Trends in Isolation and Antimicrobial Susceptibility of Enteropathogenic Bacteria in 2011-2019 at a Korean Tertiary Care Hospital

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ABBREVIATIONS

AMR	Antimicrobial Resistance
AST	Anti-susceptibility Testing
CLSI	Clinical and Laboratory Standard Institute
KCDC	Korean Center for Disease Control
MDR	Multidrug Resistance
NTS	non-typhoidal *Salmonella*
STEC	Shiga toxin-producing *E. coli*
USA	The United States
WHO	World Health Organization

ABSTRACT

Background: Trends in the isolation of enteropathogenic bacteria may differ depending on environmental sanitation. This study aimed to determine trends in the isolation and antimicrobial resistance patterns of enteropathogenic bacteria between 2011 and 2019.

Methods: A retrospective analysis was performed using data from stool cultures of *Salmonella* spp., *Shigella* spp., *Plesiomonas shigelloides*, *Yersinia* spp., *Vibrio* spp., and *Campylobacter* spp. The sample was collected at Severance Hospital between 2011 and 2019. Antimicrobial susceptibility testing was performed using the disk diffusion method for nontyphoidal *Salmonella* (NTS) and *Campylobacter* spp. following CLSI guideline.

Results: The number of specimens for stool culture significantly increased from 13,412 during 1969-1978 to 48,476 over the past nine years, whereas the ratio of positive specimens significantly decreased from 1,732 (12.9%) to 449 (0.9%). The proportion of *Salmonella* Typhi decreased from 472 (93.6%) in 1969-1978 to 4 (1.5%) in 2011-2019, whereas the proportion of NTS increased from 14 (2.8%) to 261 (96.7%). The proportion of *Shigella* among all enteropathogenic bacteria was 1,039 (60.0%) from 1969-1978, while only 7 (1.6%) were isolated from 2011-2019. *Campylobacter* is the second most prevalent organisms, which were isolated 132 (29.4%). The susceptibility rate to ampicillin and cotrimoxazole were 51.1% and 85.2%, respectively, for NTS isolated from 2016 -2019. The ciprofloxacin susceptibility rate was 15.8% for *Campylobacter* from 2016-2019.

Conclusion: The number of isolates of *Salmonella* Typhi and *Shigella* significantly decreased, while the proportion of NTS and *Campylobacter* increased. Continuous monitoring of ciprofloxacin-resistant *Campylobacter* isolates is necessary.

Key Words: *Campylobacter* species, Enteropathogenic bacteria, *Salmonella* species

I. INTROCDUCTION

1.1 Background

Gastroenteritis refers to stomach and intestinal infections, and most forms of acute gastroenteritis are known as acute diarrhea. Diarrhea is commonly characterized as the movement of an increased quantity and frequency of abnormally liquid or formless stools. It is classified as infectious diarrhea when diarrhea is caused by a source of infection and is followed by nausea, vomiting, and abdominal pain. However, in the clinic, the microorganism causing the infection is seldom confirmed. Diarrhea is defined as acute if it lasts for 14 days or less, which is the case for most infectious diarrhea [1].

Diarrheal disease is the second leading cause of morbidity and mortality, and mainly occurred in children under 5 years of age, which is one of the global public health issues, especially in developing countries. This is so in Asia, Africa and Latin America [1-3]. According to the World Health Organization (WHO), were based on 4.6 billion cases of diarrhea and 1.6 million deaths due to diarrhea were recorded in 2010 [4, 5]. The most frequent pathogens causing acute gastroenteritis worldwide are *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *E. coli* O157:H7, *Listeria monocytogenes*, *Yersinia enterocolitica*, *Vibrio cholerae*, Rotavirus, *Entamoeba histolytica*, C*ryptosporidium* spp., and *Giardia lamblia* [1, 6]. Moreover, the diarrhea-causing pathogen depends on factors such as the atmosphere, climate, season, and region, so the prevalence of pathogen separation in each region must be considered [7]. In developing countries such as

Cambodia, Kenya, and Burkina Faso, where diarrhea rates are high due to low income and undernutrition, the most frequently isolated pathogens were enteroaggregative *E. coli* [8-10], but the most prevalent in Tehran was *Shigella* [11]. However, many developed countries have a high standard of health and hygiene, so enteritis is less likely to develop, but infectious diarrhea can also occur in developed countries, as was the case with more than 3,000 infections of the *Escherichia coli* O104: H4 in Germany in May 2011 [3]. In addition, *Salmonella* (56%) and S*higella* (21%) were the most commonly detected pathogens in Europe and Latin America, as examined by the 2003 global SENTRY Antimicrobial Surveillance Program [12].

In Korea, 14.7 percent of enteropathogenic bacteria were isolated based on acute infectious diarrhea surveillance in 2017. Bacteria have been found not to account for a high percentage of cases [1]. In most cases acute gastroenteritis is a self-limiting condition that do not require antibiotic treatment. Inappropriate use of antibiotics may cause antibiotic-associated diarrhea or other complications and may also lead to antibiotic resistance in the long term [1]. With the continuous improvement of health and hygiene, the incidence of infectious enteritis is decreasing, but the resistance rate of infectious enteritis is increasing. In addition, the increase in overseas travel has increased the likelihood of the introduction or epidemic of infectious enteritis caused by contaminated food or water [6, 7].

However, studies in South Korea over the past 10 years have primarily focused on advanced genotypic and phenotypic characteristics of enteropathogenic bacteria and as a result very few studies have been done on conventional surveillance of these pathogens leading to a gap in data for monitoring the trends in isolation and resistance patterns. Conventional method, however, remains as a gold standard for the confirmation of bacteria to monitor the trend and resistance patterns of enteropathogenic bacteria.

