



Pharmacoepidemiology of Cholera in Hodeidah, Yemen: A Randomized Clinical Trial

Entebah AL-Hammadi ^{1,2*}, Maison AL-Sakkaf ¹, Amal AL_Mutawakil ¹, Tarek John ^{1,2}, Ahmed Majam ^{1,2},
Mohammed Amod Al Kamarany ^{1,2*}

¹ Center of Tropical Medicine and Epidemiology Studies of Hodeidah University (CTMES-HU), Hodeidah, Yemen

² Center of Tropical Medicine and Infectious Diseases (CTMID), Authority of Public AL Thawara Hospital, Hodeidah, Yemen

*Corresponding author E-mail: entebahalhammadi@hoduniv.net.ye ; alkamarany2022@hoduniv.net.ye

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Abstract

Background: Early diagnosis and rapid management of dehydration are crucial for increasing positive outcomes. Most cholera cases are usually mild to moderate and easily managed with an oral re-hydration solution (ORS) and intravenous (IV) solution for severe cases.

Objectives: The study aimed to monitor the impact of national guideline on cholera outcome and side effect of medications in Hodeidah, Yemen. **Methodology:** A randomized clinical trial (RTC) design encompassed, the study included 17,821 patients diagnosed and isolated based on national cholera management guideline, ranging from 1 to 97 years old. All patients were admitted to the Cholera Treatment Center (CTC) in collaboration with Tropical Medicine and Infectious Diseases Center (CTMID), Al Thawara Public Hospital Authority in Hodeidah, Yemen. The case management of cholera included five steps: assessment of dehydration status, rehydration therapy, monitoring, antimicrobial therapy and nutrition status. 10,534 patients (59.1%) were diagnosed with mild and moderate dehydration and received oral rehydration solution (ORS) alongside standard care. In addition, 7,287 patients (40.9%) were diagnosed with severe dehydration and underwent intravenous treatments (IV) based on national guideline. Additionally, 250 patients required dialysis therapy. **Results:** The results showed that the ratio of males to females 44.6% to 55.4% (0.8:1). The primary symptom reported was acute watery diarrhea. The study highlighted the substantial impact of rehydration therapy on cholera prognosis where the case fatality rate (CFR %) was 39/17,821 (0.21 %). In addition, 250/17,821 (1.40 %) cases complicated by acute renal failure (ARF) and 1595/17,821 cases (8.95 %) had shock (hypovolemic). The incidence of pleural effusion was approximately 728/17,821 cases (4.08 %). 150 of mild cases were developed into severe illness and transferred to plan C for their management. On the other hand, 10 of severe cases (0.06 %) were developed to pleural effusion because the intravenous fluid overload as the result of therapeutic side effect. **Conclusion:** Efficient cholera control, notably via rehydration strategies, markedly decreased mortality rates (less than 1 %) and the side effects was not reported. This emphasizes the critical role of prompt intervention and customized treatment strategies in outbreak situations.

Keywords: Cholera, Pharmacoepidemiology, Outbreak, ORS, IV Solution, Hodeidah, Yemen

1. Introduction

The cholera involves significant fluid depletion and electrolyte disruptions, potentially leading to hypovolemic shock and, if untreated, fatal outcomes. [1-3]. Cholera spreads through the fecal-oral route and severity varies. Swift replenishment of fluids and electrolytes is vital for proper treatment. Infection happens when contaminated food or water with high *Vibrio cholerae* levels is consumed. Transmission occurs through two main pathways: the fecal-oral route ("person-to-feces-to-person") and direct environmental exposure, leading to infection from the environment [4]. Approximately 20% of infected individuals experience acute watery diarrhea, with 10–20% progressing to severe watery diarrhea accompanied by vomiting, resulting in severe dehydration that can be fatal if untreated. The case fatality rate (CFR %) generally remains below 5%, although in densely populated refugee camps, it can spike to as high as 50% [5]. Globally, cholera cases are often underreported. An estimated 2.9 million cases and 95,000 deaths occur each year [6]. As of October 7, 2018, the World Health Organization (WHO) has reported a total of 1,236,028 cases of cholera in Yemen since the outbreak began in April 2017 [4]. 2556 of these cases have been fatal, yielding a case fatality rate of 0.21% [4]. Children constitute 58% of reported cases [7]. In our analysis of the humanitarian response, a significant finding was the lack of oral cholera vaccine (OCV) distribution by most organizations involved in outbreak control efforts, except for the WHO and Health and Wash clusters, who were considering the feasibility of OCV deployment. By Decem-

