Journal of Medical Research and Health Sciences
Received 20 May 2021 | Revised 15 June 2021 | Accepted 7 July 2021 | Published Online 19 July 2021

DOI: https://doi.org/10.15520/jmrhs.v4i7.376
JMRHS 4 (7), 1329–1341 (2021)

ISSN (O) 2589-9031 | (P) 2589-9023

RESEARCH ARTICLE Open Access Journal

Molecular study for *Escherichia coli* isolates causing diarrhea at children

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1 | INTRODUCTION

Inflammation of the stomach and intestine is a major problem because of the pathological conditions it causes Diarrhea, which is one of reasons for the high death rates among children, especially in developing countries (Bioshop, 2006; Kandakai - Olukem *et al*., 2009).

There are many causes of diarrhea, including viruses (Koh *et al*., 2008) and parasites (Nelson *et al*., 2004) in addition to bacteria . *Escherichia coli* is one of the main causes of diarrhea, and it includes a group of strains that cause diarrhea in children, including them

Enteropathogenic *E.coli* / EPEC, Enterotoxigenic *E. coli*, ETEC and Enteroaggregative *E.coli*. EAEC Enterohemorrhagic *E. coli* / EHEC (Boisen *et al*., 2009).

The coliform bacteria have a number of virulence factors that influence the body's defenses to cause infection, including adhesion factor, toxin production, protease enzyme production, capsule, and iron acquisition system (Li *et al*., 2009). On the other hand, *Escherichia coli* produces enzymes Broad-spectrum-lactamases (ESβLs), Extended Spectrum β-Lactamases (Rodriguez - Bano *et al*., 2009), which help them to exhibit multiple antibiotic resistance that aids in the spread of infection (Alsterlund *et al*., 2009), Moreover, these enzymes may be carried on the plasmid, as well as other virulence factors, and thus it is possible to transfer these traits between bacterial species, which increases the incidence of infection (Zahid *et al*., 2009). And in view of the findings of studies of increased rates of diarrhea, especially among children, as well as an increase in the rate of resistance, which causes an increase in the mortality rate among children.Accordingly, this study came to aim at: 1- Knowledge strains of *E. coli* that cause diarrhea in children under two years of age and sensitivity for antibiotics.2- Study of some virulence factors that *E. coli* bacteria possess.3- Study of the coded genetic determinants of adhesion

Supplementary information The online version of this article (https://doi.org/10.15520/jmrhs.v4i7.376) contains supplementary material, which is available to authorized users.

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factor and antimicrobial resistance in *E. coli*.

1- *Escherichia coli*: The bacterium *Escherichia coli* was first described by the German pediatrician Theodor Escherich in 1885, when it was isolated from the feces of healthy newborns as commensal bacteria. *E.coli* strains and their role in the spread of diarrhea among children have been known (Feng *et al*., 2002). In 1894, the scientist Escherich managed to isolate her by young girls have a UTI Urinary that these bacteria reach the bladder by the ascending route (Sussman, 1985).Tract Infection /, and it has been suggested **2- General characteristics of *Escherichia coli*:** Is short, gram negative bacilli, present separately or in pairs, which grow in optional anaerobic .Its optimum growth is (37) , driven by surrounding flagella.Non-sporeforming, and some of their capsule strains may possess (Darnton *et al*., 2007).. *E. coli* colonies appear on (EMB Eosin-Methylene blue agar) / with a metallic green sheen. It also has the ability to ferment the lactose sugar, so its colonies will appear pink on the MacConkey agar(Nester *et al*., 1998). Most of the strains of these bacteria are produced hemolysin on the blood agar.(Boon *et al*., 2006).