1.2 Aim of study

This study aims to determine the trends in the isolation and antimicrobial resistance patterns of enteropathogenic bacteria between 2011 and 2019 at Severance Hospital. Also, to compare the current pattern and trends of enteropathogenic bacteria's antimicrobial susceptibility with previous results in Severance Hospital.

1.3 Significance

This research will therefore be useful in providing clinical guidelines based on the latest evidence of scientific antibiotic therapy for suspected acute gastroenteritis usually seen in clinics and targeted antibiotic therapy for reported bacterial growth cases, with the aim of minimizing antibiotic misuse and preventing a rise in antibiotic-resistant bacterial strains.

II. LITERATURE REVIEW

2.1 Common Enteropathogenic Bacteria

Many types of enteropathogenic bacteria cause acute gastroenteritis, and these types are different according to regions. In the following part, we will discuss the isolated enteropathogenic bacteria in this study.

2.1.1 Salmonella spp.

Salmonella spp. are a group of bacteria that reside in human beings' intestinal tract and warm-blooded animals and can cause disease. It is a gram-negative rod that is a member of the *Enterobacteriaceae*. The genus *Salmonella* contains two species, including *Salmonella enterica* and *Salmonella bongori* [13]. *Salmonella enterica* is an important agent of foodborne illness. This species is sub-classified into six subspecies, of which *S. enterica* subspecies enterica is the most important for human health. The genus *Salmonella* can be subdivided into more than 2,400 serotypes. *Salmonella enterica* subsp. Enterica serotype Typhimurium (*S.* Typhimurium) and *Salmonella enterica* subsp. enterica serotype Serotypes are further subdivided by their resistance to bacteriophages (phage types or lystotypes), antibiotics or heavy metals; their biochemical characteristics (biovars or biotypes) or their sensitivity to or production of bacteriocins [13, 14]. *Salmonella* spp. are not particularly heat resistant. Most serotypes are killed by normal cooking conditions, i.e.

cooking to a core temperature of 75℃ instantaneously or an equivalent time-temperature combination, e.g. 70℃ for 2 minutes [14, 15].

The majority of individuals recover without antibiotics from Salmonella infection within four to seven days. When diarrhea persists, people who are ill with a Salmonella infection should drink extra fluids. Treatment with antibiotics is prescribed for patients with serious illness, people with a compromised immune system, such as people with HIV infection or treatment with chemotherapy, adults over 50 years of age with medical issues, such as heart disease, babies (children under 12 months of age) and adults 65 years of age or older [16].

2.1.2 ***Shigella* spp.**

Shigella are gram negative, nonmotile, facultatively anaerobic, non-spore-forming rods. *Shigella* are differentiated from the closely related *E. coli* based on pathogenicity, physiology and serology [17]. The genus is divided into four serogroups with multiple serotypes including A (*S. dysenteriae*, 12 serotypes), B (*S. flexneri*, 6 serotypes), C (*S. boydii*, 18 serotypes), and D (*S. sonnei*, 1 serotype). Infection is initiated by ingestion of s*higella* (usually via fecal-oral contamination). An early symptom, diarrhea (possibly elicited by enterotoxins and/or cytotoxin), may occur as the organisms pass through the small intestine [18].

Shigellosis is endemic in developing countries were sanitation is poor. Normally, 10 to 20 percent of enteric disease, and 50% of the bloody diarrhea or dysentery of young children, can be characterized as shigellosis, and the prevalence of these infections decreases significantly after five years of life [18].

People who are most likely to get Shigellosis including young children, but people of all ages are affected [19], travelers who travelled to developing countries, and to become infected with strains of *Shigella* bacteria that are resistant to necessary antibiotics [20], gay and bisexual men and other men who have sex with men who are more likely to acquire shigellosis than the general adult population [21], the person who has weakened immune systems due to illness (HIV) or medical treatment like chemotherapy for cancer can also get a more severe illness [22].

2.1.3 Campylobacter spp.

Campylobacters are defined as gram-negative rods that are motile, non-spore-forming, spiral or comma-shaped. They were originally assumed to be members of the genus Vibrio, but were assigned to the new genus, *Campylobacter*, in 1963 [23]. *Campylobacter jejuni and Campylobacter coli*, which account for most human *Campylobacter* isolates in the U.S., are both thermophilic. They grow best at 42 °C and microaerophilic, in that they grow best in an atmosphere containing 5% to 10% oxygen. Such optimum conditions of growth are likely to be a legacy of the evolutionary avian host and differ from the evolving *Campylobacter* spp. For instance, *C. Upsaliensis, C. Concisus, C. hyointestinalis*, *C. fetus*, *C. ureolyticus*, and *C. lari*, which have different reservoirs of animals and varying optimal conditions of development.

Campylobacter is a leading cause of bacterial diarrhea in developed countries, second to *Salmonella* as an agent of foodborne diarrheal illness in the United States [24] and the leading cause of foodborne bacterial illness worldwide, accounting for 96 million cases in 2010 [25].

Most infections with *Campylobacter* are probably acquired by consuming raw or undercooked poultry or by eating something that has affected it. Other foods, including fish, meat and produce, are also transmitted by *Campylobacter* through contact with animals and by consuming untreated water. Typically, *Campylobacter* does not spread from one person to another. *Campylobacter* infection is prevalent in low-resource countries and people traveling abroad are more likely to become infected [26].

