Comparison of Sensitivity and Resistance to Ceftriaxone with Chloramphenicol in the Treatment of *Salmonella typhi* Infection : Literature Review

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ABSTRACT

Purpose: To compare the sensitivity and resistance between ceftriaxone and chloramphenicol in the treatment of *Salmonella typhi* infection. *Methodology*: The study used a literature review method and research samples were obtained from search results using e-databases in the form of PubMed, Google Scholar, and Science Direct. *Results*: From the search results found 1034 articles then the researchers screened according to the inclusion and exclusion criteria, obtained 15 articles were received for review. From all studies, it was found that *Salmonella typhi* was more sensitive to ceftriaxone than chloramphenicol. *Applications/Originality/Value*: *Salmonella typhi* is more sensitive to ceftriaxone and more resistant to chloramphenicol.

INTRODUCTION

Typhoid fever is a systemic infectious disease and one of the most common foodborne disease found in all countries. This disease is classified as an endemic disease in Indonesia that is obtained throughout the year (Suwandi & Sandika, 2017). *Salmonella typhi* only attack humans, not other hosts. While in other bacteria use animals and plants as hosts. Therefore, *Salmonella typhi* more often causes disease in humans, especially typhoid fever. This disease is an interesting case to discuss because until now this case has a high prevalence rate (Prehamukti, 2018). In addition to cases that are still high, there is resistance in the treatment of typhoid fever in various regions. Research in Mexico in 1973 found *Salmonella typhi* resistant to ampicillin. In subsequent developments, several countries reported the existence of strains of *Salmonella typhi* that were resistant to two or more classes of antibiotics commonly used, namely ampicillin, chloramphenicol, and cotrimoxazole (Juwita *et al*., 2012). Research conducted by Indang *et al*, (2013) in Palu City showed that *Salmonella typhi* bacteria were resistant to 4 types of antibiotics, namely ampicillin, amoxicillin, cephalexin, and chloramphenicol (Rahman, 2019). Typhoid fever can be treated with antibiotics. The use of antibiotics must be used correctly, according to the indications of the disease, according to the dose, according to the way of administration and still pay attention to the side effect. So it is hoped that the community will be rational and not excessive in using antibiotics in accordance with WHO (World Health Organization). However, over time unprocedural and uncontrolled use of antibiotics can lead to resistance, thereby increasing mortality and morbidity (Rahman, 2019). Previous research at the PKU Hospital Inpatient Installation Muhammadiyah Surakarta in 2009 showed that the most effective antibiotics frequently used from 95 patients with typhoid fever was cefotaxime 49.47%. The use of antibiotics that are in accordance with standard therapy in terms of accuracy the indications are 100%, the right patient is 98.95%, the right drug is 96.84%, and the right dose as much as 82.10% (Safitri, 2009). Other Research in Inpatient Installation Pambalah Batung Hospital, North Hulu Sungai Regency, South Kalimantan in 2009, the most widely used antibiotics are ceftriaxone 95% and cefotaxime 8% of 109 prescriptions. Conformity with standard therapy in terms of precise indications as much as 100%, right drug 97.25%, right patient 88% and right dose 9.17% (Marhamah, 2009). Researchers choose the antibiotics ceftriaxone and chloramphenicol in this literature review because in previous studies it was found that the two drugs were the most sensitive than other types of antibiotics. However, there are differences in the level of sensitivity and resistance between the two drugs in different countries. There are studies which state that *Salmonella typhi* is more sensitive to ceftriaxone, and there are also studies which state that *Salmonella typhi* is more sensitive to chloramphenicol. The researcher has the aim to analyse several previous studies to find out which antibiotics between chloramphenicol and ceftriaxone are more effective for treating typhoid fever, so that the problem of *Salmonella typhi* infection cases can be reduced by using the right antibiotics.

p-ISSN: 2477-3328
e-ISSN: 2615-1588

METHODS

The sample of this study was obtained from the search engine on the Mozilla firefox application using several databases such as Google Scholar, Pubmed, and Science Direct.

