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Escherichia coli as a Global Pathogen

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ABSTRACT

Escherichia coli are Gram-negative bacilli belonging to the family Enterobacteriaceae, which normally resides in the intestine of warm-blooded animals, including humans. It has also been used as an indicator of faecal contamination to assess the safety and quality of water. Nevertheless, it is the most widespread pathogen that causes various infections around the world with serious morbidity and mortality rates worldwide. There are six strains of *Escherichia coli*; Enteropathogenic *Escherichia coli* (EPEC), Enterohaemorrhagic *Escherichia coli* (EHEC) Enteroaggregative *Escherichia coli* (EAEC), Enteroinvasive *Escherichia coli* (EIEC), Enterotoxigenic *Escherichia coli* (ETEC), and Diffusely adherent *Escherichia coli* (DAEC),and they have been implicated in various blood stream infection, Haemolytic uremic syndrome (HUS), diarrhoea, meningitis, urinary tract infection and various food infections. However, the clinical importance of *Escherichia coli* cannot be over emphasized, therefore, the general populace should ensure adequate safety in all the food consumed either as a ready to eat or cooked food. The need to avoid half-done meat and unsafe drinking water is key to the prevention of this global pathogen.

KEYWORDS: Enterobacteriaceae*; Escherichia coli;* Infection; Pathogen

1. Introduction

Escherichia coli are gram-negative bacilli of the Enterobacteriaceae (Gözde and Emek, 2019). They are facultative anaerobes that are non-sporulating. *E. coli* strains with the K1capsular carbohydrate matter account for about four-hundredth of cases of sepsis and eightieth of cases of infectious disease. Totally different strains of E. *coli* are attributed to variety of distinctive diarrhoeal diseases. Among these are the enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), and Shiga toxin–producing *E. coli* (STEC). Of the STEC, *E. coli* O157:H7 is that the archetypical strain. Every category of *E.coli* exhibit distinct bodily (O) and flagellar (H) antigens with specific virulence characteristics (Sejal and Leonard, 2015).

Escherichia coli, that ordinarily resides within the microorganism of homoiothermic animals, together with humans, is omnipresent within the setting associated has been used as an indicator of fecal contamination to assess the protection and quality of water (Cho *et al.*, 2018). Though most *E. coli* strains are harmless, bound strains are pathogenic and cause un-wellness that includes: watery diarrhea, bloody diarrhea, tract infection, meningitis, and sepsis, and

will result in death (Cho *et al.,* 2018). The ordinarily animal disease micro-organism has been to blame for waterborne outbreaks in humans through contaminated drinking and recreational water not solely in developing countries, however conjointly in industrialised countries (Probert *et al.,* 2017). Environmental water sources are at risk of microorganism pollution from each humans and animals. Potential human sources of pollution include: discharge of effluent, waste leaks, and failing septic tanks, further as municipal, residential, medical, and industrial waste facilities. Animal sources includes: runoffs from animal farms, land application of animal manure, pet wastes from parks, and life such as: raccoons and ruminant. Since surface waters are typically used for recreational and drinking functions, the presence of pathogenic *E. coli* in waterways could increase the probability of human infections once exposure to those water sources (Cho *et al.,* 2018).

Humans acquire the infection by overwhelming contaminated food or water. Following an incubation period of about 3–4 days, varieties of gastrointestinal symptoms appear and ranges from mild to severe bloody diarrhoea, mostly without fever. However, about 8% of patients (children under five years old and the elderly being the most susceptible) may develop "haemolytic uraemic syndrome" (HUS), characterised by acute kidney failure, bleeding and neurological symptoms. Antibiotic medication is not helpful (it might even help HUS development). The death rate of HUS is about 3–5% (Cho*et al.,* 2018).

Escherichia coli O157 infection presents with a wide range of clinical manifestations which may include: asymptomatic carriage, and this may be vital in relation to recurrent secondary spread (John, 2010). The most common clinical presentation is diarrhoea, usually having an incubation period of 1–14 days, and is frequently occurring as bloody in nature, commonly accompanied by severe, abdominal pain and cramping. About half of patients may also present symptoms such as vomiting, but fever is not common. The quantity of blood present in faeces may vary from a few streaks only, to a stool which is comprised almost entirely of blood. This severe haemorrhagic colitis (HC) may be dangerous, mainly at the dissipations of age (John, 2010)

Impairment to renal endothelial cells by this process is perhaps the principal cause of event in Haemolytic Uraemic Syndrome (HUS). Oedema of the damaged endothelial cells, hypertrophy of mesangial cells and detachment from the underlying basement membrane constricted the lumina of the glomerular vessels. Secondary activation of coagulation, with the formation of platelet thrombi and fibrin generation further block the contracted glomerular capillaries and afferent arterioles, and renal damage results from ischaemic glomerular and tubular necrosis. Equivalent, although pathologically distinct, processes occur in Thrombotic Thrombocytopenic Purpura (TTP), the other thrombotic microangiopathy which may occur following VTEC O157 infection. In both HUS and TTP, organs including the brain, myocardium and pancreas, with consequent development of encephalopathy, cardiomyopathy and diabetes mellitus (John, 2010) may also be affected in this process.

2. History of *Escherichia coli*

German microbiologist and pediatrician Theodor Escherich in 1884, began a study on infant gut microorganism and their importance in digestion and illness. During this study, a fast-growing bacterium was discovered which he called *Bacterium coli*, however, is now known as the biological rock star that is *Escherichia coli* (Zachary, 2015). *E. coli's* dramatic rise and noble status in biology stem from how easy it is to find and work with. The organism is hardy, non-pathogenic, and versatile strains that grow swiftly on many different nutrients and can be isolated from virtually any human. These traits made *E. coli* a backbone in microbiology training laboratory collections (Zachary, 2015).

Other individuals whom have work with *E. coli* included: Werkman (1927), Bordet and Ciuca (1921), Wollman (1925), Bronfenbrenner and Korb (1925),Wollman and Wollman (1937) and Bronfenbrenner (1932), who as well performed groundbreaking studies on bacterial physiology, genetics and viruses (Daegelen *et al.,* 2009). By the

1940s, its use in many foundational thesis firmly established *E. coli* as the bacterial model microbe of choice, making it the recognizable organism to work with at the onset of the molecular biology uprising in the 1950s. As a result, it became the organism in which the most basic aspects of life, such as: the genetic code, transcription, translation, and replication, were first worked out (Judson, 1996). The improved knowledge and molecular methods for investigating as well as manipulating its biology have since led to *E. coli's* reputation in academic and commercial genetic engineering, experimental microbial evolution and pharmaceutical production not to mention the biotechnology industry, which had impacted about $500 billion to the world economy in 2011 (Kawecki *et al.*, 2013). It is not exaggeration to say that *E. coli* is now the most significant model organism in biology.

3. Symptom of *Escherichia coli* Infection

Infection *with E. coli* shows symptoms typically between 3 to 4 days after being exposed to the micro-organism. Though, symptoms may occur as early as 24 hours or as late as 1 week later. These may include (Bindu *et al.,* 2010):

- Abdominal aching or severe abdominal cramping, habitually starting suddenly
- Watery diarrhea, starting a few hours after the pain begins
- Bright red bloody stools around a day later, resulting from the toxin's damage to the intestines
- Nausea as well as vomiting in some cases,
- Also, fever, usually below 101 degrees Fahrenheit in some cases
- Fatigue, resulting from dehydration and the loss of fluids and electrolytes
- Some people have no noticeable symptoms, but they can spread the infection to others.

4. Epidemiology of *Escherichia coli*

Enteric *E. coli* are constituents of the microbiota of many animals. Human can become infected through consumption of contaminated food and food products (undercooked meat, or contaminated fresh produce such as salad leaves), drinking of water contaminated with human waste or animal, or through direct person-to-person spread as a result of un-hygienic condition (Berger *et al.*, 2010).Accurate figures of the incidence of enteric *Escherichia coli* infections globally are difficult to assess, as the causative agents of diarrhogenic infections are habitually not identified. In the developing world, Enterotoxigenic *Escherichia coli* (ETEC), Enteropathogenic *Escherichia coli* (EPEC) and Enteroaggregative *Escherichia coli* (EAEC) appear to be major causes of childhood diarrhea with potentially fatal consequences when left untreated, while in the developed country these infections are mild and self-limiting. Enterohaemorrhagic *Escherichia coli* (EHEC) and more recently Enteroaggregative *Escherichia coli* (EAEC) and STEAEC are the main *Escherichia coli* pathotypes associated with food poisoning outbursts in the developed world (Peng *et al.,* 2009).

