American Journal of Biology and Natural Sciences
https://biojournals.us/index.php/AJBNS
ISSN: 2997-7185

Virulence Factors of Escherichia Coli: A Comprehensive Review

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Received: 2024, 15, Jan
Accepted: 2025, 21, Feb
Published: 2025, 28, mar

Annotation: Escherichia coli (E. coli), a diverse and adaptable gram-negative bacterium, is widely recognized for its dual role as a commensal organism and a major pathogen responsible for a variety of intestinal and extraintestinal infections. Despite decades of research, a comprehensive understanding of its virulence mechanisms and regulatory networks remains incomplete. This review synthesizes recent developments in E. coli pathogenesis, focusing on key virulence factors such as adhesins, toxins, iron uptake systems, invasion mechanisms, and immune evasion strategies. By analyzing molecular genetics, host-pathogen interactions, and resistance patterns across multiple E. coli pathotypes, including UPEC, EHEC, and EPEC, the study highlights how mobile genetic elements, regulatory systems, and environmental pressures drive virulence expression and antibiotic resistance. The findings underscore the urgent need for integrated diagnostic tools, surveillance

strategies, and alternative therapeutic interventions such as vaccines and anti-virulence therapies. This review provides critical insight into the multifactorial nature of E. coli pathogenicity and guides future research in combating its public health impact.

Keywords: Escherichia coli, virulence factors, pathotypes, antibiotic resistance, host-pathogen interaction, uropathogenic E. coli, enteropathogenic E. coli, immune evasion.

1. Introduction

Escherichia coli, commonly known as E. coli, are rod-shaped, facultative anaerobic, and gram-negative bacteria within the genus Escherichia and widely distributed in the gut of warm-blooded organisms. They are versatile organisms that can colonize various environments, including soil and water. Despite their versatility, E. coli are most commonly associated with the lower intestines of warm-blooded animals, including humans. The E. coli species were first described by Theodor Escherich in 1885 when isolating them from the stool of a pediatric patient. A few hours after birth, E. coli rapidly colonizes the gastrointestinal tract of newborns. By the end of the first week, E. coli becomes the predominant bacterial species, representing up to 1% of an individual's fecal biomass. Although colonization normally begins after birth, E. coli have been detected in the amniotic fluid of women who underwent a cesarean section before the delivery, suggesting the possibility of early colonization. There are two different phenotypes of an early onset of sepsis caused by E. coli: (1) more severe and fatal sepsis within 24 hours of life, usually attributed to a non-k-typeable organism, and (2) sepsis occurring within 24 hours to seven days of life, usually caused by certain serotypes of E. coli.

Many populations of the commensal strains of E. coli coexist harmlessly; however, under certain circumstances, such as changes in immune status or colonization with a different species, overgrowth of a particular commensal strain may occur. This may lead to tissue damage or invade local tissue, causing disease as a consequence of newly occupying a niche. Disease-causing commensal flora includes Staphylococcus aureus, Clostridium difficile, and enterotoxigenic Bacteroides fragilis. In addition to local infections, extra-intestinal infections may occur. For example, Uropathogenic E. coli strains are pathogenic extraintestinal isolates that infect the bladder and kidneys and occur primarily in women. On the other hand, ESO104, a probiotic E. coli isolated from stools, is a commensal bacterium with an L,L-diaminopimelate-L-lyase but no evidence of human virulence. In general, uropathogenic E. coli strains are responsible for approximately 85% of UTIs, with many of these infections possibly being recurrent infections. Military personnel, sexually active individuals with unprotected lower urinary tract intercourse, individuals with urinary tract abnormalities, indwelling catheterized patients, post-menopausal women with a lack of estrogen, and elderly individuals with impaired host immune responses have a higher risk of UTIs. Extraintestinal infections can also be life-threatening, such as urinary tract infections; in these cases, E. coli causes approximately 92% of cases. Additionally, ETEC-mediated diarrhea in children is rampant in the developing world, particularly Sub-Saharan Africa and South Asia. There are 26.6 cases of diarrheal disease for every death, but 72% of the people

who die from diarrheal disease are children under five. Improvements in water and sanitation would permit regular handwashing with soap after pooping or before eating and could save the lives of 2.2 million people worldwide annually. [1][2][3]

1.1. Background and Significance

Escherichia coli strains are the most common members of the human gastrointestinal tract, being both commensal bacteria and primary pathogens associated with various types of clinical infections. The ubiquity of these strains and their diverse roles make them one of the model organisms for bacterial pathogenesis studies as well as creating a huge challenge for human health [4]. These bacteria produce an extensive battery of virulence factors supporting efficient infection and afflict a wide range of diseases. The most important pathotypes involved in life-threatening illness include enterohemorrhagic E. coli (EHEC), enteroinvasive E. coli (EIEC), enteropathogenic E. coli (EPEC), enterotoxigenic E. coli (ETEC), and extra-intestinal pathogenic E. coli (ExPEC) [5]. ExPEC strains cause a variety of diseases outside the gastrointestinal tract and are often found in serious infections, such as sepsis, of either urinary, renal, and neurological origin. These bacteria contain a set of virulence properties, frequently linked with multiple-antibiotic resistance, that facilitate exploitation of distinct niches both in the host and food production environment. Several factors play a role in the expanding virulences of E. coli. Changes in gut conditions coinciding with age, immune status, or diet, appearing as a co-infection factor, might modify colonizing strains towards pathogenicity. The host (individual) factor is clearly underestimated in the context of overall virulence or virulent population prevalence with irrelevant significance concerning genome constitution. Studies on this area are mainly restricted to changes in immunological responses under the influence of specific E. coli products. However, more recent trials using correlation with cases of pyelonephritis or experimental staphylococcal infection suggest potential impact of immuno-adherence on successful colonization and progression of infection.

1.2. Objective of the Review

Escherichia coli are gram-negative Enterobacteriaceae bacteria that colonize the gastrointestinal tract of newborn and young infants and serve as commensals, keeping a balance of the intestine microorganisms and play protective and beneficial roles in the host gut. Commensal strains comprise two main phylogroups, group A and B1, and occasionally groups B2 and D. Over the past several decades, interest in pathogenicity of E. coli has attracted considerable attention as some commensal strains have become increasingly important as emerging broad-host-range pathogens. E. coli strains are among the leading causes of disease either in the form of intestinal diseases, such as diarrhea in children and elderly, and on extraintestinal diseases including neonatal meningitis, septicemia and urinary tract infections (UTIs) [6].

The first report of a distinctly defined pathogenic E. coli causing diarrhea was given two decades ago. The diversity of intestinal and extraintestinal diseases caused by pathogenic E. coli strains was later reported, and the grouping of E. coli strains based on clinical symptoms has advanced quickly. At present, isolates that produce closely related clinical symptoms are classified as belonging to the same pathotype of E. coli strains. All of the above-described progress has made E. coli one of the better understood pathogenic microorganisms. Due to the vast diversity of diseases caused by pathogenic E. coli, various pathogens have been described, each one characterized by different clinical symptoms and infection process. For example, certain lineages causing primarily extraintestinal diseases have recently been described, such as uropathogenic (UPEC) and meningitis-associated (MNEC) E. coli.

