IJPSR (2018), Volume 9, Issue 12 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 March 2018; received in revised form, 08 May 2018; accepted, 22 May 2018; published 01 December 2018

BACTERIAL DIARRHOEA: A COMPREHENSIVE REVIEW

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Keywords:

Bacterial diarrhea, Gastroenteritis, Laboratory diagnosis, Diarrheagenic *Escherichia coli*, *Clostridium difficile*, *Shigella*

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ABSTRACT: Infective diarrhoea is a common cause of malnutrition in children <5 years of age. The aetiological agents may be bacteria, viruses or parasites. The bacterial agents cause diarrhoea by either secretion of toxins which act on the small intestine to cause outpouring of fluids into the lumen as seen in *Vibrio cholerae*, enterotoxigenic *Escherichia coli*, *Clostridium perfringens, Staphylococcus aureus* and *Bacillus cereus* or by damaging mucosa resulting in dysentery like that seen in infection with *Shigella*, non-typhoidal *Salmonellae*, *Vibrio parahemolyticus, Clostridium difficile* and *Campylobacter*. This article summarizes the common bacterial etiological agents, clinical presentation of illness caused the laboratory diagnosis and antibiotic susceptibility testing of these pathogens.

INTRODUCTION: Diarrhoeal diseases are common among outpatients and inpatients especially in developing parts of the World. Acute diarrhoea is defined as the passage of three or more loose or liquid stools per day [1]. Some definitions require the passage of increased frequency of stools of decreased form from the normal lasting 14 days. Persistent diarrhoea lasts between 14 days to 30 days while chronic diarrhoea lasts beyond a month. Acute diarrhoea of infectious aetiology is also referred to as gastroenteritis. Some of these infections may present predominantly with nausea and vomiting [2]. Other symptoms include abdominal pains, cramps, fever, bloating, flatulence, blood in stools and tenesmus. Diarrhoeal diseases may result in malnutrition and severe complications in children <5 years.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(12).5015-31

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(12).5015-31

The aetiological agents may be bacteria, viruses, and parasites, however, in developed nations, diarrhoea is mostly due to non-infective causes like irritable bowel syndrome, coeliac disease and malignancies [1]. The bacterial agents may cause diarrhoea by either secretion of toxins which act on the small intestine to cause outpouring of fluids into the lumen as seen in *Vibrio cholerae*, *Enterotoxigenic Escherichia coli*, *Clostridium perfringens*, *Staphylococcus aureus*, and *Bacillus cereus* or there may be damage to mucosa mainly in ileum and colon due to inflammation or cytotoxicity resulting in dysentery where fecal leucocytes can be seen on microscopy.

The agents which cause this type of diarrhoea include Shigella, non-typhoidal *Salmonellae*, *Vibrio parahemolyticus*, *Clostridium difficile* and *Campylobacter*. Another mechanism is by penetration of reticuloendothelial cells through the mucosa as described in enteric fever and diarrhoea due to *Yersinia enterocolitica* [3]. The management is mainly supportive which aims at fluid replenishment, symptomatic relief and preventing

transmission which is important for tracking outbreaks. The bacterial culture of stool is recommended in severe cases, invasive disease and high-risk groups. American college of Gastroenterology (ACOG) recommends that stool cultures may be done if any of the following is present; cases of severe diarrhoea, temperature > 38.5 °C, bloody stools or in the presence of faecal leucocytes, lactoferrin or occult blood [2]. Infectious diseases society of America (IDSA) recommends a culture if diarrhoea lasts > 1 day, fever, dehydration, history suggestive of bacterial aetiology, bloody stools and systemic illness [1].

This review aims to summarize the common bacterial etiological agents, the laboratory diagnosis and antibiotic susceptibility testing of these pathogens.

***Aeromonas*:** The genus *Aeromonas* comprises of gram-negative, oxidase positive, facultatively anaerobic bacteria of which >90% strains produce beta hemolysis on sheep blood agar. These can be differentiated from *Vibrios* by their ability to grow on media without salt supplementation, inability to grow on TCBS medium and resistance to O129 which is vibriostatic. The members of genus *Aeromonas* have been isolated from rivers, seawater, drinking water and sewage in various stages of treatment. Concentrations of aeromonads in these sites have been reported to vary from as low as <1 colony forming units (CFU)/ml (groundwater, drinking water, and seawater) to as high as 10^8 CFU/ml or more, in sewage. A total of 24 species have been identified majority of which are considered as pathogens of fish and other cold-blooded animals. The mesophilic species are categorized under *Aeromonas hydrophila* group and cause infection in humans while the psychrophilic group is fish are placed under *Aeromonas salmonicida* group and pathogens are non-motile, pathogens growing at 22 °C - 25 °C and non-motile [5].

The genus has been described to cause infections ranging from mild acute gastroenteritis to septicaemia, myonecrosis and necrotising fascitis in humans also. The patients with malignancies, gastrointestinal tumors, and intestinal pathology are at increased risk of colonization and infection. These have not been identified as normal gut flora (<1%) [5]. Infections are more frequently observed in warmer months. The global incidence is unknown. The incidence in developing countries has been reported from 4% to 22% [6, 7, 8]. The incidence in developed countries has been estimated between 0% to 10% [5, 9]. Gastroenteritis due to *Aeromonas* can present in five different settings, enteritis, as a cause of the chronic intestinal syndrome, cholera-like the disease, traveler's diarrhoea or bloody stools. Other symptoms are fever, abdominal pain, and vomiting. The commonest presentation is that of watery diarrhoea. Most infections are self-limiting. The complications reported are septicaemia due to translocation into the circulation form gut, ulcerative colitis, segmental colitis mimicking as Crohn's disease and haemolytic uremic syndrome [10]. The attributable fatality rates are estimated to lie between 32% to 45% [5].

***Escherichia coli* (*E. coli*):** The genus Escherichia is named after the Theodor Escherichia who was a German paediatrician. The genus includes facultatively anaerobic gram-negative *Bacilli* belonging to the family Enterobacteriaceae and the type species *Escherichia coli* is a major facultative anaerobe in the large intestine of humans and warm-blooded animals [11, 12].