In the United States of America, *E. coli* sepsis was related to approximately 40,000 mortality in 2001, number that corresponds to 17% of all cases of sepsis (Biran and Ron, 2018). Relevant studies have revealed an increasing incidence of *Escherichia coli* early-onset sepsis in all age groups, superseding group B Streptoccocus for the last 10 years. Beyond that, *E. coli* resistant strains also increased equally in all age groups, with high insensitive rates to first line antibiotics available (ampicillin and gentamicin). Decreased birth weight of newborns remained the group with high rate incidence (10.4 cases per 1000 live births) and mortality (35.3%). Systematic use of Polymerase Chain Reaction (PCR) increased *E. coli* early-onset sepsis diagnosis, mainly in the newborn group. There was also an increase in resistant *E. coli* sterotypes causing early-onset sepsis, with specifically high resistance to ampicillin and gentamicin (92.8 and 28.6%, respectively) (Mendoza-Palomar *et al.*, 2017).

Likewise, 92% of EPEC isolates retrieved from children in Brazil between 2001 and 2002 were atypical, compared to 38% in a 1998-1999 study (Scaletsky *et al.,* 2010). More newly, 39.3% of

EPEC strains isolated from children with diarrhea in Iran tested positive for the bfp gene, while the other 61.7% appeared as aEPEC, and lacks bfp (Bakhshi *et al.,* 2013). Studies from Norway (Afset *et al.,* 2003) and Australia also suggest that aEPEC isolates as more commonly found among persistent cases of diarrhea than typical isolates. However, this concept cannot be universal, as other studies still report tEPEC being more widespread than aEPEC as a cause of diarrhea. Although many countries no longer regard tEPEC strains to be an important cause of acute diarrhea, the occurrence of severe disease outcomes associated with these infections has re-emerged (Mathew *et al.,* 2013).

In Nigeria, a research carried out in Abuja showed that prevalence of resistant *E. coli* was highest among farm-workers and associated with older farms/markets, occupational exposure of over 10 years and poor hygienic measures (Aworhet *et al.*, 2019). Also, Adebola *et al.* (2014) observed a total of 61 DEC strains which were isolated at a rate of 18.4% and 2.6% from children with diarrhoea and healthy controls respectively. The DEC strains recovered were Enteroaggregative *Escherichia coli* (34.4%), Shiga-toxin producing *Escherichia coli* (31.1%), Enterotoxigenic *Escherichia coli* (18.0%), typical enteropathogenic *Escherichia coli* (15.0%) and Enteroinvasive *Escherichia coli* (1.6%). Shiga-toxin producing *Escherichia coli* and Enteroinvasive *Escherichia coli* were recovered only from children suffering from diarrhoea and the overall prevalence of DEC strains was significantly higher among the children with diarrhoea (Adebola *et al.*, 2014)

In another case in Scotland in 1994, 71 cases were reported including 1 death and 11 HUS cases as a result of non-pasteurization of milk. In an *E. coli* O111 outbreak in Australia, 200 cases were reported including 23 HUS cases and 1 death due to a kind of sausage made from minced meat(Gözde and Emek, 2019).

In a study conducted on children's nursery in Japan between 2010 and 2013, it was detected that 68 of 1035 outbreaks were of EHEC origin. It is known that 30 of the 68 outbreaks (46%) were food-borne (Gözde and Emek, 2019). It is also known that there were two EIEC outbreaks reported in England in June of 2014(Gözde and Emek, 2019).

5. Classification of *Escherichia coli*

Enteropathogenic *Escherichia coli* (EPEC)

The word Enteropathogenic *Escherichia coli* (EPEC) was used first in 1995 to term a number of *E. coli* strain epidemiologically related to a series of occurrences of childhood diarrhea in the 1940s and 1950s (Ruiz *et al.*, 2011).Originally recognized serotype, EPEC are now defined as those *E. coli* strains having the ability to cause diarrhoea, to yield a histopathology on the intestinal epithelium known as the attaching and effacing (AE) injury, and the inability to produce Shiga toxins and heat-labile (LT) or heat-stable (ST) enterotoxins. Improvements in methods allowing a better understanding of the genome and virulence mechanisms among EPEC strains over the years have led to the sub-classification of EPEC into typical EPEC (tEPEC) and atypical EPEC (aEPEC)(Ruiz *et al.,* 2011).Typical EPEC strains causing human infectious diarrhea have a large virulence plasmid known as the EPEC adherence factor (EAF) plasmid (pEAF), which encodes the type IV fimbriae called the bundle-forming pilus (BFP), while aEPEC do not have this plasmid. The majority of tEPEC strains fall into well-recognized O serotypes. Classical EPEC O serogroups include: O55, O86, O111, O114, O119, O127, and O142 (Gomes and González, 2013). The most common H antigens associated with EPEC are the H6 and H2 antigens, a less common EPEC type is H34, and a number of tEPEC strains are classified as non-motile (H-) in conventional tests. Typical EPEC strains belonging to non-classical serotypes have also been reported Based on multilocus enzyme electrophoresis analysis (MLEE) of allelic differences between housekeeping genes, tEPEC strains have been subtyped into two major lineages, previously designated EPEC1 and EPEC2.(Gomes and González, 2013).) EPEC1 includes; Widespread serotypes such as O55:H6 and O119:H6, whereas EPEC2 consists of serotypes with more limited occurrence such as O111:H2 and O114:H2. Based on a whole-genome phylogeny and analysis of type III secretion system (T3SS) effectors, tEPEC strains have been demonstrated to cluster in three main lineages,

designated EPEC1, EPEC2, and EPEC4which probably acquired the locus of enterocyte effacement (LEE) region and pEAF independently (Hazen *et al.*, 2013).

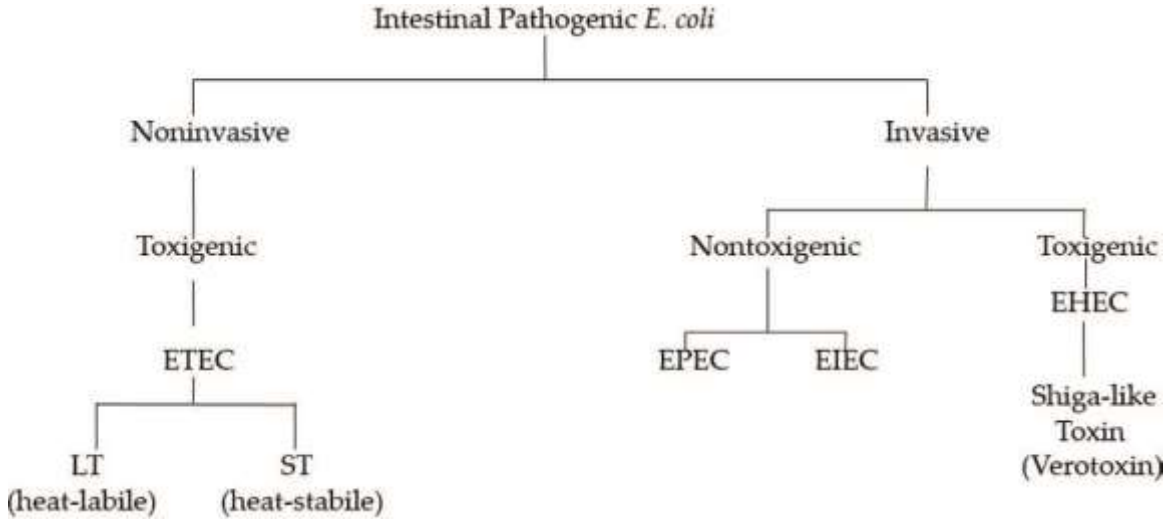

Figure 1: Classification of *E. coli* (Gözde and Emek, 2019)

EPEC was the early strain of *E. coli* generally recognized to cause diarrhogenic outbreaks in the developed country (Abigail *et al.,* 2012) its occurrence has degenerated and EPEC outbreaks are now rare in developed countries. However it does remain a vital cause of childhood diarrhea in the developing world with recent estimates of EPEC prevalence among infants with diarrhea ranging from 6–54%, although high carriage rates among healthy controls makes the contribution of EPEC to disease difficult to assess (Abigail *et al.,* 2012). Atypical EPEC (i.e., those lacking the EAF plasmid that encodes bundle-forming pili (BFP) appear to have a propensity to cause persistent diarrhea.