2.2 Diagnosis for Enteropathogenic Bacteria

The standard operation procedure for stool culture was developed at Severance Hospital Laboratory Medicine, which referred to document code CM-PD-MM-16_7 version 7. (Flow Chart) (Figure 1.).

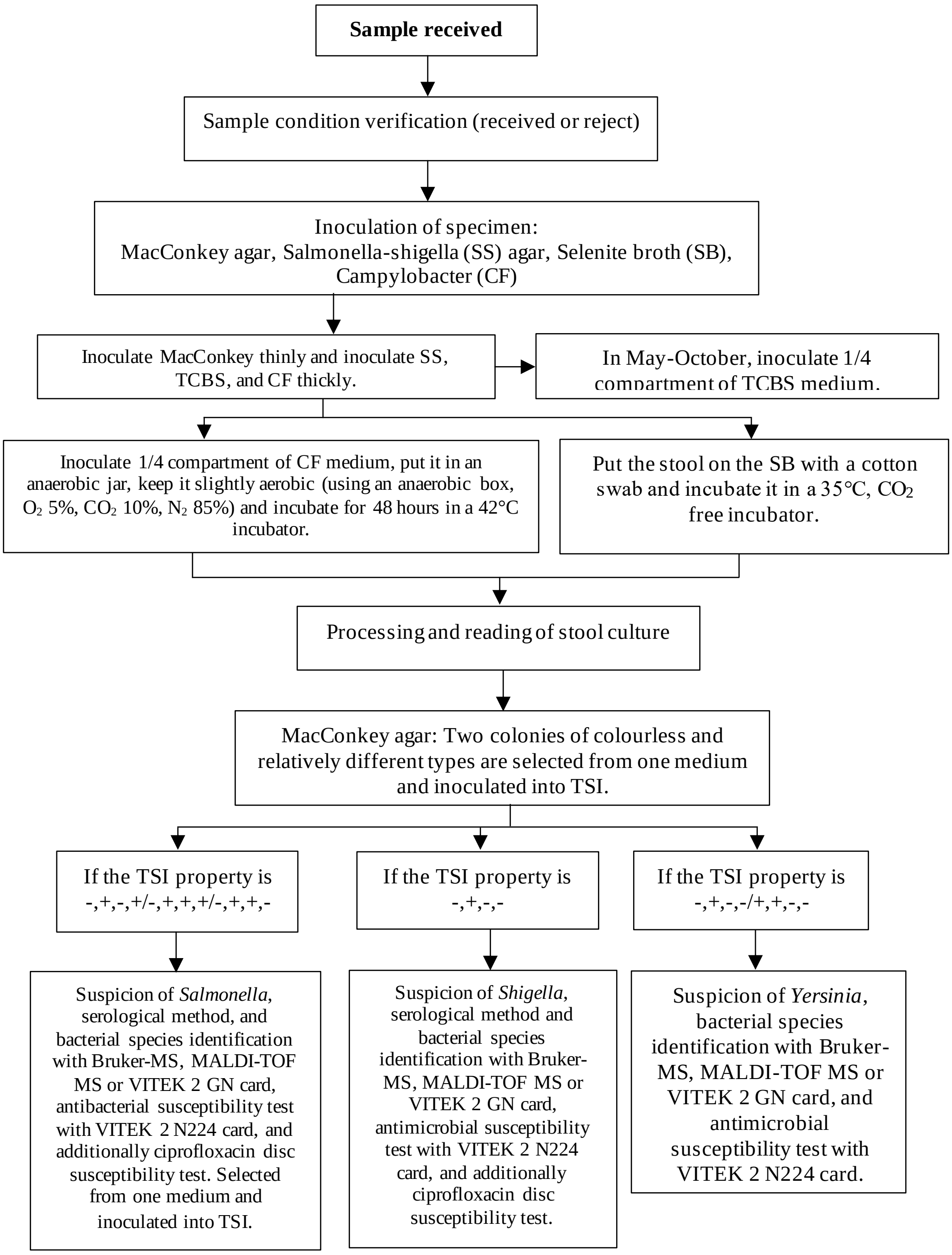

Figure 1. Flowchart for stool culture [27]

2.3 Epidemiology and Antimicrobial Resistance of Enteropathogenic Bacteria

Infectious diarrhea has different causes and incidence in different countries based public health level, lifestyle, and diet. Moreover, AMR's rate is based on their health policy approach and the implementation to control it by each country or region.

2.3.1 Epidemiology of Enteropathogenic Bacteria

Enteric fever includes typhoid fever caused by *Salmonella enterica* subspecies enterica serovar Typhi (*Salmonella* Typhi) and Paratyphoid fever caused by *Salmonella enterica* subspecies enterica serovar Paratyphi (*Salmonella* Paratyphi) A, B, and C. Enteric fever is commonly found in Central Asia and South East Asia, and is also observed in other Asian countries, Africa, Latin America, and Oceania [28].

A study in USAM by NARMS were analyzed 20 Shigella isolates with decreased susceptibility to fluoroquinolones. Most patients (80%) from whom a travel history was obtained reported travel to South or Southeast Asia. Mutations within the quinolone resistance determining regions of gyrA and parC and plasmid-mediated resistance determinants (qnrB, qnrS, and aac(6′)-Ib-cr) were identified [29].

Another study in Northwest Iran has a surveillance for enterotoxigenic and enteropathogenic *E. coli* isolates from animal source foods in 2016. It revealed that the occurrence of *E. coli was* 45% in dairy and 52.5% in meat products. The milk without pasteurization and traditional dairy products produced in unhygienic conditions are most likely the primary sources of *E. coli* pathotypes and other zoonotic pathogens. They can be considered a potential hazard to the health of the community [30].