This bacterium forms a part of the normal flora. A total of six diarrhoeagenic types have been identified which are difficult to identify and these are enteropathogenic *Escherichia coli*, Shiga like toxin producing *E. coli* (STEC), enteroinvasive E. *coli*, enterotoxigenic *E. coli*, enteroaggregative *E. coli* and adherent invasive *E. coli* [13]. These are characterised by expression of different group specific virulence factors. Most commonly identified pathotype is STEC which was previously called as enterohemorrhagic and verocytotoxin producing *E. coli* [10].

Enterohemorrhagic or Shiga Toxin-producing *Escherichia coli* or Verocytotoxin-Producing *Escherichia coli* (EHEC or STEC): STEC or VTEC denote the strains which have a gene for the toxin of Stx family. The STEC are defined by the presence of Shiga toxin 1 and/ or Shiga toxin 2 genes which are identical to the toxin produced by *Shigella dysentriae* 1 at both genetic and protein levels. The toxin inhibits protein synthesis. These are bacteriophage-encoded.

The recognition was made with the emergence of O157:H7 in 1980's. These were called EHEC because of the association with hemorrhagic colitis and haemolytic uremic syndrome. EHEC denotes the subset of STEC strains which in addition to STx gene have a 60 MDa plasmid, produce attaching and effacing (A/E) lesions and cause hemorrhagic colitis and haemolytic uremic syndrome [14, 15, 16].

EHEC can be transmitted by contaminated food and water and from person to person. Most cases are due to the consumption of bovine origin food. EHEC can cause a wide range of symptoms ranging from mild diarrhoea to severe hemorrhagic colitis as well as haemolytic uremic syndrome (HUS). This pathotype was recognized when Riley *et al*., investigated outbreaks of gastrointestinal disease with bloody diarrhoea due to consumption of undercooked hamburgers [17]. Most commonly affected are infants and children. HUS is a common cause of renal failure and manifests after 5 to 13 days of diarrhoea onset. Other complications include cholecystitis, colonic perforation, colonic stricture, intussusception, pancreatitis, post-hemolytic biliary lithiasis, rectal prolapse, appendicitis, hepatitis, hemorrhagic cystitis, pulmonary edema, myocardial dysfunction, and neurological abnormalities [18, 19].

The histopathology findings are that of haemorrhage and edema in lamina propria. This gives a 'thumbprinting impression' on barium studies of ascending and transverse colon [20]. Another important feature is the presence of a pathogenicity island locus of enterocyte effacement (LEE) which was thought to be responsible for hemorrhagic colitis and HUS but it is now known that LEE-negative strains can also cause outbreaks of HUS [21, 22, 23].

The reservoirs of STEC are cattle and poor sanitation has led to its presence in almost every consumable product. Infections is commoner in summers, begins as enteritis which may progress to hemorrhagic colitis. The CDC has estimated the annual burden of >20000 infections and 250 deaths in the United States. The incubation period is 3 to 4 days and symptoms are that of blood in stools which may be absent sometimes, pain in abdomen, nausea, and vomiting.

The most common and serious complication is haemolytic uremic syndrome (HUS) which is a triad of renal failure, microangiopathic haemolytic anaemia, and thrombocytopenia. This is more frequent in children than in adults and the risk increases if the strain is STx 2 positive, with the use of antibiotics and antimotility agents. The mortality rates are reported to vary from 3% to 5%. Non-O157: H7 serotypes are thought to be less virulent and less transmissible than O157:H7 serotype. They have been isolated from patients with non bloody diarrhoea though the significance is not yet clear [10].

The use of antibiotics to treat infections is controversial and is largely restricted to supportive care.

Enterotoxigenic *E. coli*: There are two types of syndromes caused by ETEC, one is weaning diarrhoea in infants which can be life threatening and the other entity is traveller's diarrhoea [13]. The onset of symptoms is abrupt and the incubation period is 14 h to 50 h. The diarrhoea is watery without blood or mucus, fever and vomiting are less frequent features [14, 24]. The infective dose is high and the prevalence is low in school-age children and adults [24]. The strains adhere to small intestine mucosa by means of special colonization factors (CFA). These are fimbriae which are specific for the pathogen *e.g.* K99 strains cause infection in calves, lambs and pigs while K88 strains are pathogenic for pigs only [25].

Human strains possess CFA which can be rigid rod-like, bundle forming or thin flexible structures. The enterotoxigenic *E. coli* or ETEC produce two types of enterotoxins; heat labile toxin LT and heat stable toxin ST. The labile toxin is like cholera toxin and is composed of one A subunit and five B subunits. The A subunit has an enzymatic activity while B subunit is responsible for binding to GM1 subunit. After binding, the toxin exerts its enzymatic activity by catalyzing the transfer of ADP ribosyl moiety from NAD to GTP binding protein. This leads to activation of adenyl cyclase which increases the intracellular concentration of cyclic AMP thus stimulating the chloride secretion and a decrease in absorption of sodium chloride by villi. This gives way to osmotic diarrhoea by passively drawing water into the lumen [13].

Enteropathogenic *Escherichia coli* (EPEC): EPEC is known to cause diarrhoea among children <2 years of age. Loss of receptors in older individuals is one possible explanation for protection against EPEC [13]. The incubation period is short in human volunteers (average of 2.9 h) [27]. The characteristic feature seen on histopathology is an attaching effacing lesion (A/E lesion). The bacteria are intimately attached to epithelium and there is effacement of microvilli. Sometimes, pedestals can be seen on which the bacteria rest and these can extend upto 10 µm outside the cell. These lesions can be reproduced in cell culture. Just beneath the bacteria are accumulations of polymerised filamentous actin fibres (F-actin). Other components of an A/E lesion are myosin light chains, actinin, and talin.

Many of the EHEC strains also produce A/E lesions and can be differentiated from EPEC by the presence of Stx toxin. The adherence of bacteria leads to the activation of bacterial genes resulting in signal transduction in the intestinal cells. These genes are located on a pathogenicity island called as the locus of enterocyte effacement (LEE). The eventual result increases in intracellular calcium which leads to reduced absorption of sodium and chloride ions. This results in secretory diarrhoea in addition to which effacement of microvilli results in a decrease in the absorptive surface. The diarrhoea is profuse, watery, usually accompanied by nausea, vomiting, and low-grade fever [13].