The characteristic histopathology prompted by this group of *E. coli* is termed attaching and effacing (A/E) lesions and is as a result of the intimate attachment of bacteria to the intestinal epithelial cells and effacement of enterocyte microvilli (Jafari *et al.,* 2012). Creation of the micro ulcers and exfoliation of the cells at the site of EPEC adhesion was first pronounced in experimentally infected pigs (Jafari *et al.,* 2012) and afterwards in biopsies from infected infants (Jafari *et al.,* 2012). A protein called intimin facilitates the bacterial attachment to outer cell membranes and is encoded by eae genes which along with all other genetic essentials required for this phenomenon are located on the locus of enterocyte effacement (LEE), a huge genomic pathogenicity island which was discovered in 1995. Pathogenesis of these bacteria however is many faceted which has not been fully unraveled as yet and may involve factors other than those directly responsible for A/E lesions as well as more specialized intestinal cells (Jafari *et al.,* 2012).

EPEC promotes attaching-effacing lesions in eukaryotic cells. These lesions are assisted by intimin, an outer membrane adhesive protein encoded by the EAE (*E. coli* attaching-effacing) gene (Dennys *et al.,* 2006). EPEC is currently subdivided into typical and atypical subgroups. While typical EPEC carry the EPEC adherence factor plasmid (pEAF) that encodes the bundle-forming pilus (BFP) and a complex regulator of various virulence genes (Per) (Dennys *et al.,* 2006), atypical EPEC is devoid of pEAF (or does not express a functional BFP) (Dennys *et al.,* 2006). Typical EPEC expresses the localized pattern of adherence (LA), which is characterized by compact bacterial clusters on HeLa and HEp-2 cells (Dennys *et al.,* 2006). Conversely, atypical EPEC most often expresses the LA-like pattern (with loose bacterial clusters) or adherence patterns of other DEC pathotypes.

Enterohemorrhagic*Escherichia coli* (EHEC)

EHEC are also referred to Shiga toxin producing *E. coli* (STEC) or verotoxin *E. coli* (VTEC). This is because all strains of EHEC produce Shiga toxins that injures the vero cells similarly to Shiga toxins formed by Shigella. *E. coli* O157: H7, it was earlier defined after the outbreak associated with the ingestion of rare cooked minced meat in 1982, it is associated to be the main cause of EHEC infection in developed countries including the USA, England and Canada (Ertaş *et al.*, 2013). O103, O26, O145 and O111 can be listed among the other EHEC serotypes that cause food-borne diseases. Even though the O157 strains are the ones that attract the most devotion, the strains of other EHEC serotypes, especially O111, are progressively getting described more and more around the globe. Based on the ruthlessness of the disease, EHEC is viewed as the sternest *E. coli* strain among food-borne pathogens. *E. coli* O157:H7, contrast from the other *E. coli* serogroups due to some of its characteristics, which are: not being able to grow in or above 42°C, not being able to tumult sorbitol, not having β-glucuronidase enzymes and production of entero-hemolysins. Shiga-like toxin produced by *E. coli* O157:H7 is toxic for human colon and duodenum. This toxin causes build-up of fluid in intestines and abrasions in colon via destruction of crypt epithelia.

Enzyme intimin makes grip to the intestinal canal stress-free (Ertaş *et al.*, 2013). EHEC has a wide range clinical presentation including watery or bloody diarrhea and haemolytic uremic syndrome (HUS), which is an imperative influence in acute renal failure in children. The major EHEC O104:H4 outbreak occurred in Germany in 2011 with 855 HUS cases in 3842 people and 53 deaths. This incidence, which elevated anxiety all around the sphere, shows the significance of EHEC in terms of human health. Bovines are the key reservoir for these bacteria to live on asymptomatically for centuries. Other smaller reservoirs for these microorganisms are goats, dogs, sheep, pigs and poultry. Other places where EHEC could sojourn alive for months comprise; bovine feces, soil and water. Slaughtering or dispensation of animals or contamination of plants through polluted water or compost are the chief routes for EHEC to spread to the nutrients chain (Gözde and Emek, 2019). Succeeding 3–12 days of incubation period after infection with *E. coli* O157:H7, watery diarrhea is witnessed as well as abdominal cramps and pain. In some cases, hemorrhagic colitis (HC) which is also known as blood-spattered diarrhea, thrombotic thrombocytopenic purpura (TTP), fever and queasiness are included in the important clinical findings to be observed in such patient. Most patients recuperate within 10 days, however; depending on the serotype of the EHEC strain and stx subtype, HUS may progress 1 week after the start of diarrhoea that may lead to death particularly in youngsters and aged people. HUS is observed with acute renal failure, haemolyticanemia and thrombocytopenia. Colon perforation, coma, stroke, pancreatitis and hypertension are involved among the other complications of HUS. It is predictable to lead to the early advance of chronic renal impairment in 15% of cases. Dialysis is required for HUS patients and mortality rate is 35%. Moreover, it is more commonly observed in females (70%) and during gestation (13%).Good therapy for this infection is still lacking, however; some new therapeutic strategies like the usage of anti-vero toxin (anti-Shigatoxin) antibodies have been recommended. TTP, is as well perceived to be clinically similar to HUS (Gözde and Emek,2019)and fever, abdominal pain, gastrointestinal hemorrhage and central nervous system disorders are listed among complications that may develop (Gözde and Emek,2019).

The key pathogenic element and the defining feature of this group is a phage-encoded powerful cytotoxin the effect of which was revealed to be neutralizable by anti-Shiga toxin of *Shigelladysenteriae*. The cell harmfulness effect was also established on Vero cells causing a parallel nomenclature system of Shiga/Vero toxin-producing *E.coli* (STEC) and (VTEC) respectively (Kamali *et al.*, 2010). In 1983, an *E. coli* strain serotype O157:H7, was recognised in relationship with outbreaks of a bloody diarrhea called haemorrhagic colitis (HC) resulting to the recognition of EHEC as a first-hand and progressively important class of enteric bacteria instigating intestinal and renal disease (Jafari *et al.*, 2012). The term enterohaemorrhagic *E. coli* (EHEC) is useful to those STEC serotypes that have the same epidemiological, clinical and pathogenetic characteristic related with

the prototype strain *E. coli* O157:H7. The high pathogenicity of STEC strains such as O157:H7 is not only reliant on the pathogenic factors but partly also on the pathogen's capacity to endure environmental stress conditions, such as resistance to low pH levels found in the gastrointestinal tract responsible to its very low infectious dose of 50-100 microorganisms or lower (Kamali *et al.,* 2010).

The chromosome of STEAEC 2011 outbreak strain O104:H4 is utmost similar to EAEC strain 55989.15,66. This STEAEC occurrence strain carries Pic on the chromosome and a pAA-like virulence plasmid encoding AAF, AggR, Pet, ShET1 and dispersin. A second virulence plasmid encodes several antibiotic resistances. In addition to these normal EAEC virulence elements STEAEC O104:H4 has an stx2-concealing prophage unified into the wrbA locus, and consequently can yield Stx, a defining distinctive of the EHEC pathotype (discussed under EPEC/EHEC—Non T3SS pathogenic mechanisms—Toxins). The outbreak strain has also attained the IrgA homolog adhesin (Iha) (Abigail *et al.,* 2012) and tellurite resistance cluster, which are common features of EHEC strains (Abigail *et al.,* 2012). Consequently, there do not appear to be new virulence element in this strain, quite a blend of known virulence factors from two pathotypes. The increased morbidity and mortality related with this strain may imitate the stronger attachment of EAEC compared with EHEC allowing more Stx to be conveyed and more resultant pathology (Abigail *et al.,* 2012).