E.coli have the ability to produce two types of enterotoxins. First type is heat stable Heat Stable/ST and the type Heat labile / LT (Guerrant and Steiner, 2005), also some of its strains have the ability to produce a toxin with a cellular effect. (Cytotoxigenic) (Alam and Zurek, 2004) therefore it is often called (Verotoxin - Producing E.coli)(VTEC) Or the term (Shigatoxin - Producing E. coli / STEC) (Sela *et al*., 2005),

As for biological chemical tests, *E.coli* are shown as a result.Positive for the Catalase test and negative for Oxidase test, a positive result for Indole Production test , Methyl Red Test, Citrate Utilization test and Vogas-Proskaur test, it has the ability to reduce nitrate to nitrite, degrade gelatin, it does not produce H2S gas as well as it does not degrade urea. (Crichton, 1996) **3- Classification of *Escherichia coli* :** *E. coli* were classified in the fifth group according to the classification (Bergey's manual), which includes faculative anaerobic gram negative rods which belong to Enterobacteriaceae. (Donnenberg, 2005). As for the serological classification of *E. coli*, Kaffman proposed at 1940: A special system to classify them based on the autigenic antigen Somatic antigen (O-Ag), Flagellar antigen (H-Ag) and Capsular antigen (K-Ag), based on the agglutination test for classifying strains of the species (Brooks *et al*., 2004). The somatic antigen is also called the cell wall antigen, (Cell wall antigen), consisting of long chains of lipopolysaccharide (Feng *et al*., 2005). The capsule antigen is a polysaccharide that covers antigens, while the flagellar antigen is formed from protein. (Kaper *et al*., 2004).

Serotypes of the pathogen Escherichia coli strain were distinguished Enteropathogenic E. coli (EPEC), which includes (12) different serogroups (Pabst *et al*., 2003) Table (1), and new serotypes were also distinguished which (Belongs to the Enteropathogenic E. coli (EPEC) strain, which is: - (O39: NM, O88: H25, O111: H8, O111: H9, O126: H12, O127: H4, O142: H45, O157: H8, O157: H45) (Jensen *et al*., 2007).

Table (1): Serotyping of Enteropathogenic *E.coli* (EPEC) (Jensen *et al*., 2007)

Serogroup	Serotype			
O26	O26:NM	O26:H11	O26:H34	
O55	O55:NM	O55:H6	O55:H7	
O86	O86:NM	O86:H34		
O111	O111:NM	O111:H2	O111:H25	
O114	O114:NM	O114:H2		
O119	O119:NM	O119:H2	O119:H6	
O125	O125:H -	O125:H6	O125:H21	
O126	O126:NM	O126:H2	O126:H21	O126:H27
O127	O127:NM	O127:H6	O127:H21	
O128	O128:NM	O128:H2	O128:H7	O128:H12
O142	O142:NM	O142:H6		
O158	O158:NM	O158:H23		

4- Pathogenicity of *Escherichia coli* *E. coli* have the ability to spread from their natural location in the human body and to cause opportunistic infections in other parts of the body as well as their ability to cause various hospital-acquired infections (Brooks *et al*., 2004; Olowe *et al*., 2004). Despite the fact that this bacteria lives normally in the intestine of healthy people, some of its strains can cause extra-intestinal infections (Extraintestinal infections), and intestinal infections in both immunocompromised

and healthy subjects (Paterson and Bonomo, 2005). *E. coli* is one of the most common types of bacteria that cause urinary tract infection (UTI) , with an infection rate of (80%). Especially among women (Russo and Johnson, 2003), These bacteria are also one of the most important bacterial causes of diarrhea, especially among children . In addition to their role in causing traveler's diarrhea (Diarrhoea Traveler's) (Olowe *et al*., 2003).Some strains of *E. coli* have the ability to cause infection with hemolytic uremic Syndrome / HUS, which is associated with cases of bloody diarrhea, especially in children and the elderly . It also causes hemorrhagic colitis / HC.(Vimont *et al.*, 2006).