Enteroaggregative *E. coli* (EAEC): Several foodborne outbreaks of diarrhoeal illness due to EAEC have been reported in Europe, Japan, Mexico, and India. This pathotype is defined by its characteristic aggregative adhesive lesion. The adherence is localised forming clusters or microcolonies of bacilli on the surface of Hep 2 cells giving a 'stacked brick appearance' [27]. The virulence factors are largely unknown and studies have been done only in O42 strain. The virulence factors are plasmid borne and include adhesins, toxins, and secreted proteins but none of these factors are present in all EAEC strains. These strains do not possess the genetic markers as other pathotypes do. An exception to this is O104:H4 strain which is an Stx-producing EAEC and is a hybrid between EAEC and STEC [28]. Recently a division into typical EAEC and atypical EAEC has been proposed on the basis of the presence of gene aggR which regulates the virulence factors. Its presence suggests typical EAEC which are therefore more virulent than atypical strains [29]. The first toxin identified in EAEC was the heat-stable toxin enteroaggregative *E. coli* heat-stable enterotoxin 1 (EAST-1) [30].

An acute self-limiting diarrhoea is a usual scenario but some may develop a persisting diarrhoea lasting >14 days depending on the host's immunity and genetic susceptibility. The diarrhoea is watery, with or without mucus and blood, low-grade fever and vomiting [31, 32].

Entero-invasive *Escherichia coli* (EIEC): EIEC can cause dysentery in humans and are biochemical, genetically resemble *Shigella species*. These strains give a positive Sereny test, are usually lysine decarboxylase negative, are nonmotile and non lactose fermenting [33, 34]. The infective dose is higher than *Shigella spp*. The foodborne and waterborne outbreaks have been described. Recently, two large outbreaks reported EIEC strain *E. coli* O96:H19 Italy and the United Kingdom have been described. Another study from Kolkata demonstrated a high incidence of 16.3% among 263 patients with diarrhoea. The bacteria invade the large intestine cells by endocytosis. This process depends on the presence of a large plasmid of about 220 kb (pInv) which contains a 33 kb region. This region contains 38 genes which are responsible for bacterial invasion, regulation of host immune response and secretion of a type III secretion system [35, 36, 37, 38].

EIEC enter through microfold cells called as M cells which are present in the intestinal mucosa. The pathogens reach the lamina where they are phagocytosed by macrophages and dendritic cells. This leads to an inflammatory response. The bacteria escape from macrophages and dendritic cells and invade other enterocytes from the basolateral side where they escaping from the phagosome and replicate in the cytoplasm [39, 40].

Bacillus cereus: This is a Gram-positive aerobic, catalase positive, spore-producing bacillus. It has been found in the stools of 0 to 43% healthy children and adults. It is widely distributed in the environment and its spores are resistant to heat,

freezing, pasteurization and even gamma radiation [41]. The spores are hydrophobic in nature and thus can adhere to a variety of surfaces [42, 43]. It is a common cause of food poisoning usually due to consumption of rice, pasta, and dairy product and produces only mild symptoms. Dierick *et al.,* have reported an outbreak in a Belgian family due to consumption of pasta salad [44]. Two forms of enteric diseases have been recognized; the emetic and the diarrhoeal type. The disease has an incubation period of 1 to 6 h. The emetic type is due to a heat stable toxin known as cereulide which is preformed in the food. It is resistant to heat, proteolysis and acids [45].

The symptoms usually subside within 24 h. The diarrhoeal disease is due to three enterotoxins which are hemolysin BL (HBL), non-hemo-lyticenterotoxin (NHE), and cytotoxin K. The food poisoning is most frequently associated with food like desserts, meat, and dairy products. Only two of these enterotoxins are associated with the disease. The infective dose is 105 to 107 and incubation period ranges from 8 to 16 h [4]. The enterotoxins are not preformed but are rather produced in the small intestine [45, 46]. The symptoms are abdominal pain, watery diarrhoea and occasionally nausea. The elderly and individuals with achlorhydria are at an increased risk of diarrhoeal disease [47].

Campylobacter species: Campylobacter is among the leading causes of bacterial diarrhoea throughout the world. The incidence of campylobacteriosis has increased in North America, Europe, and Australia. The epidemiological data from Africa, Asia, and the Middle East is scant. Differences in the incidence among different countries vary substantially as the methods to detect infection, the population profile and food surveillance vary greatly. In developing countries where Campylobacter is endemic, infection is usually limited to children with infection decreasing with age, suggesting that exposure in early life might lead to the development of protective immunity. It is a microaerophilic non-sporing gram-negative bacillus, spiral or curved with single or bipolar flagella [48, 49]. It inhabits the intestinal tract of animals like poultry, cattle, pigs and sheep [10]. There are 26 species, 2 provisional species, and 9 subspecies in the genus.

The most important species causing gastroenteritis are *C. jejuni* (>90% of cases) and *E. coli*, *Campylobacter fetus* subsp. fetus, *Campylobacter lari*, *Campylobacter concisus*, *Campylobacter jejuni* subsp. doylei, and *Campylobacter hyointestinalis* associated with gastroenteritis [50, 51, 52]. The transmission is by ingestion of undercooked meat and dairy products. It is due to fecal contamination of meat while slaughtering. Contact with animals may also result in infection. The incubation period is 2 to 10 days. There is watery diarrhoea with abdominal pain, malaise and myalgias. A stool examination shows polymorphs with or without blood. Usually, the illness resolves without antibiotics within a week. However, the disease may relapse in 5 to 10% of the patients [50].

Other manifestations include urinary tract infections, cholecystitis, hepatitis, pancreatitis, nephritis, meningitis, abortion, bacteremia and neonatal sepsis [53]. Bacteremia is associated with underlying liver disease, HIV infection, and malignancy. Reactive arthritis (2 - 4% cases) and Guillian Barre syndrome occurring within 2 to 21 days (in 0.1% of cases) have also been reported [4, 7, 8] The target is peripheral nerves which are attacked by auto-antibodies against lipooligosaccharides of *C. jejuni* mimicking human gangliosides [54, 56, 57].

Clostridium difficile: *Clostridium difficile* is an obligate anaerobe, spore producing, motile gram positive bacillus. It is present in soil and gut of animals and humans. It can be differentiated from other clostridia by its ability to decarboxylate parahydroxyphenylacetic acid to produce p-cresol giving it a pig like or tar-like a smell. It is also present in 50% of healthy children less than one year of age. In adults the carriage rates are 3% to 5%. It is a cause of nosocomial diarrhoea and to a lesser extent, community-acquired diarrhoea in patients receiving prolonged courses of antibiotics.