Shiga toxin family with associated structure and similar biological action is composed of Stx1 which is fundamentally identical to the toxin of *Shigelladysenteriae* differing in a sole amino acid and Stx2 with less than 60% amino acid homology to Stx1. Little sequence dissimilarity has been reported for Stx1 (Jafari *et al.,* 2012), but Stx2 has numerous subtypes which diverge in biological action and immunological reactivity (Jafari *et al.,* 2012). Shiga toxins analogous to the heat-labile enterotoxin of ETEC belong to the AB5 family of the toxins and comprise of a pentameric ring-shaped B subunit that is non-covalently devoted to the A subunit. The B subunit interrelates with globotriaosylceramides (Gb3s) on the surface of human intestinal mucosa and kidney epithelial cells causing the internalization of the toxin where the A subunit is triggered instigating cell death (Jafari *et al.,* 2012). Among the Stx2 variants, Stx2c has been isolated more regularly from HUS patients but Stx2e and Stx2f have been largely recovered from pigs and birds and seldom from humans (Jafari *et al.,* 2012). Moreover, a different AB5 toxin has been discovered in this group which varies significantly from other toxins in this group. This subtilase-like toxin (SubAB) was isolated from an HUS outbreak strain in Australia and displays superior cytotoxicity than Stx2 for a range of cell types comprising Vero cells (Jafari*et al.,* 2012). The EHEC genome comprises the same locus of enterocyte effacement (LEE) as the EPECs and the close attachment of EHEC to host cells happen through interaction between an adhesin called intimin (eaeA), and Tir (translocatedintimin receptor). This intimate attachment induces the characteristic attaching and effacing lesions (A/E),but the preliminary adherence of EHEC to colonocytes is not well clear (Jafari*et al.,* 2012). Sixteen possible fimbria-like operons, which have not been broadly studied have been documented in STEC strains, and newly a pilus associated in adherence and biofilm creation called hemorrhagic coli pilus, a type IV pilus, has also been recognized in STECs (Jafari*et al.,* 2012). However, the intimate adherence as in EPECs is as a result of interactions between Tir and intimin. At least 29 distinct intimin types with heterogeneity in the C-terminal part of the fragment that is used in binding to Tir in both STEC and EPEC have so far remained identified. The capacity of STEC to produce A/E lesions is sufficient to cause non-bloody diarrhoea but Shiga toxin is vital for the advance of bloody diarrhoea, HC, and HUC. Additional toxin found in many STEC/EHEC isolates is the enteroaggregative heat-stable enterotoxin1 (EAST1) and typically two copies of the astA gene is present in the chromosome.

Enteroaggregative *Escherichia coli* (EAEC)

This pathotype is a food-borne enteropathogen observed in severe and strict diarrhea cases in children, patients with repressed immune systems in developing nation and people traveling to endemic areas. Cognitive disorders and growth disorders in children living in developing nation, stem from EAEC

infections. In the pathogenesis of EAEC, the first phase is the solid adherence to the intestinal mucosa layer. The second phase is leading to the advance of enterotoxins and cytotoxins and the third phase is recognized to be characterized with the capacity to induce mucosal swelling. Many different pathologic factors regarding these three phases have been distinct, however; none of them are current in all strains. Three adherence models associated to EAEC have been distinct. In addition to the restricted adherence (LA) model that was defined first, there is also a diffuse adherence (DA) model and aggregative adherence (AA) model. The strains corresponding to the AA pattern were later defined as "Enteroadherent-aggregative *E. coli*". However, this term was then swapped with the current name "Enteroaggregative *E. coli*". AA phenotype has to be present in order for an *E. coli* strain of EAEC pathotype to be classified (Gözde and Emek, 2019).

It is frequently found in foods in Mexico, including desserts and salsa sauces, and the visitors of the country are acknowledged to be more subtle to EAEC toxicities throughout their stay relatively than ETEC, which they are the most vulnerable to. The aim behind this is the EAEC's capacity to overwhelm the immune system and result in chronic infection. EAEC is also further resistant to antibiotics compared to the other diarrheagenic pathogens. Insistent contamination and chronic disruption in intestinal roles cause starvation and decline in physical and cerebral development, particularly in young children. Undernourishment, which is perceived due to micronutrient deficiency, induces infection. Development of infection encourages under nourishment. This whole cycle raises the burden of acute diarrhea (Gözde and Emek, 2019).

This pathotypes is the utmost newly recognised diarrheagenic *Escherichia coli* and is the second most common reason of travellers' diarrhea after ETEC in both industrialized and unindustrialized countries. EAEC are usually being familiar as a cause of endemic and epidemic diarrhea worldwide and newly, has been exposed to cause acute diarrheal illness in new-borns and children in developed countries. This organism has also been related with insistent diarrhea. Diarrhea caused by EAEC is regularly watery, but it can be accompanied by mucus or blood.

The discovery of EAEC as well as diffusely adherent *E. coli* (DAEC) stemmed from the studies display that EPEC adhere to HEp-2 cells in idiosyncratic pattern (Jafari *et al.,* 2012). Inspection of a gathering of diarrheal *E. coli* strains that were not of EPEC serogroups presented that many of these strains also adhered to HEp-2 cells and the phenotype was diverse from that of EPEC (Jafari *et al.,* 2012). This pattern of adherence, which had been called "diffuse" which was successively subdivided into aggregative and true diffuse adherence. *E. coli* showing aggregative adherence (AA) are auto-agglutinating, but their hallmark is aggregative adhesion, which encompasses the formation of a stacked-brick pattern on HEp-2 cells. In a study in Iran (Jafari *et al.,* 2012) reported that 32% of diarrheagenic *Escherichia coli* isolated from infants and children which did not belong to any recognised *Escherichia coli* pathotypes formed AA pattern on HeLa cells and presented a significant prevalence in children with diarrhea compared to controls.

EAEC serotypes are distinct by their aggregative adherence or "stacked brick" phenotype on HEp-2 cells while in the gastric mucosa EAEC forms a biofilm with bacteria enclosed in a heavy mucus layer (Abigail *et al.,* 2012). Colonization necessitates the AAF and the regulator AggR both encoded on a great virulence plasmid pAA. AAF, of which four strains have been pronounced, facilitates attachment of EAEC to salad greeneries (in combination with their flagellation organelle) infected host cells and human intestine ex vivo but were not shown to confer a colonization benefit in a mouse model. Other than AAF and AggR, there is a countless deal of genomic variation amongst EAEC strains with corresponding heterogeneity in pathologic and few conserved virulence features. Further colonization dynamics found in some EAEC isolates comprise Heat-resistant agglutinin (Hra) 1 and 2 and Tia (also establish in ETEC) (Abigail *et al.,* 2012).The synthesized small hydrophilic protein dispers in (encoded by aap) help colonization by bonding non-covalently to the

bacterial cell surface potentially counteracting the negative charge of the Lipopolysaccharide (LPS) and allowing the positively charged AAF to spread away from the cell.

Absence of suitable animal models and the heterogeneity of virulence features caused the scarcity of details concerning the EAEC transmission, pathogenicity and epidemiology. However, colonization of gastric mucosa, mucoid biofilm formation and amplification of numerous enteric-toxins, cytotoxins and mucosal inflammation are regarded the main characteristics of EAEC pathogenesis (Croxen and Finlay, 2010). Colonization of intestinal mucosa by the EAEC happens through aggregative adherence fimbriae (AAF) encoded by a 55-65 MDa plasmid named pAA. The principal one of which, aggregative adherence fimbriae I (AAF/I), remained cloned and branded from EAEC prototype strain. A probe derived from this adhesin did not identify O42, the second EAEC prototype and later a new fimbria was characterized in this strain called AAF/II. Though, two other adherence features (AAF/III and AAF/IV) as well as a non-fimbrialadhes in have been labelled but some variants are encountered that do not comprise any of these recognized fimbriae despite revealing AA phenotype which is indicative of the as yet uncharacterized adhesins. (Aslani *et al.*, 2011), Similar to ETEC strains adhesion of EAEC to intestinal tissue is facilitated by antigenically heterogenousadhesins and multiple carriage of AAFs by an EAEC strain has been infrequent. A transcriptional activator known as "AggR," encoded by pAAs, controls the biogenesis of AAFs and is the main EAEC virulence manager controlling varied virulence genes encoded by pAAs as well as by chromosomes (Jafari *et al.,* 2012). Adherence of EAEC to the mucosa is characterized by the creation of a thick, accumulating mucus layer inside which they persist and this biofilm creation has been recognized to the activity of fis and yafK genes. However, a synthesized 10 kDa protein encoded by pAA and called anti aggregation protein (Aap) or dispersin, eases the movement of bacteria across the area of the cells for subsequent aggregation and adherence (Jafari *et al.,* 2012). Dispersin is highly immunogenic and is translocated through an ATP binding cassette (ABC) transporter complex (the Aat apparatus). Both these genes have been used for classification and recognition of EAEC isolates, but it has been noted that dispers in gene (aap) can be spotted in DAEC as well as non-pathogenic *Escherichia coli*.