These bacteria are among the causes of wound and burn infections, meningitis and mastitis , as well as cases of blood poisoning (Mokady *et al*., 2005). *E. coli* are also a source of exposure in children to infection with bacteramia, especially in rural areas (Berkley *et al.,* 2005). 5 – **Causes of diarrhea:** Diarrhea is a major problem in various countries of the world, as it is one of the causes of the high death rates among children, especially in developing countries (Tambekar and Barginwar, 2005). Recent studies have indicated an increase in mortality rates due to infection. nearly two million people in the world die every year due to diarrhea, most of them are children under the age of five (Melvin and Heyman, 2006). The etiology of diarrhea varies with respect to disease microorganisms. As most research and studies indicate that bacteria are more types microorganisms cause diarrhea in children especially *Escherichia coli*, *Salmonella*, *Shigella dysenteriae*, and *Vibrio cholerae* , as well as *Campylobacter jejuni* (Coker *et al*., 2002). There are other types of viruses that cause diarrhea, including the Norwalk virus, Cytomegalo virus, Viral hepatitis, Herpes Simplex virus, as well as both Calici virus and Astro virus (Jawetz *et al*., 2004).Some parasites are also causes of diarrhea, and they are found in several types. Each of them has a role in causing diarrhea, including Entamoeba histolytica (Nelson *et al.*, 2004) and (Jawetz et al., 2004) Giardia Lamblia as well as Cryptosporidium . There are many types of diarrhea, depending on the pathogen, including watery diarrhea acute watery diarrhoea, which occurs as a result of invasion of the small intestine by the toxin by microorganisms, including the bacterium Vibrio cholera , which is widespread in most countries of the world, especially poor countries, and the rate of deaths resulting from them reaches one million deaths per year (Nelson *et al*., 2004), acute diarrhea is characterized by Large quantities of fluids and salts (Sack *et al*., 1980), as the duration of this type of diarrhea is less than (10) days, and it is accompanied by fever and vomiting (Melvin and Heyman, 2006). It is associated with acute abdominal pain (Nelson *et al.,* 2004). As for dysentery diarrhea (Acute Dysentery Diarrhea) It occurs as a result of the invasion of the small intestine by bacteria *Shigella dysenteriae* (Nataro and Barry, 2008). These bacteria cause severe bloody diarrhea that is accompanied by mucus and blood (WHO, 1994), which is also known as (Shigellosis) after the bacteria that cause it . Also, diarrhea caused by pathological microorganisms, especially *E. coli*, This bacterium is one of the common bacterial species in human pathogenesis (Forbes *et al*., 2002). *E. coli* bacteria includes several strains of diseases that cause diarrhea, namely: -**5-1- Enteropathogenic *Escherichia coli* (EPEC):** This pattern has the advantage of being one of the main causes of diarrhea in infants. In many developing countries , This pattern is similar to ETEC, but does not have factor antigens colonization Factor Antigens (CFAs) and it does not produce Enterotoxins represented by both Heat Stable and Heat Labile (Nguyen *et al*., 2006). This pattern EPEC possesses a number of virulence factors, the most important of which is the adhesion factor (Attaching and Effacing Adherance - A / E). (Garrido *et al*., 2006) He also has the EPEC Fimbriae pattern that helps him to assembly and bundle formation (bundle) under the control of genes on Epec Adherance Factor Plasmid (EAF) (Nevesijac and Ravio, 2005). In addition to its possession of other virulence factors such as intimin protein and extracellular Serine Protease (ESPs) as such, it is similar to Verotoxin / Producing *E. coli* (VTEC / Verotoxin).(Blanco *et al.,* 2005; Cookson *et al*., 2009). **5-2- Enterotoxigenic *E.coli* (ETEC):** This type has the advantage of being the most common type of *E. coli* bacteria. It is the main cause of children's and traveler's diarrhea (Oliveira *et al.,* 2007), as this pattern causes acute watery diarrhea

(Acute Watery Diarrhea) and leads to dehydration in children. Infants, and has the ability to produce Enterotoxins (both the Heat Stable / ST) and the Heat Labile / LT type or both, as the heat-sensitive type (LT) is similar to in its composition and function the enterotoxin produced from cholera bacteria (Qadri *et al*., 2005).

ETEC is characterized by its production of special adhesion agents that differ from other types of *E. coli*, which is Colonization Factor Antigens / CFAs. The mannose-resistant type as it has an important role in the domestication of this type to the small intestine, and (75%) of the ETEC types isolated from humans have CFAs, while the rest of E.coli types have an inactivation of the mannose-sensitive type. (Nataro and Kaper, 1998).