Other risk factors include advanced age, laxative use, antacids and enemas [10]. The *C. difficile* infection (CDI) is the most frequent hospital-associated infection in the USA and as per a study, the incidence of community-acquired infection is increasing as well [58]. It is transmitted *via* feco-oral route. The infective spores are highly resistant to environmental pressure and disinfectants also.

The germination of spores after ingestion is dependent on exposure to bile acids in small intestine and glycine. The time period between ingestion of spores and onset of symptoms is up to 4 weeks [59]. It is the most important bacteria implicated in antibiotic-associated diarrhoea. The antibiotics which pose a greater risk are fluoroquinolones, cephalosporins, and clindamycin. Antibiotics change the gut microbiome resulting in increased germination of and colonization by bacteria. The most important virulence factors are toxin A which is an enterotoxin and toxin B which is a cytotoxin. These are encoded by a pathogenicity locus PaLoc. Certain strains are hypervirulent and produce a binary toxin also known as *C. difficile* transferase.

One such strain *C. difficile* BI/NAP1/027 was recognized in 2002. It has caused large epidemics in developed countries and is associated with severe disease and higher rates of mortality. Apart from production of binary toxin, the factors which are responsible for its increased potential to thrive and cause severe disease are increased toxin expression, more efficient sporulation and fluoroquinolone resistance [10, 60]. In Asia, dominant strains are non-binary toxin strains such as ribotypes 017,018 and 014.

The infection may result in either no symptom at all or result in mild to moderate diarrhoea or even pseudomembranous colitis. The presentation may be similar to profuse watery diarrhoea similar to that caused by *Vibrio cholerae*. Severe disease may be associated with fever, abdominal cramps, and leucocytosis. Abdominal pain, bloody diarrhoea, and marked leucocytosis may be present in pseudomembranous colitis (PMC). The complications include intestinal perforation and toxic megacolon. These complications are seen in 0.1% to 0.3% of cases of CDI but mortality is high especially with toxic megacolon (upto 80%) [60, 61]. Recurrent disease is seen in 10% to 20% after symptom resolution and can be due to a relapse or a reinfection by a new strain [62, 63].

Clostridium perfringens: *Clostridium perfringens* is a gram-positive, non-motile, anaerobic, a sporulating bacterium. The spores are subterminal. The bacilli are pleomorphic and occur in pairs or short chains. This bacterium is catalase and superoxide dismutase negative. It has five toxigenic types (A-E), of which A and C strains are responsible for disease among humans. It is the largest toxin producer and is found in soil and microbiota of both animals and humans. A double zone of hemolysis is produced around colonies when cultured at 37 °C on blood agar overnight.

The infective dose is 108 vegetative bacilli and ingestion of improperly cooked, stored and reheated food causes illness. The reheating of food results in germination of spores which survived the initial cooking process. This occurs in the small intestine and simultaneous secretion of an enterotoxin called *Clostridium perfringens* enterotoxin (CPE) accompanies this. Serotype A is responsible for the majority of the cases [64, 65].

In most type A food poisoning strains, the enterotoxin gene (cpe) is located on either the chromosome while in others it may be located on large conjugative plasmids. The action of CPE is exerted by cell death due to increased calcium influx. The cell death results in the destruction of the intestinal epithelium and leads to fluid and electrolyte loss. The most frequent symptoms are vomiting, severe abdominal cramping and pain and watery diarrhoea, after 8 to 24 h of ingestion of food. The illness is self-limiting, and symptoms subside within 24 h. Serotype C causes an infrequent but serious type of food poisoning which is called enteritis necroticans or“pig-bel” [66, 67]. It is associated with the ingestion of contaminated food, usually pork. This organism produces a beta toxin that causes intestinal wall necrosis. The illness has a mortality rate of 40% and primarily affects malnourished persons, especially children. It may also cause antibiotic-associated diarrhea not resulting in pseudomembranous colitis [68, 69, 70].

Listeria monocytogenes: The genus has six species but *Listeria monocytogenes* is the common human pathogen. It can cause both intestinal as well as extra intestinal disease. It is found in the environment, animals, and soil. It can grow at lower temperatures, survives acidic and high salt concentrations which gives it a survival advantage in refrigerated foods [1, 2]. A major factor associated with the development of the disease is ingestion of food heavily contaminated (107 to 109 CFU/g or ml) with the bacteria [3].

The incubation period for gastrointestinal infection usually is 24 h but can vary from 6 h to even 10 days. The illness is characterized by symptoms like fever, headache, and arthralgia/myalgia. The diarhoea lasts for 1 to 3 days and complications include abdominal pain, nausea, vomiting, dizziness, lymphadenopathy, and sometimes a rash [2, 3]. Fever, which occurs in 60% to 100% of infected persons, is a cardinal feature associated with *L. monocytogenes* diarrhoea. The risk factors for gastroenteritis are gastric acidity, antacids, use of H_2 receptor antagonists, and use of laxatives, patients with inflammatory bowel disease (IBD) and Crohn's disease [10].

***Salmonella*:** It is a member of the family Enterobacteriaceae, is a facultatively anaerobic gram-negative bacillus. It is one of the most frequently isolated pathogens from cases of food poisoning. The nomenclature is still evolving and the nomenclatural system of *Salmonella* recommended by the World health organization (WHO) Collaborating Centre is currently in use by the Centers for Disease Control and Prevention (CDC). In this system, the genus *Salmonella* is divided into two species, *Salmonella enterica* (type species) and Salmonella bongori, based on differences in their 16S rRNA sequence analysis. The species, *S. enterica*, is classified into six subspecies based on the genomic relatedness and biochemical properties [71, 72]. The subspecies are denoted with roman numerals: I, *S. enterica* subsp. enterica; II, *S. enterica* subsp. salamae; IIIa, *S. enterica* subsp. arizonae; IIIb, *S. enterica* subsp. diarizonae; IV, *S. enterica* subsp. houtenae; and VI, *S. enterica* subsp. indica. *S. enterica* subsp. enterica (I) is responsible for approximately 99% of Salmonella infections in humans and warm-blooded animals. In contrast, the other five Salmonella subspecies and *S. bongori* are rare in humans and are found mainly in the environment and in cold-blooded animals [72].