EAEC variants secretes a variety of SPATEs of either class I (cytotoxic) or class II (non-cytotoxic). Pic (protease involved in colonization, also found in *Shigella flexneri* and UPEC) is a class II SPATE with hemagglutin and mucinolytic activity which may aid to enter the mucus layer in which EAEC dwells on enterocytes. Equally, Pic can encourage mucus hypersecretion and an upsurge in the amount of mucus-producing goblet cells. Pic has also been involved in immunomodulation by cleaving leukocyte surface glycoproteins and prompting both initiation and apoptosis in T cells, but reduced migration, of polymorphonuclear leukocytes (PMNs). (Ruiz *et al.,* 2011) Pet is a well-considered class I SPATE that is endocytosed by host cells, go through backward trafficking and exploits the ER-associated degradation (ERAD) pathway to be released into the cytosol. Pet then cleaves the act in binding protein spectrin in the host cytosol, unsettling the actin cytoskeleton and triggering cell rounding and detachment. Recent indication has also suggested a role for Pet in disrupting focal adhesions. Pet is only present in a trivial minority of strains and other class I SPATES (Sat, SigA, EspP) may possess similar roles. Sat in particular has 52% amino acid identity with Pet and is discussed further under DAEC (Abigail *et al.,* 2012).

Non-SPATE toxins include the EAEC heat-stable enterotoxin 1 (EAST-1), which is encoded on pAA and is 50% similar to, but antigenetically distinct from, the enterotoxic domain of STa. Just like STa, EAST-1 triggers guanylatecyclase leading to amplified cGMP, though the toxigenic effect looks milder than forSTa. The prevalence of EAST-1 amongst EAEC variants and its influence to pathogenicity remains vague. Further toxins include ShET1 (categorized as an AB5 toxin in *Shigellaflexneri*) and HlyE (a pore-forming toxin)

have similarly been projected to contribute to EAEC virulence (Abigail *et al.,* 2012).Recent sequencing of the prototype EAEC variant 042 has shown some fascinating potential virulence factors including two T3SS and possible effect or proteins as well as a locus encoding a polysaccharide capsule, but these remain to be tested and their occurrence among clinical isolates determined. EAEC 042 also encodes three type 6 secretion systems and, like many EAEC clinical isolates, has various antibiotic resistance genes,(Cappello*et al.,* 2011)making eradication and therapy difficult.

Enteroinvasive *Escherichia coli (*EIEC)

EIEC strains producing inflammatory harm in intestinal mucosa and sub-mucosa are identical to those formed by Shigella. These microorganisms have the same dispersion and replicating abilities inside epithelial cells (Lääveri *et al.,* 2018). However, clinically, EIEC-related watery diarrhea is much more usually observed than dysentery caused by Shigella. O antigens of EIEC can cross-react with O antigens of Shigella. The illness starts with severe weakness, abdominal cramping, watery stool, difficulty urinating and fever. It could rarely worsen and turn into watery stool comprising blood or mucus. The fecal leukocytes observed in shigellosis may also be detected in the mucus smear of an individual infected with EIEC. EIEC contagions are endemic to less developed countries and are reported to be rarely observed infections in developed countries. The incubation period is observed as 10–18 hours. There is evidence showing that EIEC is transmitted via contaminated foods. Just like in shigellosis, cases of diarrhea with enteroinvasive variants can be cured by using antimicrobials effective against Shigella isolates (Lääveri *et al.,* 2018). In a study carried out to investigate the effects of antibiotic usage, stool samples were examined to find out whether it pretentious pathogen findings. Four and fifty-six travellers from Finland were all educated about antibiotic usage during tourism and stool samples were collected from them both before and after the travel. There were differences between the tourists that visited various countries before and the ones that did not use any antibiotics in terms of Enterobacteriaceae answers, as well as some health difficulties during the travel and pathogenic findings in stools (Lääveri *et al.,* 2018)

Colonic mucosa is the pathologic site of Shigella and EIEC where invasion of M cells, macrophages and epithelial cells happen resulting in a watery diarrhea, which in simple cases may be followed by the onset of scanty dysenteric stools containing blood and mucus (Jafari *et al.,* 2012). EIEC strains can also secreates a 63 kDa toxin designated Sen which contributes to the enteric-toxic activity detected in the strains carrying the gene (Jafari *et al.,* 2012).

Attainment of the aggressive plasmid (pINV) encoding the capacity to attack host tissues is perhaps the sole most significant event that has probably result to the development of both Shigella and EIEC from non-pathogenic *E. coli*. Approximately one third of this large single copy plasmid encodes IS elements and encompasses a 30 kb region aiding the bacteria to attack intestinal epithelial cells (Jafari *et al.,* 2012). Many components of type three secretion system (T3SS) such as transcriptional activators, translocators, some effectors and chaperones are coded by this region with the expression of the Invencoded genes being controlled globally by VirB and MxiE. In addition to the genes of pINV many chromosomal genes which are not exact to Shigella spp. and are carried on the chromosome are essential for pathogenesis (Jafari *et al.,* 2012).

Bacillary dysentery as opposite to dysentery caused by amoeba was defined in 1887 and *Bacillus dysenteriae* as the etiologic agent was described in 1898 by Shiga during an epidemic of 89,400 cases (Peng *et al.,* 2009). The medical prominence of Shigella strains led to their parting from *E.coli* and the freshly formed genus with its 4 species could be distinguished from *E. coli* on the basis of physiological and biochemical features. However, the detection of strains which could result in dysentery and were intermediate between Shigella and *E. coli* in biochemical characteristic in 1944 caused the separation of the two genera to be questioned (Van den Beld and Reubsaet, 2012). The

capacity of these strains which by now were called enteroinvasive*E.coli* (EIEC) to cause diarrhea was established in volunteer studies in 1971. It has been shown that EIEC strains and Shigella species are biochemically, genetically, and pathogenetically very closely related so much so that it has been suggested that they should be classified as one species in genus Escherichia.

Enterotoxigenic *Escherichia coli* (ETEC)

Individuals living in developing nation have often been reported to have this pathotype in their faeces and revealed to have established immunity against this bacteria organism (Gözde and Emek, 2019). Being a cause of death in children under, the most often observed microorganism in childhood diarrhoea is ETEC and it is also accountable for 30–60% of travellers' diarrhoea. Infection is observed by watery diarrhoea and, depending on the person, its course may range from a normal course to cholera-like excretion with the addition of indications such as vomiting and high fever (Zhang and Sack, 2015). Diarrhoea is the most common causes of death in society and among young individuals, especially those living in sub-Saharan Africa and Asia with inadequate healthcare systems and inadequate access to clean drinking water. Recent orderly studies have reported that each year an estimated 600,000 children under the age of 5 lose their lives. Diarrhoea ensues due to the ingestion of food or water contaminated with viral, parasitic or bacterial pathogens. Among these likely pathogens, the most common source of diarrhoea in children under five is the ETEC (heat-stable – ST and/or heat-labile – LT type toxin) creating *E. coli* strains. Through the creation of fimbrial or non-fimbrialadhesins, ETEC strains results hyper secretion of fluids by synthesizing enterotoxins that disrupts fluid and electrolyte homeostasis in the epithelial cells of small intestines, resulting to watery diarrhea(Gözde and Emek,2019). Without rehydration, moderate or severe diarrhoea could lead to dryness and acute mortality.

ETEC is described to be the most frequently isolated bacterial entero-pathogen in children under 5 years of age in developing countries, accounting for approximately 20% of cases, corresponding to several hundred million incidence of diarrhoea and numerous tens of thousands of deaths each year. ETEC is also the most common etiology of travellers'diarrhoea accounting for 10–60% of infections contingent on the region visited (Abigail *et al.,* 2012). Extrapolation of these facts proposes there may be 10 million cases of travellers' diarrhea as a result of ETEC per year(Abigail *et al.,* 2012). ETEC is also responsible for disease in animals such as: cattle and neonatal and post-weaning pigs with host specificity taking place through gaining of colonization factors (CF) rather than development of animal specific lineages.

ETEC is the most vital but under documented bacterial cause of diarrhoea or cholera like illness in all age groups in areas with poor hygiene and inadequate clean water. Also, of the projected one billion yearly world-wide travellers, 20-60% of those traveling to low-income countries will suffer from travellers' diarrhoea (Hill and Beeching, 2010). In almost 30-70% of traveller's diarrhoea bacteria are the etiologic agent, of which ETEC are the most frequently discovered. Development of rabbit ileal loop test which result in the discovery of cholera toxin was also used for pure cultures of *E. coli* isolated from faeces and small bowels of children and adults revealing similar symptoms to cholera. Live cultures and culture filtrates of these variants when inoculated into isolated rabbit ileal loops give strong cholera-like secretary response resulting to the discovery of the heat-labile enterotoxin of *E. coli* and identification of ETEC pathotype in 1968 (Sack, 2011).