2. Overview of Escherichia coli

Escherichia (E.) coli, rod-shaped and gram-negative bacteria belonging to the Enterobacteriaceae family, were first isolated from infant stool and characterized by Theodor Escherich in 1885 [6]. A few hours after their birth, E. coli colonize and inhabit the gastrointestinal tract of infants. Usually,

E. coli are classified into commensal strains found in mammalian guts along with few pathotypes that can cause a wide range of diseases. However, massive outbreaks of contaminated foodstuff infected by certain serotypes or pathotypes increased the scientific interest of understanding E. coli virulence and its disease-causing capabilities. Consequently, various studies have reviewed the existing knowledge and discovery of new factors over the years. There are many toxins and adhesion factors that have been reported as virulence factors in enteric pathogenic E. coli. The investigation of these virulence factors and their associated encoding genes, as well as the host proteins, can provide explicit knowledge about the interaction between these factors in E. coli pathotypes and host proteins at the molecular level.

The severity of infection is a product of many factors including the virulence properties and the antibiotic resistance of the microorganism. E. coli has been classified into 9 pathovars based on their virulence factors and diseases. Infections caused by E. coli include intestinal infections, such as enterotoxigenic E. coli (ETEC), enterohemorrhagic E. coli (EHEC), enteroinvasive E. coli (EIEC), enteropathogenic E. coli (EPEC), and enterocytoaggregative E. coli (EaggEC); and extra intestinal infections, such as ExPEC, which include neonatal meningitis-causing E. coli (NMEC), associated with septicemia-causing uropathogenic E. coli (UPEC), and bacteremia-causing E. coli (APEC) [4]. Furthermore, the wide gene pool of E. coli also facilitates the acquisition and transfer of resistance genes. On the other hand, the overuse of antibiotics increases the selection pressure acting as a driving force for horizontal gene transfer (HGT) from resistant strains to non-resistant strains. Either way, it is alarming to observe the progressive emergence of multi-drug resistant bacteria. Resistance to existing antibiotics occasionally forces the development of new antibiotics, and the maintenance of old ones. However, the very nature of the process encourages a fast response from the bacteria. New antibiotics become swiftly ineffectual as the bacteria evolve resistance. And the overuse of an old antibiotic eventually produces resistant bacteria with not many treatment alternatives left.

In the view of the threatening appearance of a post-antibiotic era with the concomitant extinction of many conventional surgical and medical practices, it has been advised to look for novel strategies for fighting bacterial infection, such as the inhibition of virulence properties since this kind of anti-infective therapeutical approach does not provide a particular advantage for bacteria to develop resistance.

2.1. Taxonomy and Classification

Escherichia coli, a rod-shaped and gram-negative bacteria belonging to the Enterobacteriaceae family, were first isolated from infant stool and characterized by Theodor Escherich in 1885. Escherichia coli (E. coli) is the most intensively and diversely studied enteric pathogenic strain among the five known human and/or animal enterobacterial strains [6]. E. coli strains preferably have fewer non-disease-causing habitats. They are usually isolated from human gut contents or associated with related foodstuffs such as plants, vegetables, fish, and meat (ruminant, turkey). Some commensal E. coli strains have industrially relevant properties, such as production of vitamins, and can protect the human gut against colonization by other pathogens. However, a minor part of disease-causing or virulent E. coli strains must be closely monitored. The distinction between virulent and non-virulent E. coli strains is arbitrary and may rely on the urgency of the situation. In this context, the distinction was based on the severity of the sequenced strain.

A few hours after birth, E. coli colonize and inhabit the gastrointestinal tract of infants. The commensal strains of E. coli in the human gut have adaptive co-evolved and synergistically adapted to the gut environment with nutritional and ecological advantages. At the genetic level, E. coli strains continue to deviate in terms of gene gain or loss and single nucleotide polymorphism (SNP) accumulation pressure for improving species adaptation and co-evolution. However, about 10% of the 38 million detected SNPs in the E. coli genome lead to gene inactivation, with the loss of function or mutation of critical pathway activation. The strains having a certain number of mutations do not obtain dissimilar adaptive advantages, but are more likely to become less

adaptable and have deleterious effects on strains. Unlike other bacterial strains, E. coli pathotypes are highly successful and have lost redundant gene function through niche differentiation over time. The strains efficiently utilize their encoded virulence factors to engage in a successful colonization of the target host.

2.2. Distribution and Prevalence

Escherichia coli is a ubiquitous bacterium found in the intestinal tract of warm-blooded animals, including humans. Most E. coli strains are commensal and harmless. However, some strains can cause intestinal and extra-intestinal infections. Infections can be endogenous, from previously colonized strains that have acquired new virulence properties, or exogenously acquired through food, water, animals, or environments likewise contaminated. The acquisition of new virulence properties can occur through the transfer of virulence genes via mobile genetic elements like plasmids, bacteriophages, pathogenicity islands (PAI), and other genomic islands. Infections ranging from mild enteritis to life-threatening systemic infections are often associated with the ExPEC (Extra-intestinal pathogenic E. coli) group [7].

Extra-intestinal pathogenic E. coli is a heterogenic group comprising many different serotypes and strains. The occurrence of ExPEC strains is usually associated with infections of non-enteric organs, frequently involving resistance to multiple antibiotics. Among E. coli isolates, ExPEC is the major pathotype causing colibacillosis, an acute and largely infectious disease that occurs in birds raised for meat or eggs. Infections of birds caused by APEC result in substantial economic losses in poultry industry worldwide. It is suggested that APEC strains can infect humans through the consumption of contaminated food, even after cooking. The foodborne transmission of APEC strains harboring virulence gene markers could pose a potential risk of extraintestinal infections in humans. Moreover, the impact of resistance to antibiotics has long been recognized. APEC strains have been isolated from retail samples, including frozen chicken pieces and tuaser meat. Systematic monitoring of various foods and surveillance of infections to implement proper public health interventions is necessary.