The keywords used were sensitive AND resistant AND (ceftriaxone OR cefaxona) AND (chloramphenicol OR amphenicol) AND "salmonella typhi". The journal technique used follows the flow chart from PRISMA. Research journals are collected and a journal summary is made including the name of researcher, year of publication of the journal, country of research, title of research, method and summary of results or findings. The summary of the research journal is entered into a table, then similarities and difference are searched and then disscussed to draw conclusions.

RESULT AND DISCUSSION

It found 42 journals from Pubmed, 42 journals from Science Direct, and 950 journals from Google Scholar, for a total of 1034 journals. Of the total journals identified there are 26 duplication journals, then the remaining 1008 journals for title screening. 90 journals with appropriate tutles were obtained, then abstract screening was carried out. 34 journals with appropriate abstract were obtained, then full text screening was carried out, so that 15 journals were obtained for review.

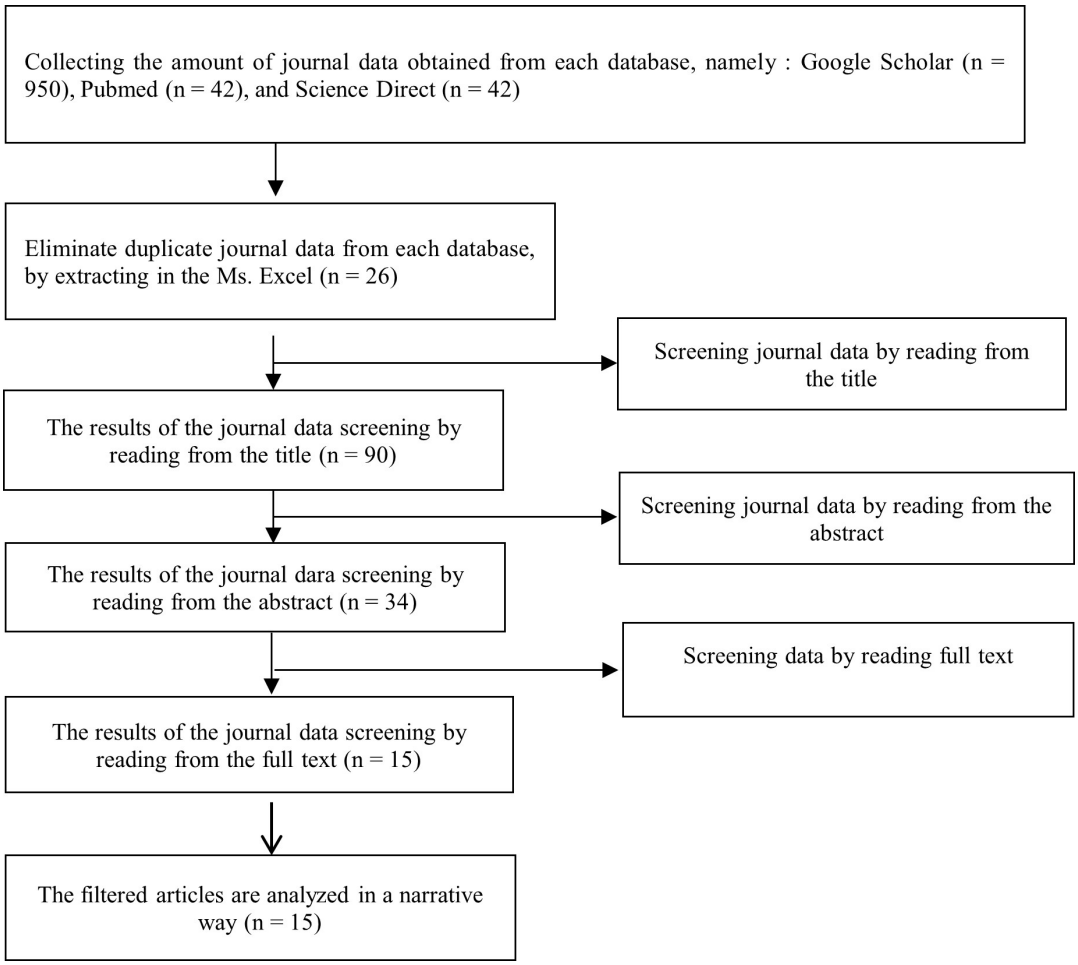

Figure 1. Flow Chart PRISMA

p-ISSN: 2477-3328
e-ISSN: 2615-1588

Table 1. General Characteristic of the Article

Research (Year)	Title	Research Sites	Research Methods	Inclusion Criteria	Result
(Adabara et al., 2012)	The Prevalence and Antibiotic Susceptibility Pattern of *Salmonella typhi* among Patients Attending a Military Hospital in Minna, Nigeria	Minna, Nigeria	*Cross Sectional*	1. There are 100 patients diagnosed with typhoid fever 2. 1-50 years old 3. All Cantontment residents consisting of military personnel and civilians with the same source of drinking water	A total of 60 samples were positive for the growth of *Salmonella typhi* bacteria. The diameter of inhibition zone for chloramphenicol was 17,3 mm, which indicated that the bacteria were sensitive to chloramphenicol. While the diameter of inhibition zone on ceftriaxone is 5,4 mm, which means the bacteria are resistant to ceftriaxone.