Another investigation from stool culture in 2016-2017 at the Madibeng District of the North-West Province of South Africa indicated *Campylobacter*, *Arcobacter* spp., diarrhoeagenic *E.coli*, rotavirus and norovirus are among the givers of diarrhea in children younger than four years old [31].

A diarrheal surveillance study in Cambodia in 2016 was observed multidrug resistance in 10 (91%) of 11 *Shigella* isolates. One isolate was resistant to fluoroquinolones and cephalosporins and revealed decreased susceptibility to azithromycin. It found mutations in gyrA, parC, β-lactamase, and mphA genes. MDR increases concern about shigellosis treatment options [32].

STEC O157:H7 is the most common serotype that causes infections in humans worldwide; non-O157 STEC can also cause symptoms. In 2011, there were outbreaks of enteritis caused by STEC O104:H4 in Germany and France; of the 3,816 cases in Germany, 22% had hemolytic uremic syndrome [33, 34]. According to 20 years of epidemiological investigation of STEC O157:H7 in 1982-2002 in USA, hemolytic uremic syndrome was found in 4% of 8,598 cases, with mortality of 0.5% [35]. Although research on STEC has lacked in Korea, a previous report suggested that STEC was identified in 0.19% of 17,148 diarrhea patients in Kwangju between 2004 and 2018 [36].

In acute infectious diarrhea surveillance in Korea conducted by the KCDC, bacterial pathogens were isolated from 11.5 to 23.7% of samples between 2012 and 2016. In 2017, bacteria tested in the surveillance projected to (*Salmonella* spp., *E. coli*, *Shigella* spp., *V. parahaemolyticus*, *V. cholerae*, *Campylobacter* spp., *C. perfringens*, *S. aureus*, *Bacillus cereus*, *L. monocytogenes*, and *Y. enterocolitica*) were isolated in 1,376 of 9,344 samples collected at 70 participating institutions, thus at a rate of 14.7%, indicated bacteria does not account for a high number of cases of acute diarrhea [1].

Korea has another surveillance system on gastrointestinal infections characterized by vomiting and diarrhea at 196 surveillance institutions including tertiary hospitals, hospitals with more than 200 beds, and public hospitals. Of the 15,717 pathogens isolated in 2017, 9,276 cases were viral (59.0%), most of which were caused by norovirus and rotavirus, and 6,373 were bacterial (40.5%) caused by *Salmonella*, *C. perfringens*, and *Campylobacter*; 68 were caused by protozoa (0.4%), most of which were caused by Giardia lamblia [37].

The most common serotype of *Salmonella* in Korea between 1998 and 2007 was Salmonella Typhi, *Salmonella enterica* subspecies enterica serovar Enteritidis (*Salmonella enteritidis*), and *Salmonella enterica* subspecies enterica serovar Typhimurium (*Salmonella* Typhimurium) [38, 39]. Moreover, *Salmonella* causes food or water-borne gastroenteritis in Korea. Although its incidence is decreasing, typhoid fever introduced from other countries has increased due to increases in travels to other countries and foreign nationals living in Korea [38].

2.3.2 Antimicrobial Resistance of Enteropathogenic Bacteria

Salmonella, Campylobacter, Shigella, and STEC are the most common pathogenic bacteria causing acute bloody diarrhea. Multiple randomized controlled studies demonstrated that empirical antibiotic therapy in these patients lead to one day reduction in the duration of symptoms compared to placebo treatment. However, antibiotic treatment increases the time for excretion of *Salmonella*, and can also cause the excretion of fluoroquinolone resistant *Campylobacter* [40].

So that is why selection of antibiotics for empirical antibiotic therapy of acute infectious diarrhea should consider the distribution and antibiotic sensitivity of pathogens in local communities or areas where the patient traveled. Although fluoroquinolone antibiotics, including ciprofloxacin and levofloxacin, have been recommended for first-line therapy, resistance against these antibiotics has increased recently. Likewise, fluoroquinolone antibiotics have risks of severe side effects, such as ligament inflammation, ligament rupture, peripheral neuropathy, and central nervous system side effects, and thus require caution [40].

In some fields, macrolides, such as azithromycin, is recommended due to increased resistance of *Campylobacter* to fluoroquinolone. In Europe in 2012, *Campylobacter* infections were three times more common than nontyphoidal *Salmonella* infections [62], and ciprofloxacin resistance of *Campylobacter* was reported to be as high as 44% in some European countries [41]. Fluoroquinolone resistance of *Campylobacter* has also been reported to be high in Mexico (56%) and Thailand (>92%) [42, 43]. Considering these, macrolides including azithromycin, may be considered for empirical antibiotic therapy in areas where *Campylobacter* is common and has high resistance to fluoroquinolone [40].

A study published in 2015 by Ghunaim et al. [44] found an erythromycin resistance of C. *jejuni*, relatively low. Only 8.6% of the isolates were resistant, while 63.2% were resistant to ciprofloxacin. A high rate of resistance to ciprofloxacin was also reported in the UAE, where 85,4% of the isolates were resistant [45]; in Poland, they were published [46] lower rates of resistance (40%) and only 2% in Australia [47].

According to the KCDC's study of 3,526 samples isolated from infectious diarrhea patients in 2014, *Salmonella* species accounted for 13.5%, and *Campylobacter* species accounted for 6.1% [48]. Moreover, 29% (63/218) of *Campylobacter* have been reported to be resistant to fluoroquinolones, although this report was made from a single institution [7]. Therefore, the percentage of *Campylobacter* and increase in fluoroquinolone resistance should be considered in infectious diarrhea in South Korea. The use of macrolides, such as azithromycin, should also be considered [40] .