ber 2017, approximately one million cases had already been reported [8]. In July 2017, three months into the outbreak, 500,000 oral cholera vaccines (OCVs) were planned to be delivered to Sana'a. However, they were rerouted as the request for them was canceled by the requester [9]. Some aid agencies expressed concerns that implementing a large-scale immunization campaign would pose logistical challenges, and they believed that the effectiveness of vaccination might be limited given the extensive nature of the outbreak [10]. This report examines the Pharmacoepidemiological aspects of cholera in Hodeidah, focusing on the connections between clinical symptoms, treatment approaches, and patient outcomes.

2. Methodology

2.1. Study area, setting and design

The case series study was conducted at the Cholera Treatment Center (CTC) in collaboration with the Center of Tropical Medicine and Infectious Diseases (CTMID), affiliated with the Al-Thawara Public Hospital Authority in Hodeidah, Yemen. Cholera has had a profound impact on almost every Yemeni family, with close to two million suspected cases since 2016.

2.2. Sample size

The study included a total of 17,821 linked by epidemiological connections with confirmed cholera cases. Among them, 1/10 fecal samples was collected in May 2017 and confirmed based on gold standard method of CTMID laboratory at Al Thawara

Public Hospital Authority in Hodeidah, Yemen. The patient selection process utilized systemic.

2.3. Inclusion and exclusion criteria

2.3.1. Inclusion criteria

The inclusion criteria included: 1) Patients with confirmed cholera diagnosis via national case definition. 2) Age range of 3-80 years old. 3) Admitted during the outbreak period 2017. 4) Patients who had received rehydration fluid with standard care for 3 days. 5) Patients whom onset of infection was no later than hospital admission.

2.3.2. Exclusion criteria

The exclusion criteria included: 1) Patients who received inadequate or unadjusted therapy, specifically fluid therapy below the approved standard, or who were treated at hospitals for less than three days, ensuring all individuals had a chance of receiving treatment. 2) Patients who died within 48 hours of admission, to avoid immortal time bias.

2.4. Ethical considerations

The study adhered to ethical guidelines, ensuring patient confidentiality and privacy. Ethical approval was obtained from the relevant institutional review board or ethics committee of Center for Tropical Medicine and Epidemiology Studies, Hodeidah University (CTMES – HU) that is academic, research and applied center before conducting the research.

2.5. Case management

In cholera is an emergency: The first treatment facility must function within 24 hours. Cholera is highly contagious: patients must be isolated immediately, without waiting for laboratory results. The case management of cholera requires: Assessment of dehydration status. rehydration therapy, monitoring, antimicrobial therapy and nutrition status [11].

2.5.1. Dehydration assessment

The assessment of dehydration is summarized in Table (1) that shows mild, moderate and severe. The authors added critical cases (severe dehydration with organs failure such as acute renal failure).

Table 1. Rehydration assessment

Severity of cholera	Mild case : No thirst, skin goes back normally when pinched, passing urine is good, pulse is normal
	Moderate case : Restlessness and irritability, sunken eyes, dry mouth and tongue, increased thirst, skin goes back slowly when pinched, decreased urine, decreased tears,
	Severe case: Lethargy, unconsciousness, very dry mouth and tongue, skin goes back very slowly when pinched, weak or absent pulse, low blood pressure, minimal or no urine
	Critical case : Organs failure such as acute renal failure

2.5.2. Rehydration Therapy

Plan A: Oral Rehydration Solution (ORS) for patients with mild dehydration :

- Patients should receive ORS after each loose stool to maintain hydration until diarrhea stops, as indicated below (Table 2 and Figure 1).

Plan B: Oral rehydration therapy for patients with moderate dehydration: Patients must be admitted to the treatment center, receive ORS as indicated below and be monitored until diar-

rhea/vomiting stops. **Plan B:** Oral rehydration during the first 4 hours (Table 3 and Figure 1).

Table 2. Oral rehydration solution in mild cases (plan A)

Age	ORS quantity needed after each loose stool	Amount of ORS
Less than 24 months	50 to 100 ml	Enough for 500 ml/ day (1 sachet)*
2 to 10 years	100 to 200 ml	Enough for 1000 ml/ day (1 sachet)*
Over 10 years	as much as wanted	Enough for 2000 ml/ day (2 sachets)*

Approximately 80–90% of patients can be treated with ORS, and patients who initially require IV therapy usually can eventually switch to ORS.