Nelson *et al*. (2004) that ETEC patterns cause diarrhea in children under five years of age, and that infection may be caused by contaminated food and drink. **5-3- Enteroaggregative *E. coli* (EAEC):** This type is characterized by the fact that it does not produce the intestinal toxins (Enterotoxins) With both Heat Stable / ST) and Heat-sensitive toxin. Heat Labile / LT) (Boisen *et al*., 2008). The adhesion of this type of E. coli to the epithelial cells of the lining of the intestine is of the aggregated type. (Aggregative Adhesion) under the control of plasmid genes with a weight of (60) Mecadleton, (Jenkins *et al*., 2005). This pattern also causes persistent diarrhea (Persistent Diarrhoea) in infants, as well as its role in causing traveler's diarrhea (Vernacchio *et al*., 2006). **5-4- Enteroinvasive *E. coli* (EIEC):** This pattern is characterized by its ability to invade the cells lining the large intestine, and its infection is similar to that of bacillary dysentery caused by the bacterium Shigella dysenteriae. (Vieira *et al.*, 2007).

The susceptibility to invasion in the EIEC and *Shigella dysenteriae* is dependent on the presence of a (140) mecadeltine plasmid that encodes for some of the proteins that help them invade the intestinal epithelial cells.

These proteins are highly antigenically similar to both EIEC and Shigella dysenteriae, as well as antigen similarity. Autosomal O-Antigen between these two bacteria, and the EIEC strains lack flagella, i.e. non-motile (Andrade *et al*., 2002).

5-5- Enterohemorrhagic *E. coli* (EHEC):

This type is also called (Verotoxin-Producing E. coli / VTEC) because it produces a toxin (Verotoxin) that influences viral cells. Genetically, combination and functionally with toxin (Shigatoxin) *Dysenteriae shigella* , which causes this pattern. Attaching and Effacing Lesion on Epithelial Cells, possessing a plasmid of weight (60) (Dhanashree and Mallya, 2008).

Symptoms of EHEC infection begin with diarrhea that is not bloody (Non Bloody Diarrhoea) and Abdominal Cramp as well as Moderate Vomiting, then the symptoms develop after that to become bloody diarrhea which is the main symptom of the infection, in addition to severe dehydration and an increase in the infection. (Nausea) and stomach cramps (Stomuch Cramp) as well as the occurrence of hemolytic anemiae as well as cases of kidney failure (Gruskin, 2000).

This pattern is characterized by the induction of two pathological cases, which are Hemorrhagic Colitis / HC Syndrome. Hemolytic Uremic Syndrom / HUS (Elliott *et al.,* 2001; Combs *et al*., 2003; Kliegman *et al*., 2006), as EHEC strains of the O157: H7 serotype are the main cause of HC and HUS (Lynn *et al*., 2005). **6- Epidemiology of *E. coli*:** *E.coli* infection occurs by eating food and drink contaminated with it, and usually the required dose to cause infection is very small (100-200) cells , as well as the possibility of infection with *E.coli* by infected and carrying animals (Durso *et al*., 2004), As there are many animals that are considered as main stores of these bacteria as in Type O157: H7 *E. coli*, for which cows are the main store, and these animals may not show any clear symptoms through which infection can occur (Johannessen *et al*., 2005). *E. coli* are also transmitted through its transmission from person to person, especially during epidemics, as it may be transmitted directly, especially through hand-to-hand contact, or it may be transmitted indirectly (Welinder-Olsson et al., 2003). *E. coli* resist the stomach environment