Azithromycin was more effective in decreasing the excretion of bacteria than ciprofloxacin in diarrhea observed in American soldiers deployed to Thailand; this finding seems to have been related to the high *Campylobacter* prevalence and fluoroquinolone resistance in the area [49]. Since antibiotic use increases recurrence and prolongs bacterial excretion in nontyphoidal *salmonella*, it is not recommended in most cases [50].

In addition, KCDC studied 219 clinically isolated nontyphoidal *Salmonella* bacterial strains between 2006 and 2008, with resistance to ampicillin, nalidixic acid, ciprofloxacin, and TMP/SMX 49%, 50%, <1%, and 8%, respectively. The use of azithromycin, ciprofloxacin, or ceftriaxone is recommended for shigellosis [1]. A Korean study reported a high resistance rate, while trimethoprim-sulfamethoxazole or ampicillin may be used when isolated bacteria are susceptible. Resistance to trimethoprim, sulfonamide, nalidixic acid and ampicillin was 100%, 99%, 70%, and 49%, respectively in 67 *Shigella sonnei* strains isolated in the province of Jeollanam in 1999-2000, but no resistance to cefotaxime or ciprofloxacin was found [51].

III. MATERIALS AND METHODS

3.1 Study Design

A retrospective analysis was performed using existing data of stool culture from the patients hospitalized at Severance Hospital from 2011 to 2019.

3.2 Microbiology Methods

3.2.1 Sample Collection

The stool samples were collected and placed it in transport mini sputum container. Bacteria to be cultured belong to *Salmonella* spp., *Shigella* spp., *Plesiomonas shigellosides*, *Yersinia* spp., *Vibrio* spp., and *Campylobacter* spp. (all spp. were included to *Enterobacteriaceae*).

3.2.2 Bacterial Culture Media

MacConkey agar base (BBL, USA), *Salmonella Shigella* agar (BBL), selenite broth (BBL) and Matrix (Bruker Daltonics, Germany) were used for *Enterobacteriaceae*. Thiosulfate citrate bile sucrose agar base (BBL) was used for *Vibrio* species. Campylobacter selective supplement (Oxoid), Campylobacter growth supplement (Oxoid) and blood agar base (BBL) were used for *Campylobacter* species culture.

3.2.3 Bacterial Culture Incubation

Enterobacteriaceae and *Vibrio* spp. cultures were incubated in aerobic condition at 35^{o}C for 24 hours. For *Campylobacter* spp. cultures with specimen inoculated mediums were incubated in a microaerophilic atmosphere at 42 °C for 48 hours [52].

3.2.4 Bacterial Isolations and Identifications

Colony shape, biochemical testing, MALDI-TOF MS, VITEK 2 ID card, and Bruker-MS were used for bacteria identification. Moreover, serological identification of *Salmonella* or *Shigella* was performed by using a slide aggregation reaction *Salmonella* and *Shigella* group diagnostic sera (National Health Research Institute).

3.2.5 Antimicrobial Susceptibility Testing

The anti-susceptibility testing (AST) was tested by VITEK 2 AST card, disc diffusion method and E-test following the Clinical Laboratory Standard Institute (CLSI) guideline [53]. A standardized 0.5 McFarland suspension was prepared, and VITEK® 2 cards (Biomerieux, Inc.NC, USA) for AST were inoculated following the manufacturer recommendation.

For AST testing of *Salmonella* or *Shigella* were tested with VITEK 2 N224 card, and additionally ciprofloxacin disc susceptibility test.

Erythromycin, ciprofloxacin, and tetracycline discs were tested at the same time for *Campylobacter* species.

3.2.6 Quality Control Methods

Quality control of identification card and susceptibility test card is performed once a week or whenever the lot number of the kit is changed using the quality control strain. Bruker-MS performs calibration once a week using the Bruker Standard. Antisera reagents are administered as standard or clinical strains once a month and when reagents are opened.

Escherichia coli ATCC®a 25922 was used for quality control for each organism [53].

3.3 Data Registration and Statistical Analysis

Data were entered into Severance Hospital Information Management System. Microsoft® Excel® 2010 (16.0.13328.20262) was used for statistical analysis.

3.4 Ethical Considerations

Ethical approval was granted from Yonsei Institutional Review boards No. 4-2020-1031 at the Severance Hospital, Yonsei University, Seoul, Republic of Korea. Patients were identified with a unique hospital number. No other data besides those noted in the routine medical files were used for the clinical and epidemiological data.

IV. RESULTS

4.1 Comparison of Trends in Isolation of Enteropathogenic Bacteria at a Tertiary-care Hospital

There were 48,476 specimens were requested for stool culture from 2011 to 2109. Among the total requested specimens, 449 specimens were positive accounted to 0.9%. The enteropathogenic bacteria isolated from the stool culture during 2011 to 2019 were distributed as 270 (60.1%) *Salmonella* spp., 7 (1.6%) *Shigella* spp., 132 (29.4%) *Campylobacter* spp., 7 (1.6%) *Vibrio parahaemolyticus,* 1 (0.2%) *Yersinia enterocolitica,* and 32 (7.1%) others isolates.