(Admassu et al., 2019)	Prevalence and antimicrobial susceptibility pattern of Salmonella enterica serovar Typhi and Salmonella enterica serovar Paratyphi among febrile patients at Karamara Hospital, Jigjiga, eastern Ethiopia	Karamara, East Ethiopia Hospital	*Cross Sectional*	1. Patiens with fever > 39 °C 2. The patient has received therapy for at least 2 weeks	Total samples of *Salmonella typhi* were 14. Nine of them were sensitive to ceftriaxone by 64,3%, while *Salmonella typhi* was sensitivie to chloramphenicol by 0%.
(Ahmad et al., 2021)	Pattern of Antibiotic Resistance in *Salmonella typhi* Isolates With Special Consideration to Extended Drug Resistant Typhoid	Saidu Hospital	*Cross Sectional*	1. Patients who have a high fever for more than 5 days with symptoms such as vomiting, anorexia, diarrhea, abdominal pain, dizzines, hepatomegaly, splenomegaly	*Salmonella typhi* has high resistance to third generation cephalosporin antibiotics and azitromycin. The sensitivity level of S. typhi to ceftriaxone was 8,14% with a resistance of 91,86%. Meanwhile, chloramphenicol has a sensitivity of 16,28% with a resistance of 83,72%.
(Ali Shah et al., 2020)	Antimicrobial Sensitivity Pattern of Salmonella Typhi: Emergence of Resistant Strains	Pakistan	*Cross Sectional*	1. 81 patients with positive culture results for *Salmonella typhi* 2. 12-91 years old	The sensitivity and resistance level of *Salmonella typhi* to ceftriaxone was 49,4%, while the sensitivity to chloramphenicol was 26%, with resistance 74%.

