

The Burden and Antibiotic Sensitivity of Salmonella Non-Typhi and Shigella Related Bloody Diarrhea in Children in the South Al Batinah Region, Oman

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Abstract

Objectives: To report the frequency of encounter of Salmonella non-typhi (SNT) and Shigella-related diarrhea and the antibiotic sensitivity in children as seen in ArRsutaq General Hospital (AGH) from June 1, 2019, to June 31, 2023.

Methods: A retrospective study describing demographic characteristics, symptoms, blood investigations, and stool bacterial culture with antimicrobial sensitivities of children with bloody diarrhea. Stools were tested only for Salmonella and Shigella growth.

Results: Out of 1160 children with diarrhea, 153 (13.2%) had bloody diarrhea and 129 children out of the 153 (83%) were under 5 years. Ninety-two children (60.1%) were positive for either Salmonella or Shigella. Among the positive cultures, 58 children (63.0%) had SNT, while 34 (37.0%) had Shigella infection. Three children had bacteremia, all under 1 year. SNT demonstrated high sensitivity primarily to ceftriaxone (n=71,70.7%), ampicillin (n=53,91.4%) and ciprofloxacin (n=54,93.1%). In contrast Shigella showed high resistance to ceftriaxone and only 15 patients (46%) showing sensitivity. Additionally, 10 children had Entamoeba histolytica trophozoites co-infection with Salmonella on stool microscopy.

Conclusions: Salmonella is more prevalent than Shigella in children under the age of 5 years, while Shigella is more common in children older than 5 years. Salmonella is quite sensitive to both ceftriaxone and ampicillin. Shigella demonstrates resistance to multiple antibiotics, including ciprofloxacin. It is recommended that children under the age of 1 year be admitted and treated empirically with either ceftriaxone or ampicillin. In older children, antibiotic therapy should be guided by stool culture results. Ciprofloxacin is not a good empirical choice for Shigella in our population due to high resistance and is contraindicated in G6PD patients.

Keywords: Salmonella; Shigella; bloody diarrhea; children; bacterial sensitivity; secondary Hospital; Oman.

Introduction

Diarrheal diseases in children under the age of 5 years are the second most common cause of death, accounting for 525,000 deaths annually.¹ Globally, the incidence of bacterial origins of diarrhea has been documented with varying degrees of occurrence. As an illustration, in South Asian nations, the occurrence has been estimated to be approximately 10%, whereas in Jordan, it reaches as high as 24% among children.^{2,3}

In a multicentered study, *Shigella* was found to be the most common organism in bloody diarrhea in children under the age of 5 years in Sub-Saharan Africa and South Asian Countries.⁴ In Oman, the reported prevalence of acute bloody diarrheal illness in a single study from Al Dhahira was 9.1% with no mortalities.⁵ In the year 2022, a total of 65,391 diarrheal cases were reported in Oman, with an increase of 35 episodes per 1000 children under 5 years of age compared to the year 2021. No mortalities were reported.⁶

Acute febrile bloody diarrhea can be caused by multiple pathogens. *Shigella* is the second most common cause of diarrhea mortality and morbidity, accounting for 60,000 thousand deaths in children under the age of 5 years annually.⁷ A recent study in Africa and Asia showed the most common organisms for acute diarrhea were rotavirus, *Cryptosporidium*, enterotoxigenic *Escherichia coli* (*E.coli*), and *Shigella*.⁸ In a regional study from Al Dammam, Saudi Arabia, the commonest organism of diarrhea in children under 5 years was rotavirus followed by *Salmonella*, *Shigella*, *Campylobacter jejuni*, enteropathogenic *E.coli*, and finally non-agglutinating vibrios.⁹

The detection of the diarrhea-causing organism employs various methods. Polymerase Chain Reaction (PCR) is primarily utilized for viruses and specific bacteria. Microscopy serves as a valuable tool for identifying parasites. Meanwhile, stool culture stands as the gold standard for enterobacteria detection, encompassing organisms like *Shigella*.¹⁰

Stool culture, although being the gold standard for bacterial identification and determination of antimicrobial sensitivity, has low sensitivity and poses many technical difficulties.¹¹

Recognizing bacterial causes, especially *Shigella*, holds significance in averting mortality and minimizing morbidity, as emphasized by the World Health Organization (WHO).¹² Data suggest that there is increased mortality in children given antibiotics for bloody or non-bloody diarrhea, and hence the use of antibiotics was proposed to be limited to patients with other comorbidities or are children younger than 3 months.¹³

The South Al Batinah region of Oman, one of 11 regions of Oman has about 476,008 inhabitants, mainly of low- and middle-income people.¹⁴ While bacterial diarrhea is known to occur in low income areas around the world there are no data on the prevalence or etiology of bloody diarrhea in South Al Batinah region.¹⁵

The study aimed to record the occurrence rate and clinical characteristics of children experiencing acute bloody diarrhea associated with *Salmonella* and *Shigella* at ArRustaq Regional Hospital (ARH). Additionally, it sought to outline the antimicrobial sensitivity profile of the stool isolates.