3. Virulence Factors

Escherichia coli, a rod-shaped gram-negative bacterium that belongs to the Enterobacteriaceae family, was first isolated from the feces of a newborn in 1885 by Theodor Escherich. E. coli colonize and thrive in the intestines of the infant within hours of birth. But note must be made that commensal E. coli, pests that are part of a natural society with hosts, could infect patients with compromised hosts, particularly through breached gastrointestinal barriers. Nevertheless, some E. coli strains have been shown to create a number of diseases in humans and domesticated livestock all over the globe, sometimes resulting in catastrophic consequences for such populations. In relation to human infections, 9 distinct pathovars were identified for the E. coli strains responsible for diarrhea and extraintestinal diseases. Seven of the 9 pathovars are defined as enteric pathogenic E. coli, which are a big public health issue globally. The enteric pathogenic E. coli destroyed the main population centers in both developing and well-developed nations, causing several deaths in outbreaks. Enteric E. coli pathotypes, with a range of pathogenicity strategies, infect patients. Virulence factors are explained by genic sequences encoding a variety of proteins that enable an organism to replicate by affecting various phenotypes of the host organism. These virulence aspects may comprise the production of particular adherence species, the formation of distinctive coagulation-like material, the secretion of cytotoxins harmful to the host cells, the creation of type-III injection structures, and the synthesis of various feces like effector proteins. Macrophages are very persistent in nature and provide a preferred intracellular environment for the replication of extraintestinal pathogenic E. coli. The growth of extraintestinal pathogenic E. coli within macrophages is as a result of the extensive use of the exonogenic and endogenic iron sources necessary for bacterial proliferation. Consequently, mutants with an interrupted arcAB gene did not grow within macrophages as opposed to the isogenic wild types. [8][9][10]

3.1. Adhesins and Colonization Factors

The potent effectors secreted by pathogenic Esherichia coli strains detectable in culture supernatants may be the result of a specific secretory process similar to other ATP-binding cassette system—dependent export systems or protease release by vesiculation of large outer membrane blebs. Intestinal inflammation in Shigellosis is the result of an interaction between Shigella flexneri, Esherichia coli strains and enteroinvasive and distinctive colonisation properties of significant enteropathogens such as invasive enteropathogenic Esherichia coli, pathogenic causing an often inflammatory local response. That the plant lectin—induced cytokine secretion was attenuated in a verotoxic gene—deleted isogenic mutant of the enterohaemorrhagic E. coli serotype O157:H7, even though the wild type was able to induce secretion cytotoxins from Vero cells. Aggregation and adherence of enteropathogenic Esherichia coli to human intestinal enterocytes translocated by Esherichia coli through tight junctions is not sufficient for apoptosis in epithelial cells as such translocation is also seen in wild-type Esherichia coli but does not trigger apoptosis in such cells. A total of 224 strains comprising 157 Esherichia coli isolates from humans, healthy bovines, and bovines with edema disease and 67 isotypes from porcine edema disease of differing serotypes were tested for F18 adhesion and possession of the F18 and variants. Many enteric bacterial pathogens produce toxins that are responsible for the symptoms of the diseases that they cause. Disease can result from the actions of either plasmid—borne or chromosome—borne toxins, respectively. Typically, enterotoxigenic Esherichia coli strains carry a plasmid of about 180 mDa that harbors the genes which encode the heat—stable and heat—labile enterotoxins [11]. Other diarrhea—associated bacteria produce distinct toxins. Invading strains, mostly of Shigellae and pathogenic Esherichia coli, are associated with a diffusely adhere phenotype in vitro. Peptides derived from the B—oligomer region of the VT signal transduction.

3.2. Toxins

Toxins produced by Escherichia coli strain cause an alteration of the cytoskeleton. This is, e.g., induction of actin stress-fiber structures found after the toxin uptake by the host cell. This process is a result of an elongate activation of the Rho subfamily of small GTP-binding proteins (Rho proteins) followed by an inhibition of their intrinsic GTPase activity that results in their accumulation in the GTP-bound form within the cell [12]. A high concentration of GTP-bound Rho leads to the modification of its effectors, which are the Rho-associated formin-homology protein and the Rho-kinase. These proteins are responsible for the actin network reorganization, which can be therefore changed by the cell. The toxin acts as a GTPase-activating protein of the Rho proteins.

Certain strains of Escherichia coli produce toxins which induce diarrhea. These toxins covalently modify the small GTP-binding proteins of the Rho- or Ras-subfamily, which run the signal transduction pathways inside the cell. The results presented here show that the mucosal enteric American pathogens Escherichia coli and Citrobacter rodentium of the HST1 group produce a toxin that transfer an adenosine diphosphate-ribosyl group from nicotinamide adenine dinucleotide onto asparagine-149 of the RhoA protein. Asparagine-41 of the Ras protein of susceptible strains of ETEC is modified by another toxin of the HST2 group. These toxins require the presence of glutamine-61 at the C-terminus of the GTP-binding proteins.

3.3. Iron Uptake Mechanisms

Uropathogenic Escherichia coli (UPEC) is thought to be the most common cause of urinary tract infection (UTI) cases and is something that can lead to serious disease and death. However, all E. coli species produce virulence factors that are a subclass of the secreted proteins that are controlled by a specific type III secretion system (T3SS). Moreover, certain E. coli strains encode a needle complex that promotes the horizontal transfer of virulence factors. Virulence factors of E. coli are mainly encoded in the DC110 and DC139 islands, which are found in highly pathogenic strains. Escherichia coli strains frequently carry plasmids that can confer resistance to antibiotics, stress resistance, and pathogenesis on the host bacterium. Some plasmids encode toxins that

enhance bacterial virulence [13]. Plasmids and pathogenic islands (PAIs) have been joined. Conjugal transfer of PAI can be promoted by increased mutations in the host strain, which facilitates the formation of niche-specific virulent strains. Enteroinvasive E. coli can attach to the host cell surface and invade the host cell by re-organizing actin by utilizing the T3SS. Enterohemorrhagic E. coli is an important cause of outbreaks of food poisoning and produces the Shiga toxin, which is a toxin that damages the host cell by promoting DNA cleavage. Sizeiultr viomi Ultra Pathogenic Vibrio strains have been shown to have the ability to conjugate the cdiB gene (CDI) on a plasmid with a colloid by contact reaction and to cause the host to die or fuse with the host. E. coli Nissle is a silcer-resistant E. coli strain isolated in 1917. E. coli Nissle is thought to inhibit the growth of other pathogenic E. coli species by producing microcins. E. coli Nissle was also thought to act as a sentinel in the intestines to detect and signal the appearance of pathogens in the intestines. It is known that commensal E. coli produces microcins through the stimulation of interferon to protect against microbiota fluctuations. E. coli Nissle produces three microcins in total, but Nissle UMXN, which cannot produce microcins, was also highly virulent. E. coli Nissle is sensitive to stress caused by reactive oxygen damage. Resting conditions are favorable for the survival of virulent strains of mazEF strains, such as Mali E., to whom Nissle belongs. In addition, the PstS protein formed by the psi gene expressed in the silenced pair interferes with the function of lum EF, contributing to the survival of virulent strains.

3.4. Invasion Factors

E. coli is the responsible agent of many illnesses, being a major factor in the emergence and re-emergence of various pathotypes like EHEC and ExPEC. The need to understand and control these pathotypes led to the investigation and recognition of some of their most important virulence factors. Virulence factors are produced by pathogenic bacteria to induce harmful effects and enhance their pathogenity [6]. There are different types of these virulence factors in the E. coli in addition to the characteristic LEE islands. Concerning attachment and invasion, E. coli has some surface factors to interact with abiotic or host surfaces. E. coli has type 1 fimbriae, curli, or several kinds of self-assembling proteinaceous filaments. Moreover, the AIDA-I outer membrane protein works as a symmetrical, trimeric adhesion similarly to pili and important protein for the initial colonization of the gut.