(Awol et al., 2021)	Prevalence of Salmonella enterica serovar Typhi infection, its associated factors and antimicrobial susceptibility patterns among febrile patients at Adare general hospital, Hawassa, southern Ethiopia	South Ethiopia	*Cross Sectional*	1. Fever 37°C 2. Patients over 15 years old 3. Typhoid fever has been diagnosed by Widal test 4. Willing to be a research respondent	The total respondents who were diagnosed with typhoid fever were 422 people. After treatment, *Salmonella typhi* had 100% sensitivity to ceftriaxone, while sensitivity to chloramphenicol was 80% with 20% resistance.
(Choudhary et al., 2013)(Choudhary et al., 2013)	Antimicrobial susceptibility of Salmonella enterica serovars in a tertiary care hospital in Southern India	Apollo, South India Hospital	Studi Kohort	*Salmonella typhi* isolates from blood cultures from South India	322 *Salmonella typhi* isolates were used. It was found that the sensitivity level of *Salmonella typhi* bacteria to ceftriaxone and chloramphenicol was both 100%.
(Hammad et al., 2011)	Ceftriaxone versus Chloramphenicol for Treatment of Acute Typhoid Fever	Cairo, Egypt	Prospective Study	Patients diagnosed with typhoid fever are characterized by positive culture for *Salmonella typhi* and are willing to be respondents	There was no *Salmonella typhi* resistance to ceftriaxone, while 8% of *Salmonella typhi* isolates were resistant to chloramphenicol.
(Makkar et al., 2018)	Epidemiological Profile and Antimicrobial Resistance Pattern of Enteric Fever in a Tertiary Care Hospital of North India - a Seven Year Ambispective Study	North India	Ambispective Study	The sample in this study used patients aged 5-46 years who were diagnosed with typhoid fever after isolation of *Salmonella typhi* bacteria by blood culture	A total of 623 isolates of *Salmonella typhi* were used in this study. These bacteria have a sensitivity level of 96,14% to ceftriaxone. While the sensitivity to chloramphenicol is 86,19%.
(MEMON et al., 2020)	Frequency and Antimicrobial Resistance Pattern of Extensive-Drug Resistance *Salmonella typhi* Isolates	Kharadar, Pakistan Hospital	*Cross Sectional*	Patients from the cities of Layari and Saddar who were diagnosed with typhoid fever after blood culture	A total of 969 cases of typhoid fever were identified by isolation of *Salmonella typhi* from blood cultures. It was found that 27,7% of *Salmonella typhi* isolates were sensitive to ceftriaxone, while the sensitivity to chloramphenicol was 17,4%.

p-ISSN: 2477-3328
e-ISSN: 2615-1588

(Mohammad Ali Rashed et al., 2021)	Sensitivity Patterns of Isolated Salmonella Typhi in Children with Typhoid Fever	Dhaka, Bangladesh	*Cross Sectional*	1. Patients diagnosed with typhoid fever and admitted to Dhaka Hospital during the study 2. Patients aged children with male and female sex.	Patients used in this study were 100 children aged 1-10 years. The results showed that *Salmonella typhi* had a high sensitivity of 100% to ceftriaxone, while it had a sensitivity of 75% to chloramphenicol.
(Niroula et al., 2020)	Antibiotic Susceptibility Pattern of Salmonella Enterica serovars Typhi and Paratyphi A Isolated From Patients Suspected of Enteric Fever	Kathmandu, Nepal	*Cross Sectional*	This study used a sample of patients aged 10-70 years who were treated at Bir Hospital, Nepal. Each patient took about 5-10 ml of blood for blood culture. Samples were incubated at 37 C for 48 hours.	There were 27 *Salmonella typhi* isolates used, of which 90% of *Salmonella typhi* isolates were sensitive to chloramphenicol. While treatment using ceftriaxone cases of resistance occur sporadically.
(Patil & Mule, 2019)	Sensitivity pattern of salmonella typhi and paratyphi a isolates to chloramphenicol and other anti-typhoid drugs: An in vitro study	Mumbai, India	Prospective Study	Patients with positive culture results for *Salmonella typhi* originating from North, South, Est, and West India	*Salmonella typhi* had 100% sensitivity to ceftriaxone, while 94,4% of these bacteria were sensitive to chloramphenicol.
(Sattar et al., 2020)	Current trends in antimicrobial suspectibility pattern of *Salmonella typhi* and *paratyphi*	Pakistan	Observasional Laboratorium	*Salmonella typhi* and *Salmonella paratyphi* bacteria isolated from blood cultures.	The sample of *Salmonella typhi* used was 44. The percentage level of sensitivity of these bacteria to chloramphenicol was 68%, while to ceftriaxone was 79,5%.
(Tarana et al., 2019)	Antimicrobial susceptibility pattern for Salmonella Typhi isolated from blood in Shaheed Suhrawardy Medical College, Dhaka	Microbiology Laboratory of Faculty of Medicine Shaheed Suhrawardy	Retrospective Study	1. Patients aged 15-30 years 2. Frequent outdoor activities 3. Blood culture was found positive for *S. typhi*	The isolates of *Salmonella typhi* used were 30. The bacteria were sensitive to ceftriaxone by 66,66%, while the sensitivity level to chloramphenicol was 40%.
(Umair & Siddiqui, 2020)	Antibiotic Susceptibility Patterns of Salmonella Typhi and Salmonella Paratyphi in a Tertiary Care Hospital in Islamabad	Islamabad, Pakistan	Cross Sectional	Patients aged 12 years and over with positive culture results for *Salmonella typhi* in 2012-2018.	A total of 158 *Salmonella typhi* isolates were found to have S. typhi bacteria that were resistant to ceftriaxone by 4,4% and resistance to chloramphenicol by 46,9%.

