infectious diseases. Preventive measures and proper treatment measures play a significant role in control of multiple infections; yet diseases caused by DEC remain widespread and often extremely severe. The factors contributing to this situation are associated not only with the evolution of the *E. coli* genome – emergence of new and/or virulent hybrids, but also with the intensive and prolonged use of antimicrobial agents in clinical practice, leading to emergence of highly pathogenic multidrug-resistant bacterial clones — "superbugs".

The intraspecific genetic diversity of the *E. coli* population underlies the importance of revising the assessment criteria used for the pathogenic potential of microbial strains.

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JOURNAL OF MICROBIOLOGY, EPIDEMIOLOGY AND IMMUNOBIOLOGY. 2023; 100(4)
DOI: https://doi.org/10.36233/0372-9311-410

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Статья поступила в редакцию 26.06.2023;
принята к публикации 08.08.2023;
опубликована 28.08.2023

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The article was submitted 26.06.2023;
accepted for publication 08.08.2023;
published 28.08.2023