Based on the clinical disease in humans, *Salmonella* strains can be grouped into typhoidal Salmonella and non-typhoidal Salmonella (NTS). The NTS strains are found in animals and cause gastroenteritis in humans. The disease occurs worldwide and is characterized by vomiting, abdominal pain and cramps, myalgias and non-bloody diarrhoea. The disease is limited to the lamina propria of the small intestine and usually antimicrobial therapy is not given. Extraintestinal features include bacteremia, septic arthritis, urinary tract infections, and osteomyelitis which may be seen in 5% of cases [73, 74, 75, 76, 77, 78]. Some individuals may become asymptomatic carriers and shedding may last for several weeks to a few months. The incubation period is short and ranges between 6 to 12 h and the disease is usually self-limiting. The population at risk include children, elderly and immunocompromised patients.

Enteric fever, caused by typhoidal Salmonella, is associated with a high morbidity and mortality rate and occurs mainly in developing countries. Higher incidence exceeding 100 cases per 100,000 population annually is found in Asian countries including China, India, Vietnam, Pakistan, and Indonesia. Pakistan and India have the highest incidence rates of 451.7 cases and 214.2 cases per 100,000 populations, respectively. Typhoid fever is caused by *Salmonella typhi*, and a similar syndrome is caused by *Salmonella paratyphi* A, *Salmonella paratyphi* C, and tartrate-negative variants of *Salmonella paratyphi* B. In typhoid, the bacteria disseminate from the lamina propria to reticuloendothelial system in phagocytes through lymphatic and hematogenous routes. Fever, malaise, anorexia, headaches, and vomiting are common symptoms of typhoid and typically start 1 to 3 weeks after infection [79]. Some patients may have a non-bloody diarrhoea. The severity of the disease depends on the bacterial load, infecting serotype and predisposing host factors like extremes of age, patients with decreased gastric acid production, gastrectomy, or H_2 receptor antagonists, are at increased risk of infection. Individuals with impaired cellular immunity (*e.g.*, AIDS) or altered phagocyte function (*e.g.*, sickle cell anaemia) are at increased risk for both invasive nontyphoidal as well as typhoidal Salmonella infections [80, 81, 82, 83].

***Yersinia enterocolitica* and *Yersinia pseudo-tuberculosis*:** In the late 1960s the genus *Yersinia* was identified as a cause of foodborne gastroenteritis. The genus belongs to family Enterobacteriaceae and consists of facultatively anaerobic bacteria as members. A total of 18 species have been identified and nine of these have been isolated from humans. *Yersinia enterocolitica*

has two subspecies identified by 16S rRNA gene sequencing, *Y. enterocolitica* subsp. enterocolitica and *Y. enterocolitica* subsp. Paleartica [10]. Pathogenic members of *Yersinia enterocolitica* are identified by biotyping and serotyping. It has six biotypes 1A, 1B, 2 to 5 and more than 50 serotypes which differ in cell wall lipopolysaccharide. The biotype 1B and 2 -5 have a 70Kb highly conserved plasmid pYV/pCD which is lacking in biotype 1A. It is responsible for the virulence and encodes virulence factors like *Yersinia adhesin* A (YadA) and Ysc-Yop type III secretion system (TTSS). Biotype 1B has a high-pathogenicity island (HPI) which facilitates the uptake and utilization of iron by bacterial cells and may help in growth under iron-limiting conditions.

Other virulence genes are inv for invasin, an outer membrane protein required for translocation of bacteria across the intestinal epithelium, ail (encodes an outer membrane protein contributing to adhesion, invasion, and resistance to complement-mediated lysis) and yst gene for a heat-stable enterotoxin. The invasive process includes a signalling process that enables the bacteria to enter a nonphagocytic cell, disrupting and invading the intestinal barrier. The internalization of the bacterial cell occurs by two mechanisms. In the "zippering" process, the mammalian cell membrane encloses the bacterial cell. In this process, the invasin (Inv) of Yersinia binds integrins of the β1 family of mammalian cell surface [84].

Yersinia enterocolitica can cause a myriad of symptoms ranging from acute self-limited diarrhoea to severe ileitis and mesenteric lymphadenitis. Certain uncommon extraintestinal syndromes have also been reported which include urinary tract and respiratory tract infection (empyema), osteoarticular infection (reactive arthritis), erythema nodosum, infected mycotic aneurysm, axillary abscesses, and endocarditis. The other important species is *Yersinia pseudo-tuberculosis* which is also an enteropathogen but has been more consistently associated with sepsis. It is commonly associated with mesenteric lymphadenitis presenting as acute appendicitis [85]. Mortality is 100% among untreated cases. Both the species have been found in animals, birds, food, and environment. Pigs are an important reservoir for both infections [86, 87]. The annual incidence of *Y. enterocolitica* in the United States was found to be 1.0 per 100,000 persons according to Food Net during 1996 - 1999. The greatest number of cases was among blacks and Asians. The incidence then declined to 0.5/100,000 persons till 2009. Children <5 years of age were at greater risk. The most important sequelae of *Y. enterocolitica* infections is reactive arthritis and erythema nodosum resulting from immunologically mediated inflammation of subcutaneous adipose tissue and painful nodular eruptions [88]. Around 80% of the patients with reactive arthritis carry the HLA-B27 allele. Patients with iron overload are at more risk as some *Y. enterocolitica* serotypes are unable to synthesize siderophores [10].

Staphylococcus aureus: It is a facultatively anaerobic, non-motile, non-sporing gram-positive coccus which is catalase and coagulase positive. It can grow at a wide range of temperature and salt concentration upto 15%. It colonizes the anterior nares and skin of humans. It is most commonly found in milk products like cream-filled pastries, cream pies, butter, cheese, and sandwich fillings. The food poisoning is due to ingestion of preformed, heat stable enterotoxin. There are 21 types of enterotoxins and phage encoded enterotoxin A is the commonest cause of food poisoning worldwide [90, 91, 92]. The symptom onset is rapid occurring within 2 - 7 h and usually resolve in 12 h [93]. General malaise, nausea, vomiting, diarrhoea, and abdominal cramps can start within 30 min of ingestion. There is the absence of fever in these patients. Severe dehydration can occur in elderly and children. Hospitalization may be required in 10% of cases [94].

***Vibrio cholerae* and Other Related Species:** *Vibrio cholerae* is a member of the family Vibrionaceae which is facultatively anaerobic, gram-negative, non-spore-forming curved bacillus. This bacterium is motile with a single sheathed polar flagellum, is oxidase positive and reduces nitrates. It is differentiated based on differences in sugar composition of somatic O antigen into O sero groups. The most established sero group is O1 which is responsible for the majority of epidemics. The sero group O1 has two biotypes; classical and El Tor. All the strains not agglutinating with O antiserum are defined biochemically and are called as non O1 sero groups.