p-ISSN: 2477-3328
e-ISSN: 2615-1588

The results of the journal analysis obtained 15 journals that met the inclusion criteria. All of these journals discuss the suspectibility of *Salmonella typhi* to various antimicrobials in several countries. *Salmonella typhi* is a gram-negative rod-shaped bacterium that does not form spores, and has a capsule. These bacteria measure 1-3.5 m x 0.5-0.8 m. *Salmonella typhi* has a cell wall consisting of murein, lipoprotein, phospholipid, protein, and lipopolysaccharide (LPS) and is arranged in layers. The length varies, and most have peritrichous flagella so that they are motile. *Salmonella typhi* forms acid and gas from glucose and mannose. This organism also produces H2S gas but only a little. Ceftriaxone is a third-generation cephalosporin beta-lactam antibiotic with a broad spectrum of action and includes many gram-positive and gram-negative bacteria (Hammad *et al.*, 2011). This antibiotic works by inhibiting the synthesis of mucopeptides required for the formation of bacterial cell walls, namely by inhibiting the third stage of the transpeptidase reaction in a series of cell wall formation reactions (Katzung et al., 2012). Ceftriaxone has high stability against beta-lactamases, both against penicillins and cephalosporins produced by gram-negative and gram-positive bacteria. Ceftriaxone works by interacting with the bacterial cell wall. This impairs the permeability of the bacterial cell wall and promotes the diffusion of antibacterial compounds within the bacterial cells. When diffusion occurs, the bacterial growth process is interrupted, resulting in inhibition of bacterial growth (bacteriostatic). In addition, antibacterial compounds can penetrate cell membranes and interact with bacterial genetics to mutate bacteria. This creates a suppression zone on the disk using the Kirby-Bauer diffusion process. The mechanism by which Salmonella typhi is resistant to ceftriaxone is to degrade beta-lactams from ceftriaxone to produce beta-lactamase enzymes that can eliminate their antibacterial effects. Chloramphenicol is a broad-spectrum antibiotic that is bacteriostatic and active against both aerobic and anaerobic Gram-positive and Gram-negative bacteria (Ali Shah et al., 2020). This medicine is soluble in alcohol, but not in water.

Chloramphenicol succinate used for parenteral administration is easily soluble in water. The drug is hydrolyzed in vivo by the release of chloramphenicol. Chloramphenicol works by inhibiting the enzyme peptidyltransferase. Peptidyl transferase acts as a catalyst for the formation of peptide bonds in the bacterial protein synthesis process. Chloramphenicol is also bacteriostatic or suppresses bacterial growth. Therefore, the suppression zone is perceived as a clear area around the area containing the antibacterial substance. The diameter of the zone that inhibits bacterial growth indicates the susceptibility of the bacterium to antibacterial substances. In addition, the suppression zones formed by bacteria should be more sensitive with larger diameters. Salmonella resistance of typhoid fever to chloramphenicol is the target of antibiotics / ribosomes, the production of inactivating agents in the form of the enzyme chloramphenicol acetyltransferase, and antibiotics from the outer membrane and antibiotics from the cytoplasm. It can be caused by a mechanism that limits the continued intrusion of. Low levels of resistance to chloramphenicol arise from a large population of chloramphenicol-sensitive bacteria by selecting mutants with low permeability of this drug.Top of Form (Katzung et al., 2012).