Moreover, AIDA-I was shown to be phylletically similar to the listerial InlA and Yersinia adhesins. Additionally, chromosonal AIDA-I gene was identified as a precursor for the Yersinial YadA adhesin. E. coli adherence suppresses Rho GTPases and Arp2/3, EPEC and EHEC E. coli uses a machinery to adhere and secures an intimate attachment to host cells. The so-called locus of enterocyte effacement (LEE) pathogenicity island contains the T3SS and the subsequent secretion of effector proteins to alter cytoskeletal structures.

4. Regulation of Virulence Factors

Escherichia coli is a gram-negative, rod-shaped bacterium, named in honour of Theodor Escherich, a German paediatrician who identified it in 1885. It is a fecal bacterium, but not strictly as such. E. coli is an adaptative and mutant bacterium, which allows growth at different temperatures, under many drugs and osmolarity, with different carbon sources, and even using heavy metals. Some strains are part of human and animal gut microbiota. They maintain intestinal equilibrium, and, in even cases, control pathogens by colonization inhibition and competition for nutrients. However, some variants hold virulence factors that produce different gastrointestinal and extraintestinal diseases. Several extra-intestinal pathogenic E. coli (ExPEC) strains hold virulence plasmids, carrying different nucleotide acid genes and two kinds of toxins. The main ExPEC diseases are (1) sepsis-psychronephritis with renal failure in women induced by UPEC; (2) animal diseases by APEC (avian), REPEC and other strains. Enterohemorrhagic E. coli and two EHEC strains, also named STEC, hold two toxins: (1) the Shigella toxin, similar to the Shigella one, inducing bloody diarrhea and Greek syndromes with kidney failure; and (2) HUS, haemolytic uremic syndrome also with RPO (red plasma organism) and terapic requirements. This syndrome

is common in children.

Enteropathogenic E. coli also induces diarrhea. Humans are the main host; neonates, infants, Gno-monogastrycets, premature, S. Bovines and diabetics may acquire diarrhea and die. The enteropathogenic Escherichia coli (EPEC) has a perfect adherence mechanism by effacing the microvilli (AE-Les, attaching and effacement lesions); the enterohaemorrhagic E. coli (EHEC) carry genes for lesions at a prophage, the LEE gene in addition to the bfp gene for plasmid born pilus; bfp+EHEC+EPEC+AI/(EC)} strains are usually LEE+ and bfp+ too. Beer is a TCS E. coli derivative of O157 holding a CDS gene in LEE and causes quarantine disease in children [14]. After infection by enteropathogenic Escherichia coli, in a few minutes it induces intimate adherence to enterocytes. For instance, LEE induction of EHEC when it is contacted with another EHEC. There are regulatory genes in the LEE gene that control it. Usually they are auto-regulated and co-regulated. Ler is an auto-regulation LEE gene that triggers the rest; in the absence of the other. Or with tips (entered) takes double action.

4.1. Global Regulators

The genetic content of E. coli is known to be controlled by a super network of regulatory systems and even post-transcriptional regulation. In E. coli, around 300 genes are under the control of global regulatory systems. Global regulator Envelope stress sigma factors Transcriptional overseers of metabolism Global regulator linking ExPEC to neonatal meningitis. Until now, the control by global regulators of known single virulence factors has been discovered.

The ArcAB system of E. coli represents a prototype for global regulators, which can be modified by the modification of the environment. Pathogenic E. coli, including enterohemorrhagic E. coli, enteropathogenic E. coli, and enterotoxigenic E. coli harbor multiple virulence factors. For a comprehensive analysis of the importance of global regulators in the control of E. coli virulence factors, an examination of a range of global regulators is reported. A correlation is found between the level of expression and phosphorylation of the virulence-regulated outer membrane proteins. Furthermore, additional virulence-associated phenotypes could be connected with the indirect regulation of OmpA production. [15][16][17]

4.2. Quorum Sensing Systems

Quorum sensing regulates cell-density dependent behavior with regard to the expression of a specific set of genes determining social behavior [18]. The implication is that unicellular organisms cooperate, invade, or cheat population structures by a selection of behaviors. Initially, quorum sensing was discovered as a cell-density controlled bioluminescence of the marine bacterium Vibrio fischeri [19]. At a late exponential growth phase, V. fischeri exclusively emits blue-green light by the recombinant enzyme luciferase generated within the bacterium. Redox reaction of reduced flavin mononucleotide and long chain fatty acid aldehyde takes place in the presence of molecular oxygen. Since quorum sensing is the only gene repression mechanism; other quenching mechanisms are required. Nevertheless, this quenching is only related to the chromosomes, but exogen complications may nonetheless occur. As a mobile consequence for the encoding plasmid, luxI and luxR genes are transferred due to IR transposon activity. However, many pathogenic and mutualistic bacteria take advantage of this quorum sensing system to regulate their complex social behavior, exoenzyme secretion, bioluminescence, biofilm formation, virulence factor expression, or antibiotic resistance. Gram-negative bacteria commonly use N-acyl-L-homoserine lactones (AHLs) for quorum sensing. AHLs are produced by the AHL synthase I encoded by luxI homologs. The luxI homolog mono acylates the acyl carrier protein with acyl-Acyl carrier membrane accumulating at the cellular level. After reaching the specific threshold, AHL expression takes place. Secreted AHL diffuses from the cellular membrane to the extracellular cell environment and returns to the cytoplasmic compartment by a luxury receptor I (luxR) type transcription regulator. Repression by AHL bound luxR activates to the numerous target genes.

5. Role of Virulence Factors in Pathogenesis

Escherichia coli bacteria are non-spore-forming, rod-shaped, gram-negative bacteria. The E. coli species consists of commensal strains of MG1655 and K-12 genotypes and pathogenic strains. The commensal strains often inhabit the gastrointestinal (GI) tract from infants and warm-blooded animals. Commensal or non-pathogenic E. coli strains multiply by colonizing the colon surface and non-aggressively excrete hazardous substances. However, unhealthy individuals, such as in immunocompromised hosts or when the GI barrier is breached, might develop disorders by infections of commensal E. coli species [6]. Certain E. coli strains comprise a heterogeneous group of pathogens and can mediate a wide range of diseases in experimentally infected animals or in people. Diseases governed by E. coli might be distributed into two broad groups; those that infect the intestinal tract and diseases of the extra-intestinal system. In humans, in accordance with their different disease groups, nine pathovars have been described for E. coli strains that are subjected to isolation. Some strains have been classified by more than one of these pathovars as they give rise to both diarrheagenic and extra-intestinal diseases. One of the described nine pathovars is EPEC, and it is a serious health problem in many developing countries. Particularly, children that die due to diarrheal disorders every year remain a serious problem in developing countries. Together with improvements in hygiene practices, this pathotype contributed to the emergence of a seriously significant situation in public health terms. Moreover, with the possibility of foodborne outrages either by domestic or dedicated sources, many people have been infected. The purpose of this review is to provide an understanding of the definition of the virulence factor concept and the role of virulence factors in the pathogenesis of EPEC infections. Moreover, information is provided on the discovery of known EPEC effectors and elucidation of unknown EPEC effectors that have a significant place in EPEC infection, as well as evaluation of the latest studies on EPEC infection. The EPEC pathotype is a bear under the spotlight; however, discovering molecular mechanisms of EPEC in infections might exhibit similar mechanisms used by other extraintestinal and diarrheagenic pathotypes of E. coli in the potential the outset of infections. Furthermore, the benefit of understanding EPEC is important for others' studies on the virulence factors and pathogenicity of unknown EPEC strains.