Two sero groups of *V. cholerae*, O1 (El Tor biotype) and O139, are responsible for the current pandemic of cholera. Other members of genus Vibrio which can cause gastroenteritis are *Vibrio parahemolyticus* and less commonly *Vibrio mimicus*, *Vibrio fluvialis* and *Vibrio vulnificus*. These bacteria are found in high salt concentration like sea water while non-halophilic species are found in freshwater environments with low salt concentrations [10].

The most common an important pathogen in the group is *V. cholerae* which is responsible for rice watery diarrhoea due to ingestion of contaminated food and water. The disease is due to the production of cholera toxin which consists of an A subunit and 5 smaller identical B subunits. The B subunit binds the toxin to the eukaryotic cell receptor, ganglioside GM1 which is enhanced by neuraminidase. The A subunit has an enzymatic activity and acts intracellularly. It increases the cellular concentration of cAMP thus resulting in enhanced secretion. The incubation period for cholera can range from 18 h to 5 days. Asymptomatic colonization is seen in endemic areas due to constant exposure. The disease is characterized by severe watery diarrhoea which is painless and not associated with fever. *Cholera gravis* is an entity which results from severe dehydration due to loss of large volumes of 500 ml to 1000 ml/h, leading to shock and even death if untreated [95].

Infection due to non-O1, non-O139 sero groups of *V. cholerae* is mild and self-limiting since they usually lack the cholera toxin gene.10 The two important risk factors for acquiring disease are the consumption of contaminated seafood and foreign travel for other *Vibrio species*. These have been isolated from different types of seafood like oysters, mussels, clams, shrimp, and tilapia. 96 In the United States, *V. parahaemolyticus* is the most common cause of Vibrio-associated diarrhoea. The most common symptoms include diarrhea with abdominal cramps and fever in half of these patients. Other symptoms like nausea (76%) and vomiting (55%), help to distinguish illness from other vibrioses [97]. Complications due to gastroenteritis are rare. The enteric infection can spread to the bloodstream, producing septicemia. Almost all bacteremias due to *V. cholerae* are caused by non-O1, non- O139 isolates [98]. Other, less common *Vibrio species* associated with septicemia subsequent secondary to gastrointestinal infections are *V. fluvialis* and *Grimontia hollisae* [99, 100].

Shigella species: The bacterial genus Shigella is comprised of gram-negative, non-motile, facultatively anaerobic bacilli closely related to *Escherichia coli* which belong to family Enterobacteriaceae. These are strict human pathogens present intracellularly and are transmitted by faecal - oral route from ingestion of contaminated food and water. It has a low infective dose ranging from 10 - 100 bacilli which makes it easy to spread *via* person to person contact. The four serogroups of Shigella are *Shigella flexneri*, *S. dysenteriae*, *S. boydii*, and *S. sonnei*. These are divided into serotypes on the basis of type specific antigens. *S. dysenteriae* has 15, *S. flexneri* has 19 serotypes and subserotypes, *S. boydii* has 20 serotypes and *S. sonnei* has a single serotype. Out of this *S. flexneri* is the most frequent cause of illness accounting for 62% of the cases while *S. sonnei* is more common in developed nations (80% cases in Europe and North America).

S. boydii and *S. dysenteriae* are responsible for <5% of the cases worldwide. The symptoms of shigellosis are self-limiting watery diarrhoea which may be accompanied by mucus and/or blood in stools, fever, malaise, and abdominal pain. In paediatric patients, sepsis may also develop and is more common with *S. flexneri* infection. Other rare complications include meningitis, urinary tract infections (UTIs) and pneumonia. These are most frequently seen in *S. flexneri* and *S. sonnei* disease. Reactive arthritis has been reported from 1 - 3% of the cases and occurs within 3 weeks of diarrhoeal illness.

The pathogen traverses through colonic mucosal cells through M cells and comes in contact with the macrophages. The bacilli are phagocytosed and induce the apoptosis in phagocyte. This releases the bacilli which invade the intestinal epithelium from basolateral surface. The bacterial adhesion activates the type III secretion system which triggers the entry of effectors into the intestinal epithelial cells. This is followed by the lysis of phagosomal membrane and release of bacilli into the cytoplasm.

The bacilli become motile due to directional actin polymerization. This allows for the cell to cell spread [101]. *Shigella dysentriae* type 1 also produces a toxin which acts like ricin and inhibits protein synthesis in mammalian cells but its role in human diarrhoea is not clear. Another complication seen after *S. dysentriae* is haemolytic uremic syndrome (HUS) seen in 13% of patients. It is seen more commonly in children under 5 years of age [102, 103, 104].

Plesiomonas shigelloides: The genus has a single species and belongs to family Enterobacteriaceae. It is a gram-negative, oxidase positive, non-lactose fermenting and facultatively anaerobic bacillus. It can be found in both sea and fresh water. Infection is seen after consumption of seafood such as oysters and shellfish. Most infections are characterized by water or bloody diarrhoea after 2-5 days of ingestion of contaminated food and resolve slowly over more than a week. Other features include vomiting, fever, abdominal pain and headache. Meningitis has also been reported and is exclusively seen in infants [105, 106, 107].

Bacteroides fragilis: The only species in the Bacteroides genus associated with human diarrhoea is *B. fragilis*. It has also been implicated in colorectal cancers. Certain strains of this species produce a zinc metalloproteinase enterotoxin, *Bacteroides fragilis* toxin (BFT) or fragilysin encoded on a 6 kb pathogenicity island which is responsible for inflammatory diarrhoeal disease in humans and animals. These are called as enterotoxin producing *Bacteroides fragilis* or ETBF. These came to be known in a study published in 1992 [109]. The majority of the studies have been conducted in children and the largest study conducted among adults was done in Sweden [110]. Recently, it has also been associated with traveller's diarrhoea [111]. The clinical disease is marked by diarrhoea, abdominal pain and tenesmus [112]. The diagnosis relies upon detection of ETBF which is difficult and requires isolation on bile esculin agar and a PCR to detect enterotoxin gene bft [10].