In a study conducted by Choudary et al. (2013) the results showed that ceftriaxone and chloramphenicol had the same 100% sensitivity, but in other studies, different results were found. Research that states ceftriaxone is more sensitive than chloramphenicol was carried out by Sattar et al., (2020) , Awol et al., (2021)especially in developing countries like Ethiopia. But there is a little information about prevalence and factors association with S.typhi and its antimicrobial susceptibility pattern in Ethiopia especially in the study area. The aim of this study was to determine the prevalence of S.typhi infection, its associated factors and antimicrobial susceptibility pattern among patient with a febrile illness at Adare General Hospital, Hawassa, Southern Ethiopia. Methods: Hospital based cross sectional study was conducted among 422 febrile patients from May 23, 2018 to October 20, 2018. A 5 ml venous blood was collected from each febrile patient. Culture and biochemical test were performed for each isolate. Antimicrobial susceptibility testing was performed for each isolate using modified Kirby-Bauer disk diffusion techniques. Result: In this study, the prevalence of S.typhi among febrile illness patients at Adare General Hospital was 1.6% [95% confidence interval (CI , Ali Shah et

al., (2020) , Makkar et al., (2018) , Tarana et al., (2019) , Admassu et al., (2019), MEMON et al., (2020), Umair & Siddiqui, (2020), Hammad et al., (2011), Patil & Mule, (2019), Mohammad Ali Rashed et al., (2021) with an average sensitivity level of 49-100%. According by Sattar et al, (2020) which found that the sensitivity level to ceftriaxone was 79.5%. Meanwhile, the sensitivity level of *Salmonella typhi* to chloramphenicol is 68%. In addition, researchers Awol et al, (2021) also found that the highest level of sensitivity was to ceftriaxone, which was 100%, while the sensitivity to chloramphenicol was 80%. Similar results were also obtained by researcher Ali Shah et al, (2020), where ceftriaxone had a greater sensitivity of 49.4%, while chloramphenicol had a sensitivity of 26%. Researcher Makkar et al, (2018) also stated that ceftriaxone has a higher sensitivity of 96.14% compared to chloramphenicol with a sensitivity level of 86.19% (Makkar et al., 2018).

There is also a study on antimicrobial susceptibility conducted by Tarana et al, 2019 where the results are that *Salmonella typhi* is more sensitive to ceftriaxone by 66.66%, while sensitivity to chloramphenicol is 40% (Tarana et al., 2019). In line with research conducted by Admassu et al, 2019 which stated the sensitivity level of *Salmonella typhi* to ceftriaxone was 64.3%, while that to chloramphenicol was 0% (Admassu et al., 2019). Researchers Patil and Mule, 2019 conducted a study on antimicrobial sensitivity in four zones in India, namely East, West, South, and North India. The results obtained in the four zones are that the sensitivity level to ceftriaxone is 100%. Meanwhile, the sensitivity to chloramphenicol is in the range of 89-95%. In a study conducted by Umair et al, (2020) recommended third generation cephalosporins to be used as empirical therapy and for the treatment of MDR cases of enteric fever. The results of a study conducted by Umair *et al*, (2020) showed a higher level of sensitivity to ceftriaxone than chloramphenicol (Umair & Siddiqui, 2020). In a study conducted by Hammad *et al*, (2011) it was found that there was no resistance to ceftriaxone, while resistance to chloramphenicol was 8% (Hammad *et al*., 2011). The study conducted by Memon et al, 2020 used a sample of 969 people diagnosed with typhoid fever. A total of 777 of them were resistant to first-line antibiotics such as ampicillin, chloramphenicol, and cotrimoxazole. A total of 517 people were resistant to second-line antibiotics, namely ciprofloxacin and ceftriaxone. In this study, it was concluded that ceftriaxone had a higher sensitivity than chloramphenicol (MEMON *et al*., 2020).