Methods

This is a retrospective study on all children under the age of 13 years seen at ARH with bloody diarrhea from June 1, 2019, to June 31, 2023. All children who presented with acute fever and bloody diarrhea seen or admitted in ARH were included in the study. Children older than 13 years, known to have other etiological causes of diarrhea, and those who did not fit the definition of acute bloody diarrhea were excluded from the study. The data were retrieved from the Al Shifa electronic database. Demographic data (name, age, sex, nationality, and residence), clinical symptoms (fever, vomiting, abdominal pain, mucus stool, and dehydration status), and laboratory details (CRP, hemoglobin, leukocytosis, stool RBC, stool WBC, stool culture, and blood culture) were collected. The degree of dehydration was categorized into mild, moderate, or severe. Mild dehydration was defined as when the child had only thirst but normal moist mucous membranes, normal pulse, normal capillary refill with good urine output. Moderate dehydration was defined as when the child had 2 of the following signs: restlessness and irritability, reduced tears, deep-set eyes, thirst, and slow return of skin pinch. Severe dehydration was defined as when the child had 2 of the following signs: lethargy or unconsciousness, sunken eyes, inability to drink or drinking poorly, and very slow return of skin pinch.¹⁶

Stool samples were collected in a wide-necked sterile container for bacterial culture and microscopy for parasites before commencing antibiotic treatment. MacConkey agar was used in the lab to identify *Salmonella*–*Shigella* agar (SSA) and thiosulfate citrate bile sucrose (TCBS) agar. After overnight incubation at 37 °C, the plates were observed for *Salmonella* and *Shigella* colonies. For stool bacterial sensitivity, the following antibiotics were tested using the disc diffusion method: ampicillin, ceftriaxone, chloramphenicol, and ciprofloxacin. At times, not all antibiotic discs

were available for testing. Only *Salmonella* and *Shigella* were cultured in ARH due to their management impact in the case of *Salmonella typhi* and the need for treatment for *Shigella*. Other bacterial causes like *E. coli* and *Campylobacter* are self-limited diseases that require only supportive care.

The data were analyzed using SPSS, version 20. Numeric values underwent a normality test prior to analysis. Results were expressed as mean with standard deviation (SD) or median with interquartile range. Statistical associations were calculated using the Student's t-test for continuous data and the chi-square test for categorical data. A P-value < 0.05 was considered significant for statistical significance.

Ethical approval was obtained from the Research Centre in South Al Batinah with the number 01062023.

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Results

A total of 1160 child were admitted with gastroenteritis at ARH from June 1, 2019, to June 31, 2023. Out of the total number of acute gastroenteritis patients, 154 (13.2%) presented with acute bloody diarrhea. One child had missing data. Among these patients, 151 (98.7%) were Omani, with a male-to-female ratio of 1.3:1. Table 1 demonstrates the demographic data of the population. Most of the patients came from the ArRustaq area, followed by Al Musanah, which is approximately 35 kilometers away.

Table 1: Demographic data of the study group.

Variable	Frequency	Percent
Sex		
Male	87	56.9
Female	66	43.1
Citizenship		
Omani	151	98.7
Non-Omani	2	13.0
Age		
Median Age	2	IQR=1-5
≤ 5 years	128	83.7
≤ 1 year	52	33.0
>5 years	25	16.3
Median Weight (Kg)	13	IQR=10.0-18.0
Residence		
ArRustaq	65	42.5
Al Musanah	34	22.2
Barka	21	13.7
As-Suwaiq	12	7.8
Al-Awabi	10	6.5
Nakhal	8	5.2

Wadi Al Muawil	3	2.0
Al-Awabi	10	0.1
Nakhal	8	0.1
Wadi Al Muawil	3	0.0

The most frequent complaint of the children was watery stools, followed by fever. Table 2 demonstrates the clinical signs, symptoms, and basic blood labs of the patients.

Table 2: Clinical characteristics of patients with bloody diarrhea.