At least 25 separate proteinaceous colonization factors (CFs) have been recognized in ETEC strains which facilitate adhesion to epithelial cells. Although 30–50% of ETEC isolates have no characterized CF by phenotypic screening, novel CFs are constantly being recognised genetically thus decreasing the number of isolates with no apparent CF. Two further proteins, the outer membrane protein (Tia) and the glycosylated auto transporter(TibA), have been described to facilitate intimate cell binding and to induce ETEC invasion into epithelial cells, for the prototype ETEC strain H10407.35 While ETEC binds to leaf surfaces

via the flagellum shaft,(Shaw*et al.,* 2011) a novel adhesin, EtpA, situated on the tip of ETEC flagella facilitates attachment to mammalian host cells. EtpA is degraded by the serine protease auto-transporter of Enterobacteriaceae (SPATE), EatA, thereby moderating bacterial adhesion and accelerating transfer of heat labile (LT) toxin into host cells (Roy*et al.,* 2011). A model of sequential attachment is proposed whereby the long-range flagella-EtpA first anchors the bacterium to the host cell and permits shorter CFs to interact. EatA then degrades EtpA and lastly intimate attachment is facilitated by Tia and TibB (Roy *et al.,* 2011).

ETEC strains adhere to intestinal epithelial cells via a heterogeneous group of proteinacious surface organelle called colonization factors (CFs) which can be fimbrial, non-fimbrial or fibrillar (Croxen and Finlay, 2010). The more recent nomenclature refer to these structures as coli surface (CS) antigen, but some of the old terms still continue such as colonization factor antigen I (CFA/I). Despite the fact that more than 25 CFs have so far been recognized, on numerous variants no CF is detected which might be attributed to the technique (s) used for recognition, true lack of CFs or as yet unidentified ones. Subsequent to the initial adhesion and colonization, ETEC strains cause diarrhea by producing heat-labile (LT) and/or heat-stable (ST) enterotoxins, which are plasmid-encoded. ETEC bacteria secretes the small STs as a 72-amino acids pre-pro/toxin which is processed into an 18-19 amino acid active toxin called (STa) and a 42 amino acid toxin referred to as (STb). STa is synthesized by both human and animal strains, whereas STb is mostly identified in strains of veterinary origins. Heat-labile(LT) like the closely connected cholera toxin is a member of AB5 family of toxins which are heterohexameric molecules comprising of five B subunits and a single A subunit (Beddo *et al.,* 2011). The A1 domain constitutes the active toxin and is linked to the A2 domain via a disulfide bond (Fleckenstein *et al.,* 2010). The A2 fragment is the helical portion of the molecule and anchors the A subunit to the B pentamer which binds irreversibly to GM1 gangliosideas receptors on cell surface. The toxin is then co-opted and the A subunit ADP-ribosylates the stimulatory guaninenucleotide-binding protein, accelerating the levels of intracellular cyclic AMP producing diarrhea (Fleckenstein *et al.,* 2010).

The key virulence of ETEC happens through synthesis of heat stable (ST) and/or heat labile (LT) toxins. Two small (2,000 Da) discrete heat-stable toxins, STa/STI and STb/STII, occur although only the former is thought to cause human disease. STa/STI resembles the native intestinal hormone guanylin, attaching to and initiating the intestinal brush border guanylate-cyclase-C (GC-C) receptor, cumulating intracellular messenger cyclic GMP (cGMP) which in turns triggers cGMP-dependent protein kinase II leading to phosphorylation of the cystic fibosis trans-membrane regulator (CFTR) and deregulated ion absorption/secretion and hence diarrhea.(Abigail *et al.,* 2012)

The LT toxins can be separated into Type I (LT-I), generally in human isolates and closely related to cholera toxin, and Type II (LT-II), which are mainly from non-human isolates. LT toxins are AB5 toxins (one A subunit linked to a pentameric B subunit) and are conveyed across the bacterial outer membrane by the type 2 secretion system.42 LT remains membrane-associated by attaching the lipopolysaccharide (LPS) and is secreted in outer membrane vesicles (OMVs) that bind to ganglioside receptors on the host cell (GM1a for LT-I or GD1a/b for LT-II) through the LT-B subunit. The OMVs are then keenly endocytosed and the LT transported through the Golgi and endoplasmic reticulum (ER) to the cytosol44 where the A1 subunit then ADP-ribosylates host guanine nucleotide binding protein α-subunit (Gsα). This inhibits the GTPase activity of Gsα and constitutively triggers adenylatecyclase resulting to unrestrained rise of the intracellular cAMP concentration (Abigail *et al.,* 2012). This has pleotropic special effects within the cell including phosphorylation of the CFTR chloride channel by protein kinase A. The combination of LT and CT eventually leads to production of electrolytes and water resulting in osmotic diarrhea.

Diffusely adherent *Escherichia coli*

DAEC is a diverse group that produce a diffuse adherence pattern on HeLa and HEp-2 cells and has been incriminated with the watery diarrhoea that may become frequent in young children in both developing and developed nations as well as recurring urinary tract infections (Croxen and Finlay, 2010). It has been revealed that the relative danger of diarrhoea related to DAEC increases with age of children from 18 months to 5 years. The intestinal carriage of these group has also been shown to be prevalent in older children and adults. The result of this persistence is not known, but several remarks have recommended a potential role in the advancement of chronic inflammatory intestinal disease (Croxen and Finlay, 2010).

Two types of adhesins facilitating the DA pattern have so far been described separating the DAEC strains into AIDA-I-dependent group and those that their adhesins is encoded by a family of connected operons, which comprise both fimbrial and afimbrialadhesins. These sets of proteins are jointly designated Afa-Dr adhesins (Croxen and Finlay, 2010). The first afimbrialadhesin (afa) operon belonging to this group was characterized and analyzed in 1984 (Jafari *et al.*,2012), and later another operon in this family as well as the adhesins receptor were pronounced (Jafari *et al.*, 2012). AIDA-I is a 100 kDa outer membrane protein which is related with DA phenotype and was described by (Jafari *et al.*, 2012) who also showed that this adhesin was not usually encountered among DEAC isolates. The afa/dr/daa operons are genes that arise and are shown in a variety of genetic circumstances and the pathogenesis of DAEC seems to be mostly facilitated by Afa/Dr adhesin interactions with host cells. In addition a secreted autotransporter toxin (Sat) has also been involved in pathogenesis, but nevertheless, the implication of Afa/Dr DAEC strains in diarrhea remains controversial. Phenotypic discovery of DEAC is based on the mannose-resistant diffuse adhesion of these strains to cultured epithelialHEp-2 or HeLa cells (Jafari *et al.*, 2012). The adhesion assay however, is not specific for Afa/Dr DAEC detection, since other pathogenic *E. coli* including EPEC strains may display this pattern of adhesion. Other phenotypic testhave also been established, but none has shown convenient and universal to be used for isolation of all Afa/Dr DAEC isolates. Colony hybridization using various probes have also been established and used in epidemiological studies, but this method is laborious and time consuming and not proper for use on individual strains. Design of PCR methods that allow identification of all known Afa/Dr adhesins has been achieved (Jafari *et al.*, 2012), but even with this simpler and faster technique no report of Afa/Dr DAEC isolation in Iran has been published.

Once the Afa/Dradhesins attach their cellular target on enterocytes (DAF or CEACAMs) they relocalize the target around the site of bacterial attachment. For the Dradhesin this relocalization has been revealed to be dependent on Src kinase activation (Quevale*t al.*, 2011). After target mobilization, enterocyte signaling pathways (e.g., MAPK and PI3K) are initiated and IL-8 is produced (for the F1845 adhesin this requires HIF-1α74) encouraging transepithelial migration of human polymorphonuclear neutrophils (PMN). This excites the enterocytes to produce TNFα and IL-1β and up-regulate DAF to reinforce bacterial adhesion (Abigail *et al.*, 2012). DAEC can interrelate with the transmigrating PMNs and induce type I pili-dependent IL-8 release. Transmigrated PMNs are also induced to undergo apoptosis after interface with DAEC and have a weakened phagocytic ability, prolonging bacterial persistence in the gut.

The only recognized secreted factor related with DAEC infection is the SPATE Sat. Sat can induce reshuffle of the tight junction proteins ZO-1, ZO-3 and occlude in increasing paracellular porousness but not transepithelial resistance and can also bind spectrin, (Abigail *et al.*, 2012) reposition focal adhesion related proteins vinculin and paxillin, and cause cell detachment and caspase-independent cell death.