and have the ability to compete with other microorganisms in the gastrointestinal tract, after which it colonizes the large intestine (colon) by attaching to the cells lining the intestine and infection occurs by the cells lining the intestine and then transmitted to the bloodstream (Mead and Griffin, 1998). There are several subtypes of *E. coli* bacteria that have a role in causing and spreading Diarrhea, especially among children (Todar, 2008). Enteropathogenic E.coli / EPEC) has been known since 1940 with its association with hospital-acquired diarrhea, especially in children under five years of age, and it is often transmitted. EPEC through contact with people as this contributes to the spread of this pattern and thus increased exposure to cases of diarrhea (Nelson *et al.*, 2004), and recent studies indicate that this pattern is widely spread in the Australian continent (Nguyen *et al.,* 2006). Enteroaggregative E. coli / EAEC has also been known since 1987 by its association with cases of persistent diarrhea in children . Often this pattern is transmitted to humans by eating contaminated food and contact with people. (Nelson *et al*., 2004). Enterotoxigenic E. coli (ETEC) is the main cause of travelers' diarrhea, as well as causing and spreading diarrhea among infants under five years of age . (20-30%) of cases of diarrhea (Nelson *et al*., 2004), and the ETEC pattern causes more than (280) million cases of diarrhea, of which (400,000) cases end in death, especially among children (Qadri *et al*., 2005).). *E. coli* enteroinvasive (EIEC) type causes bloody diarrhea. Statistics until (20%) of cases of bloody diarrhea return to this pattern. (Nelson *et al*., 2004), and that the EIEC type is less common than the EPEC and ETEC types (Nataro and Kaper, 1998). As for EHEC (Enterohemorrhagic E. coli), it is considered one of the important pathologies that cause bloody diarrhea associated with hemorrhagic colitis / HC and Colitis Hemorrhagic Syndrome (Hemi-Uremic Uremia 1997), and Ursukemia (HEM) 1997 may be mentioned. *et al*. This pattern is the third most common enteric pathogen. As for EHEC (Enterohemorrhagic E. coli), it is considered one of the important pathologies that cause bloody diarrhea associated with hemorrhagic colitis / HC and Colitis Hemorrhagic Syndrome (Hemi-Uremic Uremia 1997), and Ursukemia (HEM) 1997 may be mentioned. et al. This pattern is the third most common enteric pathogen.Often this pattern is transmitted to humans through ingestionContaminated drinking water by animals. The EHEC pattern causes diarrhea in various countries of the world. In the United States of America, this pattern causes (20,000) cases, including (250) deaths annually.(Armstrong *et al*., 1996). In 1997, 30,000 examples of diarrhea were studied, and the rate of isolation of the EHEC type was the fourth major bacterial pathogen in the United States of America (Fey *et al*., 2000). Brashears et al. (2003) reported that there are (74,000) cases of this type in the United States of America annually, of which at least (250) are deaths. On the Asian continent, specifically in the city of Sakai in Japan, the largest epidemic of EHEC infection was recorded in 1996, which included more than (6000) cases of hemorrhagic colitis (HC) and more than (100) cases of infection with hemolytic hyperuremia (HUS) syndrome. The source of infection was to meals that contained large quantities of legumes contaminated with this pattern (Paton and Paton, 1998). **7- Virulence factors**: *E. coli* possess a number of virulence factors that have a role in their pathogenicity, and these factors include: - **7-1 Adhesion factor:** The attachment of bacteria to the host cells is important steps in the occurrence of pathogenicity,represent asfirst step in the development of infection (Boisen *et al*., 2009). Studies have indicated the presence of some filamentous structures, Outer Membrane Proteins (OMPs) as well as Lipopolysaccharide (LPS), which can be considered from the structures that help bacteria to adhere (Rocha-De-Souza *et al*., 2001). Fimbriae is the most important adhesion agent and their role in it Haemagglutination and epithelial sticking (Li *et al*., 2009). There are two types of haemostasis in the *E. coli* bacterium. Depending on the sensitivity to mannose, the Type 1 Fimbriae is sensitive to Mannose-Sensitive Haemagglutination / (MSHA), and this type of fimbria is found in (80%) of *E. coli* strains that cause enteritis. (Graham *et al*., 2001), and the second type of lethargy (P - Fimbriae) is: Mannose-Resistant Haemagglutination / MRHA (Greenwood *et al*., 2002) In general, *E. coli* have many adhesion factors that help them adhere to cells and cause infection, including:Colonization Factor Antigen - CFA /), Type1-Fimbriae, P-Fimbriae, and Intimin (non Fimbriae adhesion), in addition to En-

teropathogenic *E.coli* Adherance Factor ,Colonization Factor Antigen (CFA II) and CFA I (the most common strains of E.coli bacteria that cause diarrhea(Oliveira *et al*., 2007) The process of bacterial adhesion requires the presence of two main factors, the receptor and the linker (Ligand). The receptor is usually known as specialized carbohydrates or peptide chains on the surfaces of eukaryotic cells.(Prescott, *et al*., 2005) **7-2 Toxin Production:** Gram-negative bacilli have an endotoxin that consists ofLipopolysaccharide (Mandell *et al*., 1995).Also, Exotoxins, including hemolysin and cytotoxic necrotising factor (CNFT) (Faxman *et al*., 1995). The strains producing hemolysin are characterized by being more virulent than those strains not producing it, as these strains obtain the iron element through their analysis. Human red blood cells, and that genes responsible for the manufacture and secretion of the enzyme hemolysin may be carried by large plasmids, and in practice it has been found that pathogenic strains possess a number of genes on the chromosome (Cross *et al*., 1990).As for the two factors Cytotoxic Necrotising Factor (CNF1 and CNF2). These factors are produced by some strains of *E. coli* bacteria, causing necrosis in various cells. Therefore, they are considered to be important virulence factors in the activity of these bacteria.(Li *et al*., 2009)