Symptoms	Frequency	Percent
Watery stools	136	88.9
Fever	122	79.7
Vomiting	98	64.1
Mucoid stools	54	35.3
Bloody stools	50	32.7
Abdominal pain	30	19.6
Degree of Dehydration	Frequency	Percentage
No dehydration	59	38.6
Mild Dehydration	57	37.3
Moderate Dehydration	21	13.7
Severe Dehydration	16	10.5
Type of Dehydration	Frequency	Percentage
Eunatremia	140	91.5
Hypernatremia	2	1.3
Hyponatremia	7	4.6
Basic Blood Results	Value	IQR
Median Hemoglobin gm/dl	13.0	IQR=11.4-12.3
Median C-reactive protein	45.5	IQR=20.0-126.0
White Blood Cell X10 ⁹ /ml	9.5	IQR=6.6-13.0
Median Stool white blood cells/HPF	5.5	IQR=3.0-20.0

HPF: High power field.

Table 3: Antibiotic sensitivity of isolated *Salmonella* and *Shigella*.

	Salmonella (n=58)	ceftriaxone	%	Ampi	%	Cipro	%	TMP	%
Number of patients tested									
Sensitive out of the tested	41.0	70.7	53.0	91.4	54.0	93.1	54.0	93.1	
Not sensitive out of the tested	38.0	92.7	43.0	81.1	43.0	79.6	50.0	92.6	
Shigella (n=) 34	3.0	7.3	10.0	18.9	11.0	20.4	4.0	7.4	
Number of patients tested									
Sensitive out of the tested	31.0	91.2	31.0	47.4	32.0	94.1	29.0	50.7	
Not sensitive out of the tested	4.0	12.9	5.0	16.1	15.0	46.9	5.0	17.2	

Cipro: Ciprofloxacin; Ampi: Ampicillin; TMP: Trimethoprim.

Table 4: Frequency and type of antibiotics used in children with bloody diarrhea upon presentation.

Antibiotics Prescribed	Frequency	Percentage
Both ceftriaxone and metronidazole	43	28.1
No antibiotics	39	25.5
Ceftriaxone or cefotaxime	29	19
Metronidazole alone	28	18.3
Amoxy-clavulanic acid	8	5.2
Missing	6	3.9
Total	147	96.1

Out of the 153 children, 92 (60.1%) had stool culture positive, while 61 (39.9%) had stool culture negative for either *Salmonella* or Shigella. Children with positive stool culture, 58 children (63.0%) had *Salmonella* non-typhi (SNT), while 34 (37.0%) had Shigella infection. No further identification of the type of *Salmonella* or Shigella was required for clinical management purposes.

On a sub-analysis of the population age-wise, in children younger than 1 year with bloody diarrhea, 41 children (78.8%) had fever and only 35 (67.3%) had stool culture positive for bacteria. Thirty-two children (61.5%) had *Salmonella* growth, and 3 children (5.8%) had Shigella growth in the stool. No significant statistical association was noted between fever and stool bacterial growth ($P=0.676$) in children under the age of 1 year.

Only 39 patients (25.5%) were not given antibiotics while the rest of the patients did receive antibiotics.

Bacteremia with blood culture positive for the same organism as isolated from the stool was evident in only 3 children. All of these children were under the age of 1 year (10 months, 7 months and 8 months), and all had *Salmonella* growth. The *Salmonella* causing bacteremia was sensitive to ceftriaxone, ampicillin, and trimethoprim. All children under the age of 1 year had a normal leukocyte count. None of the children had further complications from *Salmonella* bacteremia, and none of them had sickle cell disease.

For children under the age of 5 years altogether, 55 children (43%) had *Salmonella* isolated, and 26 (20.3%) had Shigella isolated. Forty-six children (35.9%) had no growth in stool cultures. In contrast, among children older than 5 years, only 3 (8.3%) had *Salmonella*, and 8 children (32%) had Shigella.

Regarding antibiotic sensitivity, some patients were not tested for the whole panel of antibiotics sensitivity based on test availability. However, the lowest number of patients tested for antibiotic sensitivity was for ceftriaxone, which was 41 patients (70.7%). For the rest of the patients, more than 90% of the isolates were tested for the whole panel of antibiotics, except for trimethoprim for Shigella, where 58 children (85%) were tested.

Thirty-eight of the children (92.7%) with *Salmonella* were sensitive to ceftriaxone, and 43 (79.6%) were sensitive to ciprofloxacin. The 3 (7.3%) patients with *Salmonella* resistant to ceftriaxone were all sensitive to ciprofloxacin.