5.1. Gastrointestinal Infections

Escherichia coli (E. coli) are rod-shaped and gram-negative bacteria belonging to the Enterobacteriaceae family, isolated and characterized by Theodor Escher, initially classified as Bacterium coli. At first, E. coli was isolated from the infant feces in 1885 then described by Theodor Escherich, a German pediatrician, and bacteriologist. The infant received milk from mother depression and food mixture movements, E. coli lived and proliferated in the gastrointestinal tract enzymes' stimulation of its food utilization and proliferation. In a few hours, approximately, the newborn received the colostrum, colostrum had a high pH since it contained basic milk, understanding the basic pH E. coli, which is acid-sensitive, could grow and proliferate in the intestine [6]. Commensal E. coli often lived on the mucosal surface of the gastrointestinal tract.

Gastrointestinal Diseases are pathogenic E. coli pathogens that still inhabit the gastrointestinal tract of a healthy adult. When the gastrointestinal barrier was breached or when confronted by the host's immunocompromised state, these bacteria could turn out to be pathogenic, causing diseases to the host. However, such a commensal situation was changed when the gastric juice entered the small intestine and then the large intestine due to the withdrawal of the food mixture. Since E. coli didn't have a motility flagella, such E. coli could not find its way back to the infant stomach. At the same time, due to the food mixture depression, food could not contain high antimicrobial agents such as spices and high levels of salt.

5.2. Urinary Tract Infections

Urinary tract infections (UTIs) are common infections caused by Escherichia coli. Moreover, UTIs are frequently affected by uropathogenic types of E. coli (UPEC). In order to counter

defense systems, UPEC strains have several virulence mechanisms in order to maintain their survival in the host. For example, UPEC isolates frequently harbor several genes encoding surface polysaccharides, adhesins, immune evasion factors and protein transport systems [20].

Adhesins are primarily responsible for colonization of the epithelia. Fimbriae or pili promote adherence to transitional epithelia urothelium by forming cellular attachments, or through a lock and key-type mechanism based on the surveyor receptor. Agglutinin-like adherence molecules (Afa) are a family of adhesins that encode pili whose receptors are DAF (CD55) and CR3 (CD11b). Dr, DraE and FaeC adhesins are encoded by operons of the same family. Dr-fimbriae bind to the Dr-blood group antigen. Sfa/foc adhesins bind to protein moieties, on the whole, human umbilical vein endothelial cells with a lesser degree of binding to human medical paratus urothelium. The O antigen capsule protects UPEC from attack by the immune system by limiting phagocytosis opsonization, and serum killing. The O antigen is a polymer of repeating carbohydrate structures that are linked to the lipid A-core part of the lipopolysaccharide. Each capsule is crucial for the virulence of the pathogen, the lack of the capsule decreases its virulence. In addition, free swimming E. coli bacteria are killed by neutrophils, while encapsulated bacteria survive. The ability to resist the bactericidal activity of serum is an essential virulence factor for the invasion of UPEC into the host.

5.3. Extraintestinal Infections

Escherichia coli (E. coli) are rod-shaped gram-negative bacteria of the Enterobacteriaceae family that colonize the gastrointestinal tract of infants. Commensal E. coli are relatively innocuous, but can cause disease under certain conditions in patients with compromised gastrointestinal barriers like infants lacking a protective microbial community. There is an increasing range of physiological and extraintestinal disorders that are being reported in association with E. coli. Many human diseases can be caused by E. coli through the production of specific virulence factors. Nine pathovars of E. coli are responsible for diseases in humans, either by inducing diarrhea or through extraintestinal infections, which represent a significant public health and economic concern [6]. Seven of the described pathovars can be characterized as enteric E. coli Uropathogenic E. coli (UPEC), avian pathogenic E. coli (APEC), and neonatal meningitis E. coli (NMEC). The enteric-pathogen oblige (ExPEC) pathovar of E. coli has consistently been associated with infections in non-intestinal sites and may be carried asymptomatically in the gut [7]. The isolates often come from multiple sequence types (STs) and are highly diverse. Due to this heterogeneity and the lack of well-understood pathogenic mechanisms, the elimination of foodborne sources of ExPEC is challenging. Hence the prevention of the diseases caused by ExPEC can benefit from a better understanding of their epidemiology and pathogenesis. In such context, the characterization of several key virulence factors may provide crucial insight into ExPEC infections and the subsequent development of preventive strategies.

6. Host-Pathogen Interactions

Escherichia coli are rod-shaped and gram-negative bacteria that were first isolated from infant stool by Theodor Escherich in 1885 [6]. After a few hours of normal and term birth, E. coli colonize mainly the gastrointestinal tract of infants. For some undefined reasons, this process can be delayed in preterm infants, allowing the staphylococci to dominate instead of E. coli. Commensal E. coli strains coexist with humans without adverse effects for long periods; however, they may cause diseases in patients with compromised or breached gastrointestinal barriers or immunocompromised hosts. Many of these strains do so by external intervention, including mild-to-severe disorders of intestinal and extraintestinal organs. In the early 1980s, a few disease-causing pathovars of E. coli, diversified as enteric and extraintestinal pathovars, were recognized. A total of nine pathovars of E. coli strains are described because of their causing of distinctive diarrheagenic and extraintestinal diseases. Seven pathotypes have been described as enteric pathogenic E. coli, which include EPEC, ETEC, EHEC, EAEC, EIEC, EAggEC, and DAEC. EPEC and EHEC were singled out among these pathotypes due to their being implicated as

foodborne pathogens causing widespread outbreaks, resulting in high case fatality rates. The E. coli 0157:H7 strain that caused these cases has proven its zoonotic pathogen carriageway. Another potentially fatal extraintestinal disease caused by uropathogenic E. coli is sepsis. It is often caused because UPEC strains rapidly evade neutrophil immunity to proliferate in blood. To evade neutrophil immunity, they often resist the phagocytosis of neutrophils, forming biofilm-like intracellular bacterial. Some E. coli strains evade the host's defense mechanisms, multiply in substantial numbers compared with host cell phagosomes, and move into the bloodstream, wreaking grand havoc. Subsequently, these Extraintestinal pathotypes are rapidly anaphylaxis leading to septic shock and death, as some membrane and cytosolic proteins are altered.