Another study which stated that chloramphenicol was more sensitive than ceftriaxone was conducted by (Adabara et al., 2012), (Ahmad et al., 2021), and (Niroula et al., 2020) with an average sensitivity level of 16-96%. Research conducted by Adabara et al, (2012) used the measurement of the inhibition zone to determine the sensitivity of Salmonella to antimicrobials. The results showed that chloramphenicol had the largest inhibition zone diameter of 17,3 mm, while the diameter of the inhibition zone in ceftriaxone was 5,4 mm (Adabara et al., 2012). Researcher Mohammad Ali Rashed *et al*, (2021) conducted a study on the sensitivity pattern of *Salmonella typhi* in children with typhoid fever. The samples used were pediatric patients who had been diagnosed with typhoid fever and treated at the hospital. The results showed that ceftriaxone had the highest sensitivity of 100%, while the sensitivity of chloramphenicol was 75%. The risk factor for typhoid fever is dominated by boys because boys are more independent and have more opportunities to be exposed to street food. Many studies show a higher prevalence in low socioeconomic status. In addition, other factors are the lack of availability of clean water, and exposure to contaminated food is increasingly rampant (Mohammad Ali Rashed et al., 2021). Typhoid fever therapy can use antibiotics, with rational use and not excessive. Research conducted by Niroula et al, (2020) stated that antibiotics such as amoxicillin, cotrimoxazole, and chloramphenicol have been used previously as first line drugs to fight Salmonella infections. However, recently there is resistance to first line drugs. Since 1940, chloramphenicol has been used as the gold standard in the treatment of enteric fever, but due to the emergence of resistance, this drug is no longer the drug of choice for the treatment of enteric fever (Niroula et al., 2020). Research conducted by Ahmad et al, 2021 also obtained the same results as Niroula et al, 2020 where *Salmonella typhi* was more sensitive to chloramphenicol with a percentage of 16.28%, than ceftriaxone with a percentage of 8.14% (Ahmad *et al*., 2021).

In a recent study, a scientist has identified the genetic basis of an XDR-resistant strain of

p-ISSN: 2477-3328
e-ISSN: 2615-1588

typhoid fever that emerged in Pakistan. They sequenced the genome of the *Salmonella typhi* XDR strain isolated from the outbreak area. They sequenced the genome of the *Salmonella typhi* XDR strain isolated from the outbreak area. Genome sequencing revealed that all containing the H58 gene confer resistance to chloramphenicol, ampicillin, and trimetropin. Further analysis showed that they hardbored a plasmid (IncY) carrying the blaCTX-M15 that mediates resistance to ceftriaxone and fluoroquinolones (MEMON *et al.*, 2020).

From various results in 15 reviewed journals, the most obtained results were that *Salmonella typhi* was more sensitive to ceftriaxone than chloramphenicol. The occurrence of sensitivity to ceftriaxone is caused by a decrease in fever in a short time. This is in line with the mechanism of ceftriaxone which can inhibit bacterial cell wall synthesis, causing bacterial cell death and a rapid decrease in fever. Meanwhile, chloramphenicol experienced resistance due to genome sequencing which revealed that all containing the H58 gene provided resistance to chloramphenicol. In addition, increased resistance to chloramphenicol is also caused by mobile genetic unit (including plasmids, gene cassettes in integrins and transporons), inadequate access to effective drugs, and brief antimicrobial therapy (Awol et al., 2021)especially in developing countries like Ethiopia. But there is a little information about prevalence and factors association with S.typhi and its antimicrobial susceptibility pattern in Ethiopia especially in the study area. The aim of this study was to determine the prevalence of S.typhi infection, its associated factors and antimicrobial susceptibility pattern among patient with a febrile illness at Adare General Hospital, Hawassa, Southern Ethiopia. Methods: Hospital based cross sectional study was conducted among 422 febrile patients from May 23, 2018 to October 20, 2018. A 5 ml venous blood was collected from each febrile patient. Culture and biochemical test were performed for each isolate. Antimicrobial susceptibility testing was performed for each isolate using modified Kirby-Bauer disk diffusion techniques. Result: In this study, the prevalence of S.typhi among febrile illness patients at Adare General Hospital was 1.6% [95% confidence interval (CI.

CONCLUSION

Salmonella typhi bacteria are more sensitive to ceftriaxone than chloramphenicol. Ceftriaxone is said to be more sensitive because of its shorter time in reducing fever. Meanwhile, chloramphenicol resistance occurs due to the presence of the H58 gene, mobile genetic units, inadequate access to effective drugs, and short antimicrobial therapy.

ACKNOWLEDGEMENT

The author would like to thank the people who supported and encouraged the author in this study.

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