Regarding Shigella, out of the 31 children tested only 4 (12.9%) patients were sensitive to ceftriaxone. Regarding ciprofloxacin, out of the 32 children tested only 15 (46.9%) were sensitive while 17 (53.1%) resistant to ciprofloxacin. Additionally, none of the 17 patients with Shigella resistant to ciprofloxacin were sensitive to ceftriaxone.

Overall, 111 patients (72.5%) received empirical antibiotics, while 39 (25.5%) did not receive antibiotics. The most common prescription pattern was the combined use of ceftriaxone and metronidazole ($n=43$, 28.1%), followed by ceftriaxone or cefotaxime alone. Table 5 demonstrates the pattern of empirical antibiotics used for the patients.

Table 5: Detection of Parasites on Stool Microscopy in Children with Bloody Diarrhea.

Parasites	Frequency	Percentage
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E. Histolytica cyst	63	41.2
E. Histolytica trophozoite	29	19.0
Giardia lamblia	2	1.4
Hymenolepis nana	1	0.7
Taenia species	1	0.7
Nil	56	36.6
Missing	1	0.4
Total	153	100

Using Analysis of Variance (ANOVA), no association was detected with fever, abdominal pain, leukocytosis, C-reactive protein (CRP) and stool culture positivity for *Shigella* or *Salmonella*. However there was an associations noted between stool leukocyte count and stool culture positivity ($P=0.026$)

In addition to bacterial growth, the study also showed that 10 children had a coinfection of *Salmonella* and Entamoeba histolytica (E.histolytica) trophozoites, while 4 children had *Shigella* and amoebic trophozoites. Table 5 demonstrates the isolated parasites as detected on stool microscopy.

Regarding the seasonal variation of the incidence of bloody diarrhea, the months from January to July had most of the recorded cases, while there was a sharp decline immediately after July until the end of December. This phenomenon was consistent over the years of the study. Figure 1 demonstrates the frequency of encounters over the year.

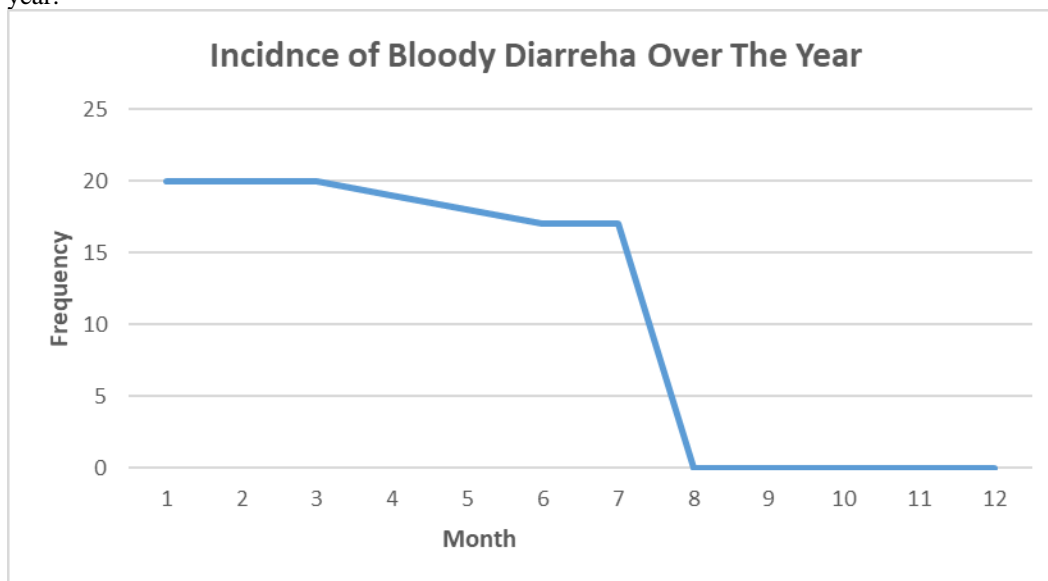


Figure 1: The frequency of encounter of bloody diarrhea in ArRustq General Hospital during the year.