6. Laboratory Diagnosis of *Escherichia coli*

*Escherichia coli*can be grown both anaerobically and aerobically in the laboratory, preferably at 37°C, which can exist as non-motile or motile, with peritrichous flagellation. *E. coli* is readily retrieved

from fecal samples by culturing it on selective media (Matthew *et al.,* 2013). The change in pH as a result of lactose fermentation can be used to distinguish between lactose-fermenting and non-lactose-fermenting strains, as lactose-positive *E. coli* colonies will be seen red or pink on culture media like: Mac-Conkey agar. Not all *E. coli* strains, particularly most EIEC and *Shigella* strains, ferment lactose, so caution must be employed when using this diagnostic. While this selective culture plating can aid in isolating *E. coli* from Gram-positive organism and some other *Enterobacteriaceae* members, further morphological, phenotypic, and genotypic features need to be examined for further identification and verification of pathotypes (Matthew *et al.,* 2013)

Blood culture

Blood culture is an integral routine examination of patients with alleged bloodstream infection, and is essential to guide therapeutic intervention. The ideal technique for collecting blood culture is venepuncture, since it increases investigative yield, and has minimal rates of contamination, according to some studies. Since the timing of blood culture collection does not affect the detection of clinically pertinent microorganisms, most authorities endorse collecting several sets concurrently or for a short period of time, with the exception of patients with endovascular infection who need acknowledged continuous bacteremia (Wilson, 2007).

Two to four sets of blood samples would be collected, whenever possible, at independent locations. For adults, the volume required for the examination differs between 40 and 160 mL of blood, and for babies and children, the volume is age-based and does not exceed 1% of the patient's total blood volume. The prominence of blood culture, as well as urine, is related to the determination of the bacteria and the antibiogram, which guides the treatment to the best antibiotic to be administered (Kirn and Weinstein, 2013).

Biological scanning

Imaging strategies that uses biological radionuclides to trace hid infections and advance the specificity of the infection analysis that permits the invention of early pathophysiological changes even once there are not any obvious anatomical changes. compared to ex vivo methodology (blood culture), in vivo biological screening is most popular since it is correct, does not require a sterile surroundings and does not expose the health team to the danger of contamination by blood-borne pathogens (Akshay *et al.,* 2018). This sort of tool is employed chiefly in patients suspected of infection or symptom, however World Health Organization have had negative results for the cross-sectional image. Thus, the employment of marked blood cell traffic lets a response to hidden sites, supported the popularity of white blood cells marked with radionuclides. The marked leukocytes jaunt the infection sites and permit non-invasive pictures in areas of hidden infection, like osteitis, orthopaedic restorative, carditis or inflammation and enteral malady (Ady and Fong, 2014).

Pathogenesis of *Escherichia coli*

E coli's relationship with a number of individual virtually begins at birth. Neonate area unit are generally inoculated with maternal E. coli through exposure to her stool throughout birth and from future handling (Leimbach *et al.,* 2013). Though maybe upsetting to think over, this vaccination appears to be quite necessary. Indeed, *E. coli* becomes additional prevalent within the mother's microbiome throughout maternity, increasing the possibilities of her newborn's vaccination (Koren *et al.,* 2012). The colonizing strains generally have secretion systems and pili that enable them to connect to and act with the infant's gut animal tissue (Muinck *et al.,* 2013). This recently established and quickly growing *E. coli* population then changes the structure and performance of the animal tissue cells in ways in which seem crucial for healthy microbiome development.

Adherence patterns of enteric *E. coli*. and unhealthful *E. coli* needs adherence to the host animal tissue. Enteropathogenic *E. coli* (EPEC) and LEE-positive Shiga toxin-producing *E. coli* (STEC) area unit living thing pathogens that attach to the enteral animal tissue and efface microvilli, forming characteristic A/E lesions (Mathew *et al.,* 2013). Due to the presence of bundle-forming pili, EPEC is capable of forming

micro-colonies, leading to a localized adherence (LA) pattern. Enterotoxigenic *E. coli* (ETEC) uses colonization factors (CFs) for attachment to host enteral cells. Enteroaggregative *E. coli* (EAEC) forms biofilms on the enteral tissue layer, associated bacterium adhere to every different still on the cell surface to create an aggregated adherence pattern (AA) referred to as "stacked brick." Diffusely adherent E. coli (DAEC) is distributed over the surfaces of enteral cells, leading to a diffuse adherence (DA) pattern. Adherent invasive *E. coli* (AIEC) colonizes the enteral mucosae of patients with Crohn's disease and is capable of offensive animal tissue cells still as replicating at intervals macrophages. AIEC uses kind I pili to stick to enteral cells and long polar fimbriae that contribute to invasion. Enteroinvasive *E. coli* (EIEC)/Shigella area unit living thing pathogens that penetrate the enteral animal tissue through M cells to achieve access to the connective tissue. EIEC/Shigella escape sub-mucosal phagocytes by induction of macrophage necrobiosis followed by basolateral invasion of colonocytes and lateral unfold (Mathew *et al.,* 2013)

7. *Escherichia coli* as a Global Pathogen

Among gram-negative bacilli, *E. coli* is that the most widespread infective agent that causes numerous infections round the world. It has caused serious morbidity and mortality rates worldwide (Uçar *et al.*, 2015).

During 2003–2012, a complete of 390 *E. coli* O157 outbreaks were recorded. These outbreaks resulted in four,928 diseases, 1,272 (26% of illnesses) hospitalizations, 299 (6%) physician-diagnosed Hus cases, and 33 (0.7%) deaths (Katherine *et al.,* 2015). The median eruption size was six diseases (range 2–238). Primary transmission modes were food-borne (255 outbreaks, 65%), animal contact (39, 10%), person-to-person (39, 10%), waterborne (15, 4%), and different or unknown (42, 11%). Food-borne illness outbreaks caused the foremost diseases (3,667, 74%), hospitalizations (1,035, 81%), physician-diagnosed Hus cases (209, 70%), and deaths (25, 70%) (Katherine *et al.,* 2015).

Escherichia coli ranked first and second because the most typical reason for community-acquired and hospital-acquired infection, severally (Laupland *et al.*, 2008). *E. coli* infections sometimes arise as a complication of focal infections of the urinary or gastrointestinal tracts, though sometimes they conjointly cause primary bacteraemia while not a defined supply. *E. coli* is additionally a significant reason for invasive infections, together with bacteraemic infection and infectious disease within the time of life (Laupland *et al.*, 2008).

However, the kinds and amount of microorganism on food can be altered due to food processing, inappropriate purchasing, preparing, storing, serving or cooking. Rise in the number of these microorganisms due to the abovementioned changes can lead to spoiling of the food, causing a pathogenic effect on humans (Ibrahim, 2015). The foremost vital of food-borne morbific bacterium is *Escherichia coli*. It is transmitted through feculent or oral route and it ought to, beneath no circumstances, be present in any food. The foremost distinguished symptom caused by this being is its diarrheagenic impact. Moreover, it is famed to cause infection, infectious disease and lots of enteric diseases. Inability to make sure food safety is one in every of the largest food-related issues. Food safety suggests that guaranteeing necessary hygienical conditions and taking protecting safety precautions for a healthy and safe food production throughout all processes from getting raw materials to production, transportation, storage, distribution and consumption of food (Ertaş *et al.,* 2013).

8. *Escherichia coli*as a Source of Blood Stream Infection

Isolates that square measure capable of gaining access to and living within the blood square measure referred to as extra-intestinal morbific E. *coli* (ExPEC) (Russo and Johnson, 2003) and cause a spread of infections, as well as urinary tract infections (UTI), sepsis, and neonatal meningitis (Mora-Rillo *et al.,* 2015). The foremost common extra-intestinal website settled by these bacterium is that the tract, that successively, could be a common supply for blood infections (Micenková *et al.,* 2017).The mortality related to bacteraemia are associated *to E.*

coli was 33.3%. According to Russo and Johnson (2003), *E. coli* bacteraemia features a case-fatality rate of 5 to 30% associate degreed represents a progressive vital endemic drawback, accounting for many thousands of lives lost and billions of health care currencies spent every year.

ETEC are shown to be the foremost common microorganism enteric microorganism, accounting for roughly 20% of cases *E. coli* infection. The age at that a primary ETEC infection will be documented depends to some extent on the composition of ETEC that's infecting the kid.

In a study in Guinea capital of Guinea-Bissau, it absolutely was reportable that within the youngest age bracket, 3 months, ETEC strains produce growth hormone and LT were most typical, whereas at 6 to 7 months ETEC strains manufacturing STP, STpLT, and SThLT predominated (Firdausi *et al.,* 2005).