Salmonella spp. and *Campylobacter* spp. were the most common pathogen 60.1% and 29.4%, respectively. Followed by *Salmonella* spp., there were separated 4 (1.5%) *Salmonella* Typhi, 0 (0.0%) *Salmonella* Paratyphi-A, 111 (41.1%) *Salmonella* serogroup B, 82 (30.4%) *Salmonella* serogroup C, 63 (23.3%) *Salmonella* serogroup D, 5 (1.9%) *Salmonella* serogroup E and 5 (1.9%) *Salmonella* another serogroup. (Table 1.)

Table 1. Comparison of trends in isolation of enteropathogenic bacteria at a tertiary-care hospital

Characteristics	**Period of data acquisition**				
	1969-1978	**1979-1988**	**1989-1998**	**2001-2010**	**2011-2019**
No. of specimen cultured	13,412	37,846	51,441	60,714	48,476
No. of positive specimen	1,732	3,503	2,140	648	449
% of positive specimen	12.9	9.2	4.2	1.1	0.9
No. of positive patient	1,677	3,182	1,531	565	449
***Salmonella* Typhi**	472	469	58	1	4
***Salmonella* Paratyphi-A**	18	101	3	2	0
***Salmonella* serogroup B**	3	245	564	86	111
***Salmonella* serogroup C**	4	108	126	89	82
***Salmonella* serogroup D**	5	107	341	157	63
***Salmonella* serogroup E**	2	32	55	22	5
***Salmonella* other serogroup**	0	40	39	2	5
All *Salmonella* isolates	504	1,102	1,186	359	270
***Shigella* subgroup A**	16	5	2	0	0
***Shigella* subgroup B**	781	1,246	30	3	1
***Shigella* subgroup C**	8	43	0	0	6
***Shigella* subgroup D**	234	214	19	95	0
All *Shigella* isolates	1,039	1,508	51	98	7
***Campylobacter* spp.**	NT	185	239	85	132
Yersinia enterocolitica	NT	29	18	1	1
Vibrio parahaemolyticus	45	96	42	27	7
Plesiomonas shigelloides	NT	4	11	0	0

*Abbreviation: NT, not tested.

*1969-2010 tables were adapted from reference [7].

4.2 Number of Patients with nontyphoidal *Salmonella* and *Campylobacter* spp. Isolation by Month in 2011-2019

The findings were figured out of the number of patients with nontyphoidal *Salmonella* (NTS) and *Campylobacter* spp. isolation by month in 2011-2019. Among 261 strains of NTS were positively identified in the month of August 43 (16.5%), September 40 (15.3%) and October 40 (15.3%). Moreover, 132 of *Campylobacter* spp. were positively identified in the month of June 15 (11.4%), July 18 (13.6%) and August 28 (21.2%). (Table 2.)

Table 2. Number of patients with nontyphoidal *Salmonella* and *Campylobacter* spp. isolation by month in 2011-2019

Month	No. of patient with:	
	Nontyphoidal *Salmonella* (%)	*Campylobacter* spp. (%)
January	12 (4.6)	5 (3.8)
February	5 (1.9)	5 (3.8)
March	14 (5.4)	14 (10.6)
April	16 (6.1)	9 (8.6)
May	21 (8.0)	9 (8.6)
June	23 (8.8)	15 (11.4)
July	26 (10.0)	18 (13.6)
August	43 (16.5)	28 (21.2)
September	40 (15.3)	8 (6.1)
October	40 (15.3)	8 (6.1)
November	12 (4.6)	4 (3.0)
December	9 (3.4)	9 (6.8)
Total	261 (100)	132 (100)

4.3 Number of Patients with nontyphoidal *Salmonella* and *Campylobacter* spp. by Age Group

The patient under 5 years and older than 60 years of age were found highly infected by NTS *and Campylobacter* spp. However, *Campylobacter* was isolated, not only under the age of 5 and more than 60 but also found highly infected at 10-19 and 20-29. (Table 3.)

Table 3. Number of patients with nontyphoidal *Salmonella* and *Campylobacter* spp. by age group

Organism	**No. of patients by age group (year)**								
	≤5	6-9	10-19	20-29	30-39	40-49	50-59	≥60	Total
Nontyphoidal *Salmonella*	118	27	24	9	10	11	18	44	261
***Campylobacter* spp.**	11	7	28	33	12	5	12	24	132

4.4 Comparison of Trends in Antimicrobial Susceptibility of nontyphoidal *Salmonella*

As shown in table 4, the susceptibility rate of NTS between 2011 and 2015 was ampicillin (53%), sulfamethoxazole-trimethoprim (93%), cefotaxime (92%), ceftazidime (92%), and fluoroquinolone (84%). Similarly, the susceptibility rate of NTS between 2016 to 2019 was ampicillin (51%), sulfamethoxazole-trimethoprim (85%), cefotaxime (74%), ceftazidime (81%), and fluoroquinolone (73%).

Table 4. Comparison of trends in antimicrobial susceptibility of nontyphoidal *Salmonella*

Year	No. of patients	% of isolates susceptible to:					
		AMP	CHL	SXT	CTX	CAZ	FQN
1979-1983	211	98	99	100	NT	NT	NT
1984-1988	337	54	64	98	NT	NT	NT
1989-1993	420	67	77	90	NT	NT	NT
1994-1998	865	76	NT	90	98	98	100
2001-2005	210	65	NT	93	99	100	100
2006-2010	141	61	NT	92	96	98	98
2011-2015	108	53	NT	93	92	92	84
2016-2019	153	51	NT	85	74	81	73

*FQN: ofloxacin (1994-1996), levofloxacin (1997-1998), levofloxacin (2001-2010) and levofloxacin (2011-2019).