In addition to the above, *E.coli* secrete Enterotoxins, and it is of two types, namely, the heat-stable toxin (ST)and the heat-sensitive toxin (LT).It was found that the strains of *E.coli* that produce toxins Heat Stable (ST) causes cases of diarrhea in children, and there are several types of this toxin produced from *E.coli* bacteria isolated from humans and animals (STh, ST1b, STp and ST1a), and it was found that the two types(STh and ST1b) are the two predominant in humans, and two (ST) toxins resist boiling for (Todar, 2008).

As for the toxin Labile Heat (LT), it was mentioned by Guerrant and Steiner (2005). The strains that produce this toxin cause watery diarrhea in children, as well as this toxin. The toxin in the cholera bacterium is similar to the toxin called (Cholera toxin). Some strains of *E. coli* are able to produce toxins.The toxin-like produced by the Shigella dysenteriae bacterium, represented by toxin(Shiga toxin), which is also known as two toxins (Verotoxin) (Jandu et al., 2009). These two toxins are composed of two subunits: 5B: 2A, which, under Unit B, bind to the Glycolipid receptors, namely the Globotriasyl Ceramide (Gb3) present. On the surfaces of eukaryotic cells(Greenwood *et al*., 2002), While the A1 unit possesses the toxic activity of the enzyme N-glycosidase, which leads to cell killing by inhibiting the structure of protein, as it works on the ribosome (under the large unit 60S) and the A1 part of the toxin affects the rRNA 28S and thus affects the elongation phase within the translation process when building the protein, which leads to the death of target cells such as endothelial cells of the kidney and epithelial cells of the intestine or any cell possessing the receptor Gb3, and this causes various conditions including hemorrhagic colitis (HC) and the syndrome Hemolytic hyperuremia (HUS) induced by EHEC patterns (Abe *et al*., 2008), and thus it is a major virulence factor for EHEC in humans (Hoey *et al*., 2002) **7-3 Protease Production:** The protease enzyme is one of the important virulence factors possessed by bacterial species that help them in causing infection, as this enzyme works to decompose the protein, and it is excreted outside the cell and can be extracted from the external environment, this enzyme is produced by many bacterial types including: *Escherichia coli*, *Staphylococcus aureus*,*Bacillus spp*. ,*Pseudomonas* spp., *Streptococcus pyogenes, Proteus mirabilis*(Buhling *et al.,* 2004). Protease enzymes have different characteristics depending on their activity and composition, and they can be classified according to the molecular weight and the charge they carry, or according to the base material they work on, or according to the active site (Jewell, 2000) The protease enzymes were divided into two types on the basis of the site of action of these enzymes, namely the first type, called Exopeptidases, which work on the peptide chains of the carboxylic end or the amino end, and the second type of these enzymes are called Endopeptidases and work on the internal protein bonds . Protease enzymes are also divided on the basis of the organisms that produce them, as these enzymes are produced by bacteria, fungi, and protozoa (Atlas *et al*., 1995). The most important division in the