Virulence factors are specific molecules produced and released by bacteria, fungi, protozoa, and viruses that allow them to better invade and cause diseases on their hosts by aiding colonization or dissemination and evasion or suppression of the host's natural defenses. Each pathotype of E. coli has its characteristic pathogenicity mechanisms and a specific profile of associated virulence factors. There is a total of 21 types identified belonging to nine classes infecting a wide variety of cells and covering a range of cellular ligands preventing engulfment, recruiting F-actin, and thereby engulfing itself. In 2012, E. coli infected ACK and HeLa cells were used to identify 224 proteins representing 74 different protein factors found to be 'up-regulated' in each cell line. Moreover, these infection conditions slowly progressed, with around 10% of these proteins significantly alternated as identified via Proteome analysis, most of which were not found on the current proteome method, or genes with unknown or uncharacterized functions. These changes are more significant and time-dependent with EPEC in the case of the infected cells used in this study. Substantial evidence suggests that the infectious method of E. coli, ECIs, varies based on host cell types. Defects in the host cell phagocytosis machinery or the host cell binding receptor induced disulfides activate N-WASP brought on by the formation of actin pedestals. It is noteworthy that bacteria inscribe two categories of effector proteins, one amongst which antagonizes pedestals induced actin polymerization by binding to N-WASP to reduce elongation of branched actin. Despite the low success rate with 0.1 count per bacterium case, evidence has been building up both statistically by the number of cases and by gene expression studies linking the E. coli infections occurring in EHEC and wild-caught patients on phagocytosis and cellular invasion to the formation of pedestals. Many of these diversified effectors with unknown function(s) identified in this study represent a brand of untested proteins with no similarity to their neighboring protein relatives.

6.1. Immune Evasion Mechanisms

Two immune evasion mechanisms of bacterial pathogens, complement system evasion, and mimicry of host proteins, have experimentally been assessed in commensal, extraintestinal pathogenic and enterohaemorrhagic Escherichia coli strains. Infections with pathogenic microorganisms are commonly controlled and eliminated by the immune system. The first line of host defence is the innate immune system, which includes anatomical barriers, cellular and molecular components. The complement system is ancient and part of the innate immune system. To respect host "self" and avoid damage to host cells, commensal bacteria have developed different strategies to evade complement system activation. The acquired immune system comprises T and B cells capable of creating immunological memory, which is the conceptual basis for vaccines. To infect a host, microorganisms must circumvent the innate and adaptive immune systems, often mediating various mechanisms capable of suppressing or evading host defences. Epididesmiological data reveal that the host is the natural reservoir of enterohaemorrhagic (EHEC) and extraintestinal pathogenic E. coli (ExPEC) strains, and commensal E. coli strains may give rise to disease or persistent infection [6].

These observations indicate that the interaction between the E. coli strains and the host may change between physiological and pathogenic conditions. Alterations of the host associated with physiological or pathological conditions may either inhibit the immune response or give beneficial conditions to the bacterium. Some of these alterations include suits of antimicrobial peptides,

alterations of the redox state, the relative amount or type of innate sensor, and so forth. How well commensal, extraintestinal pathogenic, and enterohaemorrhagic E. coli strains avoid the immune response of bovine plasma proteins is explored. Bovine plasma because both ExPEC and EHEC have a bovine host. In order to explore whether the ability to avoid the immune response is similar between strains of these two pathotypes and also to compare their behaviour to that of commensal strains, evasion of the opsonization of bacteria is measured. Circulating in bovine plasma, there are several proteins able to detect and tag bacteria for its ingestion by phagocytic cells (aka opsonization). The commensal E. coli strains show higher resistance to opsonophagocytosis than the pathogenic strains. The strain most sensitive to opsonophagocytosis is EHEC O157:H7 EDL933, which presents the highest phagocytosis rate while the phagocytosis rate of EHEC O157:H7 isolated from a human clinical case are far lower. On the other end of the spectrum are E. coli K-12 and O157:H7 C9490. The results indicate that commensal strain E. coli K-12 might avoid opsonophagocytosis and has a lower phagocytosis rate than EHEC and ExPEC strains. These data suggest that the evasion strategies of Extraintestinal Pathogenic, Enterohemorrhagic, and commensal E. coli strains to the bacterium's opsonization differ.

6.2. Inflammatory Responses

Literature suggests that bacteria have evolved specific virulence factors for efficient translocation across the gut barrier and dissemination via the blood stream to the organs [21]. Neutrophils are the first line of defense against bacterial pathogens and are essential for host protection, especially during the early stages of infection. At the gut mucosa, however, neutrophils transmigration normally only happens during the pathogenesis of inflammatory bowel disease or bacterial infection. Prior studies have demonstrated that the presence of polymorphonuclear cells nearby the intestinal epithelium enhances STx translocation and that NE development of a T84 monolayer infected with an enterohemorrhagic Escherichia coli strain promoted the appearance of gaps in cell-cell contacts adjacent to neutrophils. Furthermore, LPM are involved in the induction of T84-NE transepithelial migration in a way dependent at least in part on mTORC2 signaling.

EHEC-induced T84 cells inflammatory responses involve the ERK1/2, and JNK mitogen-activated protein kinases, and the NF-κB and AP-1, but not the p38 pathways. Mutation of tir reduced EHEC-induced IL-8 secretion while loss of intimin had no effect, suggesting that observed responses involve a not-known-host interaction(s) other than Tir. LEE deletion mutant strains (ΔescN, and ΔescV, not T3SS effectors), as well as not TTSS-secreted proteins mutants (tirY474F, and ΔtopA) do not significantly activate the transcription factors nor promote IL-8 release, indicating that EHEC secreted proteins induce this response. spiC::TnphoA and invF mutant strains (inv/spi-1-encoded proteins) are less potent in eliciting activation of these signaling pathways. The proinflammatory response of T84 cells to EHEC infection is dependent on autophagy activation, as inhibition of this process by Atg5 knock-down or pretreatment with wortmannin abrogates the activation of ERK1/2, JNK, NF-κB, and release of IL-8 [22].

7. Antibiotic Resistance Mechanisms

Multi-drug resistance of Escherichia coli is a major problem in clinical settings. E. coli strains that acquire resistance to multiple antibiotics are often more virulent and more likely to cause severe illness or death. These strains are resistant to the majority of antibiotics, which considerably limits alternative choices. The problem is compounded by horizontal transfer of antibiotic resistance genes between bacteria. Studies show the presence of macrolide, fluoroquinolone, aminoglycoside, and tetracycline resistance genes in a community E. coli strain.

The development of antibiotic resistance in pathogenic E. coli isolates has retarded the efficacy and success of treatment of E. coli associated health complexities. Many E. coli are resistant to numerous antibiotics, which compounds the clinical challenge of treating these species. This review underlines the past and contemporary character of acquired forms of antibiotic resistance in pathotypes of E. coli. wParamHL bioinformatics tools are employed for the investigation of gene carriers from 864 more than a few well-ordered finished genomes of E. coli and the

subsequent study of their functions and similarity. The presence of a variety of forms of acquired antibiotic resistance in Escherichia coli pathotypes is pointed out. Efflux-driven resistance is an old phenomenon and the ompJ gene is a prelude to beta-lactamase-driven resistance, which took off in the mid-to-late 1960s, coinciding with their early predictions [23]. The review also underscores a genomic perspective of regulon evolution in E. coli, which resulted in integrated machinery capable of multidrug efflux and display a diversity of efflux pumps protecting cell in a broad antibiotic spectrum.