In Egypt it was revealed to be the most significant cause of diarrhoea in the study infants, accounting for about 70% of the first episodes. The incidence was greater in males than females. In a detailed examination in children 0 to 5 years in Bangladesh, 90% of cases of ETEC diarrhoea reporting to the hospital were children aged from 3 months to 2 years (Firdausi *et al.,* 2005). In an on-going birth cohort study in Bangladesh, it was establish to be the most common cause of diarrhoea in children 0 to 2 years of age, accounting for 18% of all diarrhoea.

In the report by Iregbu *et al.* (2013) on "Neonatal Infections Caused by *Escherichia coli* at The National Hospital, Abuja: A Three-Year Retrospective Study" it was observed that 251(33.2%) bacteria were isolated and 17(6.8%) were *E. coli* out of a total of 757 specimen submitted for analysis within the period under review (Iregbu *et al.,* 2013).

In the United States of America, *E. coli* sepsis was associated with nearly 40,000 deaths in 2001, a number that corresponds to 17% of all cases of sepsis (Akshay *et al.,* 2020).

In 2017, almost half of all global sepsis cases occurred among children, with an estimated 20 million cases and 2.9 million world-wide deaths in children under five years of age with *E. coli* reported as an emerging threat (Rudd *et al.,* 2020)

STEC *E. coli* O104:H4 has been responsible for a large number of outbreaks in the recent years (Nerino *et al.,* 2013). During the spring of 2011, a novel *E. coli* O104:H4 serotype infected about 4,000 individuals in Central Europe, mainly in Germany, provoking more than 900 cases of HUS. This particular pathogen demonstrated a combination of virulence factors from both EAEC and EHEC strains. A strain similar to the current outbreak strain had been previously isolated and characterised in Republic of Georgia (Nerino *et al.,* 2013).

9. *Escherichia coli* in Urinary Tract Infection

In a study conducted by Ndako *et al.* (2019) on the Incidence of Urinary Tract Infection in a Rural Community of South-West, Nigeria. *Escherichia coli* were found to be responsible for 28.17% of the cases associated to Urinary Tract Infection (UTI). Also, (Bankole *et al.,* 2011) reported *Escherichia coli* as the predominant isolate causing UTI in a study carried out on "Urinary tract infection in a rural community of Nigeria".

Also, UTI prevalence among patients attending hospitals in Bushenyi District, Uganda. *Escherichia coli* was reported as the most prevalent bacterial uropathogen with 36/86 (41.9%)(Martin *et al.,* 2019).Reports on etiology of UTIs uropathogens at KAMC in Riyadh, a capital city of Saudi Arabia recorded 93.55, 60.24, and 45.83% of the uropathogens which is similar to previous studies that conducted in Saudi Arabia making *E. coli* the majority of pathogen isolated from urine culture in pediatric, adult, and elderly (Menyfah *et al.,* 2018) as also reported in other countries (Menyfah *et al.,* 2018).Almost 25% of sepsis cases originate from the urogenital tract. Considering this percentage, the most common pathogen that causes urinary tract infection (and, consequently, urosepsis) is *Escherichia coli* (50%) (Akshay *et al.,* 2020)

10. *Escherichia coli* in Meningitis

A great degree of bacteremia was also revealed to be a primary cause for penetration into the brain by circulating *E. coli* in neonatal and adult animals with experimental haematogenous *E. coli* meningitis (Kwang, 2016), but an approximately 106-fold greater inoculum of *E. coli* is required to induce a similar high-level bacteremia in adult animals compared to neonatal animals (Kwang, 2016).

Data obtained from England and Wales from 1985 to 1987 and from 1996 to 1997 showed *Escherichia coli* is responsible for (18% to 26%) cause of neonatal meningitis over this period (Ogunlesi, 2013). *E. coli* K1 has also been reported by (Meng *et al.,* 2021) to plays an important role in the pathogenesis of meningitis. The adhesion of *E. coli* K1 to human brain micro-vascular endothelial cells is one of the key issues in the pathogenesis of bacterial neonatal meningitis (Meng *et al.,* 2021).

Between 2013 to 2014 *E.coli* was identified as the most common causes of bacterial meningitis in the first 90 days of life in Canada with a prevalent rate of (n = 37; 33%) (Ouchenir *et al.,* 2017).

11. Lettuce and Green Leafy Vegetable associated with *Escherichia coli* outbreak

United State Food and Drug Administration (FDA) has completed its investigation of the multistate outbreak of Shiga toxin-producing *E. coli* 0151:H7 that happened last fall and was related to leafy greens. The FDA and CDC found the outbreak was caused by an *E. coli* strain that was genetically related to the strain found in the fall 2019 outbreak involving romaine lettuce from the Central Coastal growing regions in northern and central California. (CDC, 2020).

At least 32 people have been sickened in the US, with 13 taken to hospital, while another 18 people have been stricken in Canada as a result of infection associated with *E. coli* consumption from green leafy vegetable (CDC, 2020).

In the United States, from 1990 to 2005, the Food Safety Project reported that at least 713 produce-related outbreaks were associated with food-borne disease, of which 12% involved fresh fruits and vegetables (Goodburn and Wallace, 2013). In 2011, the Advisory Committee on the Microbiological Safety of Food (ACMSF) reported that, in the UK, there were 531 cases of reported illness, including one death, related to the ingestion of vegetables and fruits between 2008 and 2010 (Luna-Guevara *et al.,* 2019).

In the same year, Germany recorded an outbreak of Shiga toxin-producing *E. coli* (STEC) serotype O104 : H4; at the end of the outbreak, 3785 cases of illness were reported outside of Germany, recognizing contaminated sprouted seeds as accountable for the food-borne outbreak (Luna-Guevara *et al.,* 2019).

In Nigeria, Bako *et al*. (2018) detected three hundred (300) samples of vegetables and fruits gotten from five (5) different Markets in Kaduna State Metropolis, Nigeria and examined for *Escherichia coli*. It was analyzed using the Spread Plate Method. The number of positive samples ranged between 6-10 and the total number of positive samples is 38. The highest number of *Escherichia coli* was as a result of poor hygiene practice and handling (Bako *et al.,* 2018).

12. Milk associated with *Escherichia coli* outbreak

Outbreaks of VTEC infections involving serogroup O157 have been reported from different nations of the world as well as United States, Canada, Asia, Australia, Europe, and Africa through various sources of infection and different case fatality (Nigatu *et al.,* 2017). In southern Africa and Swaziland in 1992 an outburst of *E. coli* O157:H7 affecting thousands was credited to contamination of surface water with cattle dung and animal carcasses. Dairy products (milk and cheese), both pasteurized and unpasteurized, of bovine and ovine source have been involved in VTEC infections. This has included a number of outbreaks among children that have been credited

to the consumption of raw milk and dairy products (Nigatu *et al.*, 2017).

13. Water associated with *Escherichia coli* outbreak

In the United States, the first reported drinking water outbreak of *E. coli* O157:H7 infections happened in 1989 in rural Missouri (Sonja *et al.*, 2002). Since this outbreak, six others have been connected with drinking water. Three were small and occurred in a camp, a recreational vehicle park, and a well (Centers for Disease Control and Prevention [CDC]). More recently, three highly publicized drinking water outbreaks of *E. coli* O157:H7 infections (one each in Wyoming, New York, and Canada), have focused increased attention on the safety of drinking water (Sonja *et al.*, 2002). In Nigeria, The frequency of isolation of *Escherichia coli* was reported to be high during the wet season because of pollution of the well waters which is in agreement with the findings of Kisteman *et al.* (2002).

14. Conclusion

Escherichia coli remains a foremost pathogen worldwide. Many studies have implicated *Escherichia coli* in various foods and blood stream infection ranges from bacteraemia to haemolytic uremic syndrome. However, its role in various food poisoning all over the world cannot be over emphasized. This is because food is the major vehicle of its transmission. Therefore, effort should be made at ensuring proper hyginecity and strictly compliance to the safe food practise by all the food vendor. Above all, preservation of the processed food in appropriate places and temperatures, checking proper packaging and proper storage, cooking in proper temperatures, allowing proper cooling and keeping the cooked food away from raw food is key to the prevention of *Escherichia coli* infection.

15. Recommendation

The clinical importance of *Escherichia coli* cannot be over emphasized, therefore, the general populace should ensure adequate safety in all the food consumed either as a ready to eat or cooked food. The need to avoid half-done meat and unsafe drinking water is key to the prevention of this global pathogen. It is therefore recommend that consumers should develop their own safety methods at home by following the above mentioned measures.

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