classification of these enzymes is on the basis of groups catalytic groups present in the active site four groups include serine and metal proteases Proteases Metallo and Proteases Aspartic as well as Cysteins Proteases, and these four groups of Proteases are of the Endopeptidase type and are found in all living organisms, and three of these four groups are produced by the bacteria which are Serene, Metallic and Systeine(Jewell, 2000). **7- 4 the capsule:** The capsule is one of the virulence factors that it consists of Polysaccharide, which may be possessed by *E. coli*, which is an extracellular substance that has a role in the serotyping of bacteria, as well as its role in Protecting bacteria from the process of phagocytosis and thus increase their pathogenicity(Johnson and O'Bryan, 2004).It has been indicated that the type K1 *E. coli* causes many different diseases, especially in children, including sepsis and meningitis, as well as other clinical diseases (King *et al*., 2007). **8- Antimicrobials:** Antimicrobial resistance by bacteria is one of the biggest health and economic problems in the world, prompting researchers to investigate modern antimicrobials to overcome resistant bacterial isolates that increase the mortality and epidemiology (Preston *et al*., 1997;Ang) and antibiotics are organic substances produced by microorganisms that have effectiveness against other types of microorganisms, and at the present time their production has become synthetic on a large scale(Prescott *et al*., 2005) for its use in treating various infections. Antimicrobial agents differ in terms of their mechanism of action and their effect, and that depends on their chemical composition, and the persistence of the action depends on the appropriate dose and the permeability of the antimicrobial to the tissues (Greenwood *et al*., 2002). Antimicrobials are divided in terms of action into two groups: Broad Spectrum Antibiotics, which have an effect on Gram-negative and positive bacteria, and Narrow-spectrum antibiotics. (Narrow Spectrum Antibiotics) which have an effect on a specific or individual group of microorganisms (Doi *et al*., 2002).

It is necessary to distinguish between bacterial and viral infections to avoid the unnecessary use of antimicrobials that lead to the development of resistance to these antibiotics, as the administration of antibacterial drugs depends on knowledge of the patient's age and diagnosis of the condition, as well as the severity of symptoms (Ebell, 2004).The indiscriminate use of antimicrobials, as well as taking them in high doses, may lead to the emergence of bacterial isolates resistant to many of the antibiotics used, which threatens the health of the patient.(Damoiseaux, 2005).

8-1- Lactamases: There are many different types of beta-lactam antagonists that are of great therapeutic value and importance as an anti-bacterial material, including: **8-1-1- Penicillins:** It is a group of antagonists that contains a chemical nucleus (6-amino pencillanic acid) that consists of a ring of-lactam fused with a ring (Thiozalidin) connected to the nucleus. Side chains with different roots added to obtain different derivatives of Atlas *et al*. , 1995),The mechanism of action of these antibodies is to inhibit the process of building the cell wall of the bacteria by binding to the target site represented by the proteins associated with penicillin (PBPs) (Levinson and Jawetz, 2000). A- Pipracillin: This antagonist belongs to the Ureido pencillin group, as it contains in combination a penicillin nucleus and a side chain derived from urea, the benefit of which is to facilitate the passage of the antagonist through the channels found in the cell membranes of bacteria, as well, tfhis antagonist has broad activity against gram-positive and negative bacteria, and is effective against aerobic bacteria (Mahon and Manuselis, 2000). **B- Ticarcillin:** This antagonist belongs to the Carboxy pencillins groupIt has activity against *E.coli* and Pseudomonas aeruginosa, but it is less effective against bacteria that produce the enzymes that degrade them, especially *Klebsiella pneumoniae*.(Mandell *et al*., 1995). **8-1-2 Cephalosporins:** It is a group of antibiotics that contain a nucleus (7- amino cephalosporinic acid), Which consists of a beta-lactam ring fused with a ring (dihydrothiazine) and connects to the nucleus by side chains to which different roots are added to obtain different derivatives of cephalosporins, cephalosporins are similar to penicillins in terms of the mechanism of action and the target site of the antagonist (Murray *et al*., 1999). **A- Cefotaxime, Ceftazidime, and Cefixime:** These antagonists belong to the third generation cephalosporin group and have a wide spectrum of action, especially against Gram-negative selective anaerobic bacilli such as

E. coli and spp. Proteus (Murray *et al*., 1999) and its high affinity for binding to the target site in the cell wall (Baron *et al.*, 1999), and it is noticeable nowadays that the high level of resistance to Cefotaxime is due to the ability of E.coli bacteria to produce that –Lactamase is broad-spectrum enzymes, particularly CTX-M-15, which is characterized by a high affinity for this antagonist (Woodford *et al*., 2006). **B- Cefoxitin:** It is an antagonist belonging to the second-generation cephalosporin group, this antagonist contains an α-methoxy group that is associated with the-lactam ring.It is resistant to most types of beta-lactamase enzymes, and is considered an effective antidote to som Gram-negative bacteria, such as *E. coli* and *K.pneumoniae* (Philippon *et al*., 2002). **C- Cefepime:** It is an antagonist belonging to the fourth-generation cephalosporin group, and it is considered one of the modern, broad-spectrum antibiotics that are effective against members of the intestinal family, includingEnterobacter as well as Pseudomonas and Neisseria (Baron *et al*., 1999). **8-1-3 Monobactam:** Aztreonam was the first antagonist in this group, and it has lethal activity against Gram-negative bacteria, and inhibitory activity for members of the intestinal family.(Baron *et al*., 1999). **8-1-4- Carbapenem:** For example (Imipenem and Meropenem), these antibiotics have broad-spectrum efficacy against most types of the intestinal family, and are used to treat bacterial infections *E. Coli, P.aeruginosa,* and *Klebsiella* spp., Which are resistant to penicillins, and is used to treat bacteremia, endocarditis and acute urinary tract infections (Christopher *et al.*, 1991).