*Abbreviation: AMP, ampicillin; CHL, chloramphenicol; SXT, sulfamethoxazole-trimethoprim; CTX, cefotaxime; CAZ, ceftazidime; FQN, fluoroquinolone; NT, not tested.

*1969-2010 tables were adapted from reference [7].

4.5 Comparison of Trends in Antimicrobial Susceptibility of *Campylobacter* spp.

As shown in Table 5, the rate of susceptibility to erythromycin and fluoroquinolone was 87.03% and 25.4%, respectively, for *Campylobacter* spp.; they were isolated from 2011 to 2015. On the other hand, the rates of susceptibility to erythromycin, fluoroquinolone and tetracycline were 98.2%, 15.8% and 51.4%%, respectively, for *Campylobacter* spp.; they were isolated from 2016 to 2019.

Table 5. Comparison of trends in antimicrobial susceptibility of *Campylobacter* spp.

Antimicrobial agents	% of isolates susceptible						
	1981-1982 (n=29)	1986-1991 (n=127)	1994-1998 (n=138)	2001-2005 (n=41)	2006-2010 (n=39)	2011-2015 (n=72)	2016-2019 (n=60)
Erythromycin	100	NT	92.0	95.1	87.2	87.03	98.2
Fluoroquinolone	NT	NT	74.2	53.8	79.5	25.4	15.8
Ampicillin	83.8	60.6	72.0	82.9	69.2	NT	NT
Cephalothin	0	7.9	8.8	4.9	7.7	0.0	NT
Amikacin	86.2	86.3	98.2	97.6	94.9	NT	NT
Gentamicin	86.2	85.6	98.2	90.2	92.3	NT	NT
Tobramycin	82.8	84.1	77.8	85.4	92.3	NT	NT
Cotrimoxazole	64.3	19.2	22.1	4.9	7.7	NT	NT
Tetracycline	76.9	44.5	13.9	12.2	0	NT	51.4

*Fluoroquinolones used: ofloxacin (1994-1996), levofloxacin (1997-1998), ciprofloxacin (2001-2010) and ciprofloxacin (2011-2019).

*Abbreviation: NT, not tested.

*1969-2010 tables were adapted from reference [7].

V. DISCUSSION

In this study, we compared the results of the separation of enteropathogenic bacteria in 2011-2019 with the results of separation in 1969-2010. Moreover, we analyzed the trend of enteropathogenic bacteria and examined the antibiotic resistance pattern. The number of requests for stool culture testing during this study period increased by 3.6 times compared to 13,412 samples from 1969-1978. The number of samples positive for culture decreased significantly from 1,732 (positive rate 12.9%) to 449 (positive rate 0.9%). Due to an increase in the number of patients with an increase in the number of beds, an increase in hospitalized infection monitoring culture, and improved health and hygiene [54]. *Shigella*, *Vibrio*, and *Salmonella* are mainly isolated among enterocolitis in developing countries, but *Shigella* and *Salmonella* Typhi are very rare in developed countries. In developed countries, *Campylobacter* and NTS became the major isolates. A USA study reported that 42% of the enteritis bacterial causative agents were *Campylobacter* 32%, NTS 32%, and *Shigella* 13%, supporting the changes in these isolates [55, 56]. Another report regarding traveler diarrhea investigated tourisms from South East Asia countries including Thailand where commonly identified *Campylobacter* and *Aeromonas* [57].

Particularly, *Salmonella enteritidis* belonging to the *Salmonella* serotype D group, is one of the most common *Salmonella* serotypes prevalent all over the world and is known to be the main causative agent of foodborne salmonellosis [58]. During this study period, 2011-2019, NTS was found in 261 patients, and it was the most isolated isolate, accounting for

58%. *Salmonella* isolated in 1969-1978, 472 (93.6%) were *Salmonella* Typhi, but in 2011-2019, there were only 4 (1.5%) isolated. The number of *Salmonella* Paratyphi-A was 101 (9.2%) in 1979-1988, but it decreased significantly to 0 (0.0%) in 2001-2010. On the other hand, NTS's trend gradually increased and separated from 14 cases in 1969-1978 to 261 cases in 2011-2019. In the past, there were many *Salmonella* serogroup B and D among NTS, but the isolates started to be decreased since 2010. Despite, compare to some developing countries were remained highly infected as a massive typhoid fever outbreak in Pakistan resulted in 5,372 extensively drug-resistant (XDR) Typhi cases stated during 2016-2018, and five travel-related cases in the United States [59].

Shigella was the most common enteritis bacterium, accounting for more than 50% of the total number of isolates, separated from a total of 2,547 isolated in 1969-1988, but the trend decreased significantly after 1989. In this study, a total of 7 (1.6%) isolates were separated from 2011-2019. In the developing countries, there were many *S. dysenteriae* and *S. flexneri* infections, but in developed countries, there were many *S. sonnei* infections [60]. In the recent year, *S. dysenteriae* infection has been rare in Korea [61], the number of *S. flexneri* was the most prevalent until the late 1980s, and *S. sonnei* has been the most prevalent since 1990 [62]. Nonetheless, even after the late 1990s, it was decreased, *Shigella* infections often occurred, it is requiring continuous culture [62]. On the other hand, Thailand reported that the most commonly isolated *Shigella* species over the past two decades have been *S. flexneri* (79%) and *S. sonnei* (15%) and the incidence of *S. sonnei* were predominated over 80% in children under 5 in their country [63]. Even though, Thailand is a developed country, *Shigella* remains highly infected by, if compare to South Korea's current situation.