Edwardsiella tarda: It is the only species in genus Edwardsiella which is pathogenic to humans. It is a commensal in fish, marine birds, animals and reptiles. It is rarely pathogenic in man and 80% of infections due to this species involve gastrointestinal tract. Infection occurs due to consumption of contaminated seafood. The most susceptible age groups are children<5 years of age and those above 50 years of age. The most common presentation is that of watery diarrhoea but can also cause dysentery and chronic diarrhoea.

Diagnosis: Specimens are collected for isolating the pathogen and include stool, vomitus and even food samples. Outbreaks of diarrhoeal disease are investigated by collecting several stools samples from the affected population. The samples are transported in a suitable medium and processed as soon as possible. Fresh stool samples are the best when it comes to visualization of typical characteristics of pathogens on microscopy and the bacteria remain viable too. Routine culture and molecular identification are two methods of reaching a diagnosis. Culture methods include inoculation of specimens before and after enrichment onto suitable media for isolation [116, 117].

Specimen Collection: Faecal samples are collected during the acute phase of illness if a bacterial aetiology is suspected. The yield from samples of patients hospitalized for more than 3 days is lower except in cases of *Clostridium difficile*. Testing for *C. difficile* is not done in infants as the rates of colonization is high. Testing should not be done in asymptomatic patients except if an ileus is suspected [118]. Clear instructions and a clean container are given to the patient for the sample collection. The sample should not be mixed with urine, barium and toilet paper. Approximately 5 ml of the liquid sample and 0.5 to 2 g of the formed stool should be collected. The container should be labelled with the patient's details including his/her name, registration number, age, gender, provisional diagnosis, and location.

Another type of sample which can be obtained in young children are rectal swabs. These are considered as less sensitive than stool samples. The swabs are inserted beyond the anal sphincter to collect the faeces. For suspected typhoid cases, blood and urine samples may also be collected.

Several transport media are available for faecal samples like Cary-Blair, Stuart's, Aimes' and buffered glycerol saline. Fresh samples should be

transported and processed within 2 h. Cary- Blair medium preserves all enteropathogens except Shigella. Buffered glycerol saline is used for transport of *Shigella species* but it is unsuitable for *Vibrio cholerae*. The WHO recommends Cary-Blair medium is the only recommended medium for *Vibrio cholerae*. Alkaline peptone water can also be used in its place if Cary- Blair is not available and subcultures can be done within 6 hours. When transport medium is not available, samples from suspected cases of cholera can be soaked onto a piece of filter paper, gauze or cotton [119, 120, 121, 122].

Sample Processing: The samples should be macroscopically examined first to look for parts with visible blood and mucus. These areas are likely to contain high numbers of pathogens and samples should be taken from these areas for further processing. Gram staining is not routinely done except for observing the sea-gull appearance of Campylobacter species when carbol fuchsin is used as a counter stain. The primary plating should be done on Mac Conkey agar and a medium selective for *Salmonella* / *Shigella species*. Blood agar with 5% sheep blood is used to enhance recovery of *Aeromonas, Plesiomonas* and *Vibrio cholerae*. Enrichment is very useful for recovery of *Vibrio cholerae* and failure to do so may result in false negative reports of culture. Selective media for different enteropathogens are listed in **Table 1**. Salmonella-Shigella agar is a good selective medium but it inhibits *Shigella dysentriae* serotype 1. Various chromogenic media are also available for rapid identification [10].

TABLE 1: CULTURE MEDIA USED FOR ISOLATION OF VARIOUS ENTEROPATHOGENS

Culture medium	Type of medium	Use
Gram-negative broth	Enrichment broth	Isolation of Gram-negative bacilli, more effective than Selenite F broth for *Shigella* spp., subculture after 6-8 h of incubation
Selenite F broth	Enrichment broth	Isolation of Gram-negative bacilli, especially *Salmonella* and *Shigella* spp. subcultured after 18-24 h of incubation
Alkaline peptone water	Enrichment broth	Isolation of Vibrio from fecal samples when subcultured in 6-8 h
Mac Conkey Agar	Differential/ Selective agar	Selective for gram-negative bacilli and differentiates between lactose fermenting and lactose non-fermenting bacilli
Salmonella-Shigella agar	Selective/ Differential agar	Selective for gram-negative bacilli differentiates between lactose fermenting and lactose non-fermenting bacteria and detects hydrogen sulphide production
Xylose lysine deoxycholate agar	Selective/ Differential agar	Selective for gram-negative bacilli, differentiates between lactose fermenting and lactose non-fermenting bacteria and detects hydrogen sulphide production
Hektoen enteric agar	Selective/ Differential agar	Selective for gram-negative bacilli, differentiates between lactose fermenting (yellow-orange) and lactose non-fermenting bacteria (blue or green) and detects hydrogen sulphide production
Bismuth sulphite agar	Highly selective agar	Isolation of Salmonella
Cefsulodin Irgasan novobiocin (CIN)	Highly selective agar	Isolation of *Yersinia enterocolitica* (colonies with a deep red centre and transparent periphery) and Aeromonas (pink colonies)
Blood agar with Ampicillin	Selective	Isolation of Aeromonas
Campy Blood	Highly selective agar	Isolation of Campylobacter
Charcoal cefoperazone deoxycholate agar	Highly selective agar	Isolation of Campylobacter
Inositol brilliant green bile salt	Highly selective and differential agar medium	Isolation of *Plesiomonas shigelloides* (white to pink in color) and Aeromonas (colorless)
CHRO Magar Salmonella	Differential and selective medium	Isolation of Salmonella (mauve colored) other bacteria (inhibited / blue or colorless)
CHRO Magar STEC	Differential and selective medium	Isolation of six most common STEC (mauve colored)
CHRO Magar O157	Differential and selective medium	Isolation of O157 (mauve colored)
Sorbitol Mac Conkey Agar	Differential and selective medium	Isolation of O157 (colorless)
Cycloserine cefoxitin egg yolk/ cycloserine cefoxitin fructose agar	Selective medium	Isolation of *Clostridium difficile*
Thiosulphate citrate bile salts sucrose agar	Selective medium	Isolation of *Vibrio cholera* (yellow) and *Vibrio parahemolyticus* (green)

A single drop of liquid stool is used for inoculation of selective media. If a rectal swab is being used, an area of 2.5 cm *i.e.* 1 inch approximately should be seeded. This is then streaked for isolation and

more overlapping is needed for highly selective media. Plates are then incubated for 18 to 24 h at 37 °C temperature. The cultures of Campylobacter need micro-aerophilic incubation with 85% nitrogen, 10% carbon dioxide and 5% oxygen at 42°C for 24 to 48 h [123]. Similarly, Yersinia also grows slowly and is usually seen as pinpoint colonies on Mac Conkey agar after 24 h. Both *Yersinia enterocolitica* and *Yersinia pseudo-tuberculosis* are motile at 25 °C and non-motile at 37 °C. After incubation, colonies are examined for phenotypic characteristics which are suggestive of pathogenic bacteria. Further identification is done by putting up biochemical tests and serotyping. Biochemical properties of different bacteria are given in **Table 2**. Sometimes, it is difficult to differentiate between closely related bacteria which react in a similar fashion in biochemical tests like atypical *Escherichia coli* and *Shigella species*. The common biochemical tests used are sugar fermentation tests, oxidase test, indole production, methyl red test, triple sugar iron, citrate utilization test, urease production, lysine and ornithine decarboxylases, and arginine dihydrolase [10].