7.1. Resistance Genes

Carbapenems are considered the last line therapy for treating severe gram negative infections because it is less likely to be hydrolyzed by ESBL producing bacteria; so, E. coli isolates resistant to imipenem, meropenem or ertapenem considered one of the most hazardous resistant isolates [4]. In 2017, a global priority pathogens list included 12 families of bacteria resistant to multiple antibiotics, carbapenem-resistant Enterobacteriaceae, and 3rd generation cephalosporin-resistant Neisseria gonorrhoea are in the critical priority group. There were 832 people involved with E. coli and (1 in 4) people who became ill from parasites were involved with E. coli because it is well known pathogens that can affect various parts of human beings and demonstrate a wide battery of virulence and resistance determinants. Bla-CTX-M-15 and bla-oxa-2 genes were the most prevalent resistance genes of extended spectrum beta lactamase (ESBL) E. coli among collected samples, having roughly (8 in 10) of the 56 resistant ones and were distributed in more than (8 in 10) of their resistant isolates that can relate an extra-intestinal infection with imipenem, meropenem and ertapenem resistance. Resistance to more than two antibiotic families was found in (7 in 8) of E. coli resistant isolates. ESBL Escherichia coli are conjugative or co-transferrable with other resistance plasmids which might create a multi-resistant battery of isolates. 33 resistance genes are associated with the tested virulence factor genes and whose resistance phenotype significantly matched the resistance genotype. It has a formidable effect on the public health status of developing nations like Egypt especially with the presence of wide spectra of resistance genes and their distribution between different clinical E. coli strains.

7.2. Plasmid-Mediated Resistance

Extensive genetic diversity among the multidrug resistance and virulence genes on IncFII virulence plasmids makes it necessary to monitor their development and to form preventive strategies to restrict them. In part, Escherichia coli in extra-intestinal infections is pathogenic. For instance, uropathogenic E. coli (UPEC) harbors several virulence factors for colonization in host tissues, and for evading the host immune system. Plasmids contribute to pathogenesis by conveying virulence factors, such as toxins and adhesins. Many of these plasmids are also conjugative, allowing them to be transferred to other E. coli strains. H30, a sequence type of the B2 phylogroup with plasmid-mediated mutation, is linked to fluoroquinolone resistance. The emergence of H30-R reduced fluoroquinolone susceptibility within the dominant fluoroquinolone-resistant clonal group. Fluoroquinolone use exerted strong selective pressure, driving the global dissemination of H30-Rx. In conjugation assays, all IncF plasmids transferred successfully into EC302/04 and E. coli DH10B transconjugants, suggesting that these strains possess similar transfer functions. As IncFII plasmids can occur in diverse E. coli strains, it is necessary to monitor the development of multi-replicon IncFII plasmids and to form preventive measures to restrict the spread of antimicrobial resistance among uropathogen bacteria [24].

8. Clinical Implications

Escherichia coli is commonly found in the intestinal tract of humans and warm-blooded animals as a part of the normal intestinal microflora. However, some serotypes can cause different diseases, including urinary tract infections, meningitis, and septicemia. This is partly explained by the presence of virulence determinants, which make certain strains pathogenic. Although many epidemiological studies of E. coli virulence factors have been conducted, it may be helpful to collect and assimilate the data in a single systematic study. This article provides a comprehensive,

structured, and updated overview of the molecular genetics, relevant diagnostics, and epidemiology of virulence factors in both human and animal pathogenic E. coli. In addition to diarrheagenic E. coli, several pathovars have been implicated in extraintestinal human infections. Three of these, uropathogenic E. coli (UPEC), neonatal meningitis E. coli (NMEC), and sepsis-associated E. coli (SEPEC), are among the most common Gram-negative bacterial pathogens causing urinary tract infections, neonatal meningitis, and neonatal sepsis. These extraintestinal pathogenic E. coli (ExPEC) have been associated with a diverse array of diseases, including cystitis, pyelonephritis, prostatitis, septicemia, endocarditis, pneumonia, and meningitis. A pathogenic clonal group of E. coli isolates from human blood, designated B2, was most commonly associated with ExPEC-related illness. One unique feature of the ExPEC is the extensive array of virulence factors they possess. However, besides virulence genes, multiple other factors play a critical role, and the host-infected immune and homeostasis state represents a determinant for the sepsis outcome [5].

8.1. Diagnostic Methods

It is very important to detect pathogenic bacteria, such as Escherichia coli O157:H7, at farms and various food products due to the diseases and deaths resulting from food poisoning by such bacteria. Many studies have been performed for the sensitive and rapid detection of E. coli O157:H7 by using various microbiological, immunological, and molecular biological methods, and they have developed a variety of systems and methods for the detection of E. coli O157:H7. However, it is very difficult to rapidly and accurately determine the food safety when purchasing food since most of these detection systems and methods have been confined to laboratories. Thus, secure and user-friendly on-site monitoring systems need to be developed as research into easy-to-use, rapid, and portable systems for detecting pathogenic bacteria continues to be at the forefront [25]. In recent years, many studies have been conducted to develop E. coli O157:H7 sensor systems that allow easy and rapid detection through simple operations and procedures. Among various sensory materials, aptamers are short, single-stranded oligonucleotides that can be generated easily and efficiently within the lab, with superior chemical stability. Additionally, aptamers can provide high selectivity and specificity due to their simple production process. Therefore, aptamers coupled with nano-carbon materials can be highly sensitive. For instance, they can be used to detect the entire bacteria immediately without the need for DNA extraction, enzymatic amplification, or antigen–antibody responses.

8.2. Therapeutic Strategies

The ubiquitous bacterium E. coli has excellent capabilities to adapt and survive in fluctuating environmental conditions, which is reflected by its large number of sequenced strains and related work on the functional and metabolic characterization of ever more strains. Throughout the last 50 years, an increasing number of pathogenic E. coli arose, which in turn resulted in the corresponding study of their virulence attributes. In the 1980s and 1990s, new molecular biological techniques such as DNA sequencing and polymerase chain reaction enabled many investigations of the structure and function of virulence determinants of pathogenic E. coli.

Due to the many thousands of publications, many excellent review articles of E. coli pathogenesis, this overview will rather elucidate some nowadays profiling methods and methodologies on the topic of E. coli virulence factors. One of the central hypotheses in this field is the "Gene For Gene" or "Matched Filter" Theory. This theory suggests that the recognition of avirulence genes or gene products from an attacking pathogen by a corresponding resistance gene or gene product from a host confers resistance. In turn, the presence or absence of the avirulence gene is necessary for the successful infection of the invading pathogen. This model was mainly devised and tested on plant-microbe interactions, where the host plant detects the proteins from the pathogen and in case resistance gene is present can either inhibit the pathogen development or induce the host defense mechanisms. For this mechanism to be successful, both matched genes and corresponding detection mechanisms need to evolve together. However, due to many pathogenic mechanisms

stemming from bacteria's original strategy to compete with other strains, this model is also applicable across the animal- and insect-infecting bacteria domain. With the rise of our understanding of the host immune system and pathogenic mechanisms stemming from many sequencing and proteomics platforms, it became clear that pathogen's "elusive" strategy has to be matched by the host "sampling" capabilities.