C. jejuni is a major cause of bacterial diarrheal illness in the USA and in many other countries, with an estimated 845,000 foodborne cases per year in the USA alone, third in the number of estimated bacterial foodborne disease cases after *Salmonella* and *Clostridium perfringens* [60]. Severance Hospital began separating *Campylobacter* from 1981 and was identified 239 isolates in 1989-1998, 83 isolates in 2001-2010 and 132 isolates in 2011-2019. Among the 132 isolates of *Campylobacter* in 2011-2019, *C. jejuni* was the most common pathogen. By the way, a study in Cambodia found in multiplex PCR among 681 stool samples were 82 (12%) tested positive followed by *C. jejuni* in 66 samples and *C. coli* in 16 [64] with *Campylobacter* positive rates for Vietnam and Laos were below 5% [65]. Thus, it showed that the rate *of Campylobacter* infection in developed country is higher than in developing countries.

V. parahemolyticus was isolated 7 (1.6%) during the investigation period. The number was small because patients with this enteritis recovered naturally after 2-3 days of infection, so there was little opportunity to isolate the bacteria from tertiary medical institutions. In Korea, it is projected that the number of infected patients is high because they often reproduce fish and shellfish [66]. In fact, due to the food poisoning statistics from 2003-2016 from Korea Ministry of Food and Drug Safety in 2017, 225 cases and 4256 patients were reported in outbreaks caused by *V. parahaemolyticus*, accounting for

5.8% of total outbreaks and 4.1% of total patients, respectively, based on all food-borne illnesses occurring in Korea [66].

Some various studies have been reported *Y. enterocolitica* distribution, is mostly in Northern Europe and northern states of the USA, reflecting its increased growth at cold temperatures [67]. In Korea, have been reported 47 cases of *Y. enterocolitica* and 15 cases of *P. shigelloides* in 1979-1998 [54], but *Y. enterocolitica* was found in only one isolate during this study period.

NTS and *Campylobacter* were highly isolated in patients under five years of age, similar to those of other domestic and foreign researchers [55, 68]. However, *Campylobacter* was isolated, not only under the age of 5 but also at 10-19 and 20-29. While infection with *C. jejuni* or *C. coli* can occur in patients of all ages [69], a recent study from Denmark showed that infection is more common in children (1 to 4 years) and young adults (15 to 24 years) than in other age groups [70] and slightly older patients (34.6 years versus 27.5 years) and those who traveled abroad were at a greater risk of being infected with *C. coli* than with *C. jejuni* [71]. Moreover, infections with *C. jejuni* and *C. coli* are more common during the summer months [70, 72]. Similarly, this study found that *Campylobacter* was positively identified in June, July, and August.

In this study, NTS resistance to ampicillin and cotrimoxazole was higher than in the past. Furthermore, in the last four years in 2016-2019, the susceptibility rate in cefotaxime, ceftazidime and fluoroquinolone was decreased significantly. The generation of extended-spectrum β-lactamase (ESBL) resistant to third-generation cephalosporin in Korea was first reported in 2003. It had been increasing since then, presumably due to CTX-M-type ESBL [73, 74]. Even though, ciprofloxacin resistance rate has good activity against *Salmonella*; continuous monitoring is still necessary because *Salmonella,* which is resistant to ciprofloxacin, has increased in foreign countries [75]. KCDC analyzed NTS between 2006 and 2008, reported the resistance to ampicillin, nalidixic acid, ciprofloxacin, and TMP/SMX was 49%, 50%, <1%, and 8%, respectively [51].

Erythromycin and ciprofloxacin are recommended for the treatment of *C. enteritis*, and recently increased resistance to these drugs has been reported. Although, it is difficult to make a direct comparison according to the change of the standard for analyzing the antimicrobial susceptibility test of *Campylobacter*, the ciprofloxacin susceptibility was 79.5% in 2006-2010 [7], and the susceptibility was 25.4% in 2011-2015 and 15.8% in 2016-2019. Thus, we observed the resistance rapidly increased. On the other hand, the erythromycin and tetracycline susceptibility in 2016-2019 were gradually decreased to 98.2.% and 51.4%, respectively, compared to the previous period. In other studies in Europe in 2012, ciprofloxacin resistance of *Campylobacter* was reported to be as high as 44% in some European countries [41]. Fluoroquinolone resistance of *Campylobacter* has also been reported to be high in Mexico (56%) and Thailand (>92%) [42, 43]. Despite, in Japan showed that macrolide resistance was in a low rate in *C. jejuni* and *C. coli* isolated, but resistant *Campylobacter* spp. were emerged to quinolones [76]. Considering these, macrolides including azithromycin may be considered for empirical antibiotic therapy in areas where *Campylobacter* is common and has a high resistance to fluoroquinolone [40].

VI. CONCLUSIONS

This showed an increase in the incidence of enteropathogenic bacteria infection in Severance Hospital throughout the study. The pathogens with the most significant increase in incidence were non-typhoidal *Salmonella* and *Campylobacter* spp., even though there was a decrease in *Salmonella* Typhi and *Shigella's* incidence. Enteropathogenic bacteria resistance to commonly prescribed antibiotics is steadily on the rise, as shown in this study. Non-typhoidal *Salmonella* resistance increased to ampicillin, sulfamethoxazole-trimethoprim, cefotaxime, ceftazidime, and fluoroquinolone. *Campylobacter* resistance to fluoroquinolone increased significantly over the study period, but *Campylobacter* isolates remained susceptible to erythromycin. Continuous monitoring of resistant enteropathogenic bacteria is necessary.

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