Discussion

This study reports a prevalence of 13% for bloody diarrhea among children admitted to a regional area with low resources and acute diarrhea. While *Shigella* has been reported as the most common bacterial pathogen in multiple studies,²⁻⁴ in our study, *Salmonella* was the most common (60%) among the whole group and particularly in children younger than 5 years, mainly with *Salmonella*. Our findings are similar to a study from Brazil on 260 children, which showed that *Shigella* occurred mostly in children older than 5 years, while *Salmonella* was more common in younger children.¹⁷

The use of antibiotics is recommended mainly for *Shigella* as it leads to improvement of symptoms within 48 hours and prevents the prolongation of disease over many weeks.¹⁸ On the other hand, treatment of *Salmonella* non-typhoidal (SNT) is mainly supportive except for infants younger than 6 months or immunocompromised patients.¹⁹ Unlike *Shigella*, *Salmonella* is also a self-limiting disease.²⁰

Regarding antibiotic sensitivity, our study demonstrated that 92% of the *Salmonella* isolates were sensitive to ceftriaxone, and nearly 80% were sensitive to both ampicillin and ciprofloxacin. The low resistance to ceftriaxone is similar to the prevalence reported in the Eastern Mediterranean (EM) study, where resistance was only about 10%.²¹ Our study was also in line with the reported resistance to ciprofloxacin for *Shigella* in the South-East Asian Region, which rose from 4% to 76% in 2008, close to our *Shigella* resistance to ciprofloxacin of 53%.²¹

Antibiotic use in cases of *Salmonella*-related diarrhea is not routinely recommended. *Salmonella* enterocolitis is a self-limited disease.²² Moreover, antibiotic use in *Salmonella* infection might trigger hemolytic uremic syndrome and possibly prolong the duration of illness.^{23,24} In our setup, as *Salmonella* was the most common pathogen in children under the age of 1 year and few children had bacteremia, it is reasonable to start children under the age of 1 year with either ampicillin or ceftriaxone until stool culture results are available.

In contrast, the situation is reversed with *Shigella*, where about 80% of the isolates are resistant to ceftriaxone and ampicillin, and more than 50% are resistant to ciprofloxacin. Hence, it is not effective to use any of these medications for *Shigella* enterocolitis. WHO recommends ciprofloxacin as an oral medication for ambulatory care for bloody diarrhea in children related to *Shigella* mainly.¹² However, glucose 6-phosphate dehydrogenase deficiency (G6PD) represents an extra obstacle to tackle in our population, as G6PD deficiency reaches 26% of the general population.²⁵ Therefore, in children with G6PD deficiency or of unknown status, macrolides like clarithromycin might be a more appropriate option.²⁶ This however needs to be tested in our population.

The children who were stool culture negative (n=60, 39.2%), even though they had fever and bloody diarrhea, are likely to have another pathogen that was not tested, mainly *E. coli* and *Campylobacter*, which were not tested. Acute bloody diarrhea is not commonly attributed to amoebic diarrhea. Amoebic colitis is usually an insidious process and does not present with acute febrile diarrhea. Moreover, it is important to note that *Entamoeba histolytica* can be easily confused with the normal gut flora of *Entamoeba dispar* and the low-virulence *Entamoeba moshkovskii*.^{27,28}

It is interesting that 75% of the population received antibiotics regardless of age or clinical condition of the child. Moreover, nearly 50% of the patients received metronidazole in combination with cephalosporin or in isolation. The use of metronidazole is not indicated in acute febrile diarrhea. The over use of antibiotics in general and using inappropriate antibiotics or bloody diarrhea raise concerns on the medial awareness amongst physicians in the institution.

Of interest is the seasonal distribution of bloody diarrhea as seen in ARH, as it is almost confined to the first half of the year with no reported cases during the second half. Infective diarrhea is not commonly associated with seasonal changes, and this phenomenon needs to be further studied.

The limitations of the study mainly include the absence of any data on the growth of *E. coli* or *Campylobacter* due to the unavailability of testing means in a resource-limited secondary hospital like AGH, particularly as the management is not affected by these organisms. Additionally, there was no testing done for macrolide sensitivity for either *Salmonella* or *Shigella* organisms.

Conclusion

Acute bloody diarrhea is a significant problem, as seen in AGH. Fever and mucoid loose stools are the most common symptoms associated with bacterial pathogens. SNT is more common than *Shigella* in children under the age of 5 years and is sensitive to a wide range of antibiotics. *Shigella*, on the other hand, is less common but is resistant to multiple antibiotics, including ciprofloxacin. There is a significant overuse of antibiotics in children with bloody diarrhea. The study advocates for starting antibiotics only after verification of the organism by stool culture, except

for children under the age of 1 year or those who are immunocompromised. G6PD is of concern in our population, and macrolides might be a safer option than fluoroquinolones for the treatment of Shigella.

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