9. Future Directions in Research

Escherichia coli (E. coli), a widely distributed enteric bacterium in nature, has a complicated pathogenicity, which includes gastrointestinal infection and extraintestinal infection in human beings and animals. Extraintestinal pathogenic E. coli (ExPEC) causes a wide variety of mild to moderate localized infections (e.g. urinary tract infections and meningitis) but can also cause severe invasive infections (bacteremia and septiciemic infections) [7]. It is well known that ExPEC may produce a variety of virulence factors necessary to cause extraintestinal infections, which may be located on conjugative plasmids, pathogenicity islands (PAIs), bacteriophages and other mobile genetic elements. It has been suggested that poultry meat may be an important reservoir of ExPEC strains that possess virulence factors, suggesting potential for zoonotic transmission with serious health consequences in human beings [4]. Taking into consideration the extensiveness of their pathogenic potential, a virulence factor can be defined either based on its functionality, according to which it assists in the colonization and establishment of the bacteria in a certain niche and/or causes damage to its host, or based on its genetic basis, according to which it is any element of the genetic material that determines the pathogenic potential of the microorganism. Several aspects of E. coli virulence factors can be investigated further in order to gain a better understanding of how this potentially harmful pathogen adapts to and interacts with its natural hosts, including host transition, niche colonization and infection, and the subtle yet fascinating balance between colonization and establishment simultaneously at several different sites in the host. With recent advances, studies conducted in fields encompassing genetics, genomics, physiology, and modeling tailored for the investigation of diverse host models and E. coli strains can provide invaluable new insights with respect to the pathogenicity of E. coli. However, the implementation and improvement of laboratory animal models, which mirror much more closely the course and infection in human and animals beings, will most likely play a significant role in deorphaning the complex interplay of pathogenic determinants associated with E. coli multifactorial infection and in assessing the potential threat the existing and emergent E. coli pathovars pose to human and veterinary public health.

9.1. Emerging Virulence Factors

Diarrheagenic E. coli strains colonize the gastrointestinal tract of infants 2 weeks to 6 months of age before they can acquire immune protection, and these bacteria can cause diarrhea. Diffusely Adherent E. coli (DAEC) is the pathotype most frequently isolated from extraintestinal infections, and UPEC is the most frequently isolated combined E. coli pathotype from extraintestinal infections. DAEC contact with cells of the urinary tract and stimulate sheddase activity to facilitate adherence to the urinary tract stimulating the establishment of a complicated infection [6]. Recent studies have considered associated diseases, virulence genes descriptions, and symptoms observed to discuss UPEC extraintestinal infections. Together, these data show that the clinical isolates of DAEC had the potential for biofilm formation in vitro and it has been thought that this phenomenon may also happen in vivo to strengthen adherence to and invade cells of the urinary tract leading to complications.

Extraintestinal pathogenic E. coli strains can infect many sites such as the urinary tract, bloodstream, or central nervous system. E. coli strains circulating as commensal, asymptomatic intestinal colonization in hosts may cause disease when they reach a site where they are not normally present. The most commonly infectious extraintestinal pathotype is UPEC, causing 85% to 90% of all urinary tract infection, the most common of all extraintestinal infections. UTI is most frequently caused with type 1 fimbriae and pili encoded by genes fimCDAHFJ. A pathology of

UPEC is biofilm formation mediated by the type 1 fimbriae; these adhesins are responsible for UPEC attachment to the apical surface of the bladder and promote invasion of the superficial umbrella cells [4]. Time-lapse microscopy images show that internalized UPEC, through a filopodia-like process, spreads within the umbrella cell, establishing intracellular bacterial communities. Invasion Bridging proteins such as FimH may aid bacterial invasion and intracellular community formation within the urinary tract.

9.2. Vaccines and Immunotherapies

Vaccines are important public health measures and have shown to display success in stemming outbreaks and reducing the prevalence of diseases. E. coli vaccines, such as O- and F-pilus vaccines, have shown protective efficacy in both experimental models and farm animals. In recent years, the use of adjuvants intensified the search for new candidates for antigens that are more suitable for improving vaccine responses. Antigens with moderate adjuvantation properties enhance the vaccine-specific immune response when co-administered with vaccine antigens. Antigen adjuvants belonging to different classes of compounds or conjugated antigens may represent a novel approach in this direction. Antigen adjuvants can consist of a fusion protein created by connecting genes encoding the immunogenic domain of proteins that have widely recognized adjuvant properties to a gene that encodes for the vaccine antigen. Additionally, in recent studies it has been shown that dead E. coli were useful in regulating immune responses and provided protection against challenge infection. An effective E. coli vaccine or antimicrobial drug for livestock can provide multiple benefits, including animal welfare, food safety, and economic gains for the livestock industry [26]. Intensively farmed species, such as poultry and pigs, have become important reservoirs of E. coli, mainly due to their large populations and the accumulation and disposal of a large amount of feces. Several methods have been developed for the prevention of E. coli infections in farmed animals, including non-antibiotic farming, improved hygiene, supplementation of organic acids, and probiotics. Despite preventive methods, bacterial-fungal pig meningitis and mastitis in cattle, caused by various pathogenic E. coli strains, continue to occur worldwide, leading to significant economic losses. Developmental research has been conducted in the livestock industry about new vaccine technologies and immunization strategies aimed toward the administration of fewer doses, as well as vaccines to be administered post-illness.

10. Conclusion

Escherichia coli, a member of Enterobacteriaceae, is a gram-negative bacterium that usually colonizes the gastrointestinal tract of newborn mammals. E. coli is the predominant facultative anaerobe in the intestine of infants and is a common commensal. Although many commensal E. coli strains are a natural part of the intestinal flora, these strains can be potential pathogens and may cause disease in immunocompromised hosts. Certain E. coli strains mediate a wide range of intestinal and extraintestinal diseases. In 1985, a group of different pathogenic strains, each associated with a specific disease, was designated as distinct seropathotypes. Since then, nine pathovars have been recognized for strains of E. coli causing diarrheagenic and extraintestinal diseases. Seven distinct pathotypes can cause intestinal diseases, and these are collectively designated as enteric pathogenic E. coli (EPEC). The remaining two pathotypes, Enteropathogenic E. coli (EPEC) and shiga-toxin producing E. coli (STEC) strains, are usually extraintestinal pathogens.

Although EPEC and EHEC belong to separate pathotypes with different disease manifestations, they share similar mechanisms of host cell colonization involving a similar set of genetic determinants located on the Locus of Enterocyte Effacement (LEE). LEE encodes a type III secretion system composed of a complex molecular syringe that injects bacterial proteins called effectors into the host cell. These proteins manipulate the host cell to promote colonization by E. coli. Certain EHEC strains possess, in addition to LEE, other virulence factors, one of which is the capability to produce a potent subtilase cytolethal cytotoxin. This is the primary virulence factor of the EHEC pathotype that is responsible for causing diseases such as Hemolytic Uremic

Syndrome (HUS). Therefore, host cell colonization and consequent disease may be initiated by common mechanisms.

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