8-2 Aminoclycosides (Amioglycosides

It is a group of antibacterials that share common properties Synthetics and pharmacokinetics, they act inside the cell by binding to ribosomes.In a way that causes wrong amino acid sequences to enter the peptide chains, So the resulting abnormal proteins would be fatal to the bacteria(Tierney *et al*., 1999).

Amikacin: It is an antagonist of the aminoclycoside group, bacteria resistance develops, It has a pronounced slow (Tierney *et al*., 1999). Amikacin is used against many types of Gram-negative intestinal bacteria, including *E. coli, Proteus*, and *Enterobacter* as well as *Pseudomonas*. This antagonist is characterized by its neurotoxicity.Ototoxicity and (Nephrotoxic) levels should be taken into account in patients with renal failure (Tierney *et al*., 1999). 8-3 Quinolnes: They are different derivatives of the antagonist Nalidixic acid, these antagonists have a wide spectrum of activity against many bacterial species, and the way all quinolins act is to inhibit bacterial DNA synthesis by inhibiting the action of an enzyme Topoisomerase II, or the DNA gyrase, is responsible for making the bacterial chromosome super-coiled, leading to rapid death. Bacteria (Madigan *et al*., 2006) In addition to inhibiting the action of the enzyme (Topoisomerase IV), as this hinders the separation of DNA replicated during the process of cell division (Katzung, 2001). Fluoroquinolinate antagonists have high efficacy against the intestinal family, reach high levels of tissue and are excreted with diuresis, which makes them important in the treatment of urinary tract infection (Well *et al*., 1998). **8-4-Lactamase Inhibitors:** Beta-lactamase inhibitors are called suicide inhibitors (Francioll, 1991) because they create stable complexes between them and the enzyme as a result of a chemical reaction consisting of several steps leading to cutting the way to the enzyme. Thus, it prevented it from breaking down the effective beta-lactam antagonist (Rotschafer and Ostergarrd, 1995). These inhibitors are weak antibacterial agents, but are able to inhibit plasmid and chromosomal (Mims *et al*., 1995). **Salbactam:** Salbactam is a semi-finished antibiotic, and the combination is(6- desamino pencillin sulfone), an effective inhibitor of most clinically important beta-lactamase enzymes, it is more broad-spectrum than clavulanic acid but less effective, Imitazhma inhibitor not to possess viability inducing enzymes Chromosome so used mixed with anti-B-lactam antibiotics to treat the resulting injuries from the intestinal bacteria producing enzymes Cephalosporins Induced (Inducible -Cephalosporinase), inhibitor and has Alsllbecktam the effectiveness of the synergistic with anti-B-lactam antibiotics it is there Mixed with ampicillin in a ratio of 1-2(1 g ampicillin - 0.5 g sulbactam), which is poorly absorbed by the intestine, is therefore taken intravenously (Ripa *et al*., 1990) (intravenous administration). The mixture (ampicillin - sulbactam) has efficacy against both negative and

gram positive bacteria, as well as against anaerobic bacteria, as most studies indicate the possibility of using the mixture (ampicillin - sulbactam) as a preliminary treatment for its high efficacy and low toxicity, as well as the absence of side effects and its low cost. The mixture is used to treat many infections, including urinary tract infections (Oliver *et al*., 1999).

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How to cite this article: M.A.I.A.L.M. **Molecular study for *Escherichia coli* isolates causing diarrhea at children**. Journal of Medical Research and Health Sciences. 2021;1329−1341. https://doi.org/10.15520/jmrhs.v4i7.376