TABLE 2: IMPORTANT BIOCHEMICAL PROPERTIES AND OTHER DIAGNOSTIC MODALITIES FOR DIFFERENT BACTERIA

Bacteria	Culture characteristics	Biochemical reactions	Antigen detection test	NAAT
Aeromonas spp.	B/A- beta-hemolytic colonies	Positive - Oxidase, nitrate reduction, glucose, and trehalose fermentation, ONPG, TSI-K/A, gas	_	_
Campylobacter spp	Medium Gray white colonies, microaerophilic conditions	Oxidase positive, *C. jejuni* Sodium Hippurate positive	Enzyme immunoassays for antigen detection in stool	-
Bacillus cereus	B/A – beta- haemolytic colonies		-	-
Yersinia enterocolitica	B/A – translucent, glistening colonies, beaten copper appearance, M/A- non-fermenter, CIN agar- pink bull's eye colonies	Motile at 27°C, Positive - Nitrate reduction, Voges Proskauer reaction at 27 °C, TSI-A/A, Urease produced	-	-
Vibrio cholerae	B/A – haemolytic colonies M/A – non-fermenter TCBS- Ferments sucrose, color changes from green to yellow	String test with sodium deoxycholate positive, oxidase and nitrate reduction positive, TSI-A/A or K/A	-	-
Clostridium difficile	-	-	Glutamate dehydrogenase (GDH) in both toxigenic and non-toxigenic strains	Real-time PCR and Loop-mediated isothermal amplification of DNA
Escherichia coli (STEC)	B/A- usually non-hemolytic M/A- Lactose fermenting colonies, Sorbitol-Mac conkey agar - sorbitol fermenting colonies	Motile, Indole positive, TSI-A/A, gas	Enzyme immunoassays for Shiga toxin	PCR for genes Stx1 and Stx 2
Escherichia coli O-157	M/A- Lactose fermenting colonies, Sorbitol-Mac conkey agar - non-sorbitol fermenter	TSI-A/A, gas		PCR
Shigella spp	Lactose non-fermenter on M/A, XLD, HE and SS agar	non-motile, oxidase negative, urease negative, catalase positive (except *S. dysenteriae*type 1 and *S. flexneri* type 4a), TSI-K/A)	-	Real time PCR
Edwardsiella tarda	Lactose nonfermenter with H_2S production on HE, MAC, XLD, SS agar	Motile, indole production and methyl red positive, TSI, K/A, H_2S, +/-gas	-	-

Non-culture Methods for Identification of Bacterial Enteropathogens: Commonly used for diagnosis of *Clostridium difficile* associated diarrhoea, the non- culture methods include detection of glutamate dehydrogenase, toxin A/ B detection by enzyme immunoassays (EIAs) and nucleic acid amplification tests (NAATs) for toxin genes. The enzyme glutamate dehydrogenase is a cell wall component of *C. difficile* and can be detected by EIAs but is less specific as it cannot differentiate between toxigenic and non-toxigenic strains. The presence of toxin is detected by either cell culture cytotoxicity neutralization assay, enzyme immunoassays or NAATs. Detection by EIAs has low sensitivity when compared to culture (50%) [124]. Thus, NAATs are the only available tests which have high sensitivity and specificity but are costlier. A sample positive by NAAT but negative for toxin by culture or EIA may just be reflective of colonization rather than infection. An algorithm which uses one or more than one test out of these three tests can help in reaching a diagnosis.

Antibiotic Treatment: Treatment with antimicrobial agents is not routinely recommended as most of the bacterial diarrhoeas are self-limiting. Rather, treatment may increase the risk of toxin production and persistent carriage. Routine antibiotic susceptibility testing is not recommended for isolates from stool culture except for infants, elderly, immunocompromised individuals or in cases of prolonged diarrhoea. Antibiotic use in STEC infections enhances the risk of HUS. Oral rehydration therapy remains the mainstay of management. Broad spectrum antibiotics are usually preferred but resistance to cotrimoxazole and ampicillin are increasingly becoming a problem in the management of traveller's diarrhoea. The treatment of choice is now fluoroquinolones for a duration of 3 - 5 days. For pregnant women and children, azithromycin is the treatment of choice instead of fluoroquinolones. Tetracyclines are used in the treatment of cholera. Erythromycin and Ciprofloxacin are the treatment of choice for Campylobacter [10]. Resistance to fluoroquinolones has been reported from the United States from both human and animal isolates. The mechanism of resistance usually points mutations in DNA gyrase *A. macrolide* resistance is due to methylation or point mutations in ribosomal target and efflux [10, 125, 126].

CONCLUSION: The bacterial species with the potential of causing gastroenteritis is estimated to be more than 40 species. The culture and routine diagnostic molecular methods have a limited capability to identify all of these. Thus, a microbiology laboratory on receipt of samples must work in accordance with factors like local epidemiology, patient's clinical history. This will allow targeting the most relevant bacteria in a given scenario. Non-culture methods are not available at all centres and are costly too. There is a need for a better physician- microbiologist communication.

ACKNOWLEDGEMENT: The authors acknowledge the contribution of Dr. Ravi Uniyal for helping us with the grammar and literature search.

CONFLICT OF INTEREST: All authors declare no conflict of interest.

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How to cite this article:
Tejan N, Datta P and Gupta V: Bacterial diarrhoea: a comprehensive review. Int J Pharm Sci & Res 2018; 9(12): 5015-31. doi: 10.13040/IJPSR.0975-8232.9(12).5015-31.