Table 3. Oral rehydration solution in moderate cases (plan B)

Age	Less than 4 months	4-11 months	12-23 months	2-4 years	5-14 years	14 years and older
Weight	Less than 5 kg	5-7.9 kg	8-10.9 kg	11-15.9 kg	16-29.9 kg	30 kg or more
ORS in ml	200-400	400-600	600-800	800-1200	1200-2200	2200-4000
ORS in 200 ml cup	1-2 cups	2-3 cups	3-4 cups	4-6 cups	6-11 cups	11-20 cups

Plan C: IV Rehydration of severe dehydration

- Intravenous rehydration (IV) treatment must be given quickly to restore normal hydration within 3 to 6 hours.
- Hang the infusion bag as high as possible to facilitate rapid flow
- Ringer Lactate solution (Hartman's solution) is the best option. It provides an adequate concentration of sodium, some potassium and enough lactate, which is metabolized into bicarbonate for the correction of acidosis.
- How do IV fluids? Start I/V fluid immediately at the volume of 100 ml / kg as follows : (Table 4 and Figure 1)

Table 4. IV rehydration solution in severe cases (plan C)

Age	First give 30 ml/kg in:	Then give 70 ml/kg in:
Children less than 1 year or malnourished	1 hour (repeat once if radial pulse is still very weak or non-detectable)	5 hours
Adults and Children > 1 year to 14 years	30 minutes (repeat once if radial pulse is still very weak or non-detectable)	2 and half hours
- Intravenous rehydration with Ringer's lactate or similar balanced solutions is crucial for correcting hypovolemia. If unavailable, normal saline can be used temporarily. - Oral rehydration solution (ORS) is essential once the patient stabilizes and can tolerate oral intake.		

2.5.3. Monitoring

Regular assessment of urine output and electrolyte levels is essential to monitor kidney function. Blood urea nitrogen (BUN) and serum creatinine should be evaluated to detect acute kidney injury (AKI).

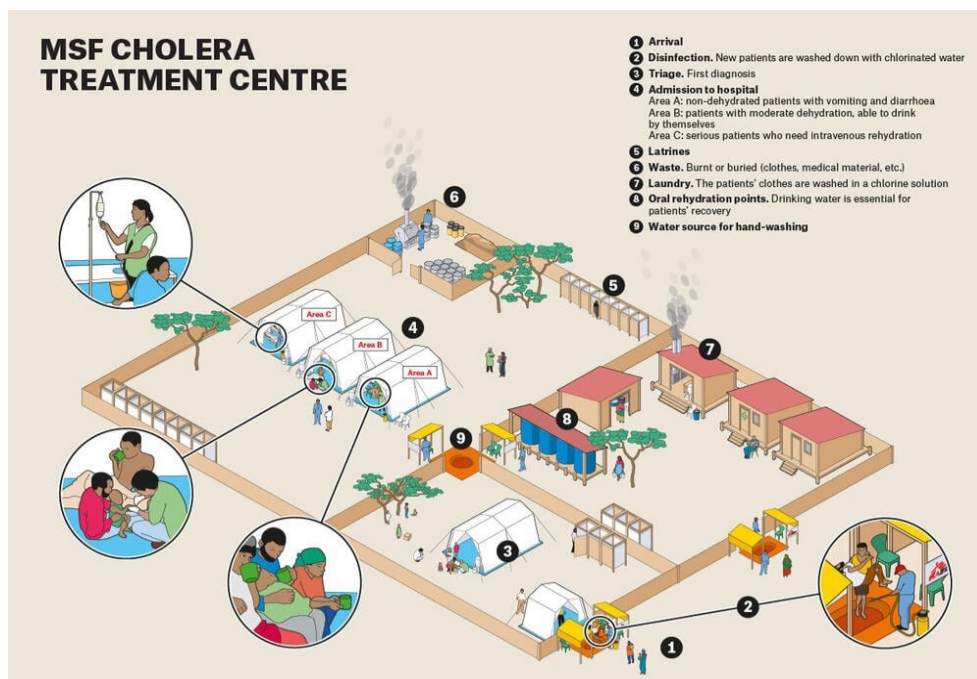


Figure 1. Structure of Cholera Treatment Centre (CTC) (MSF) [12]

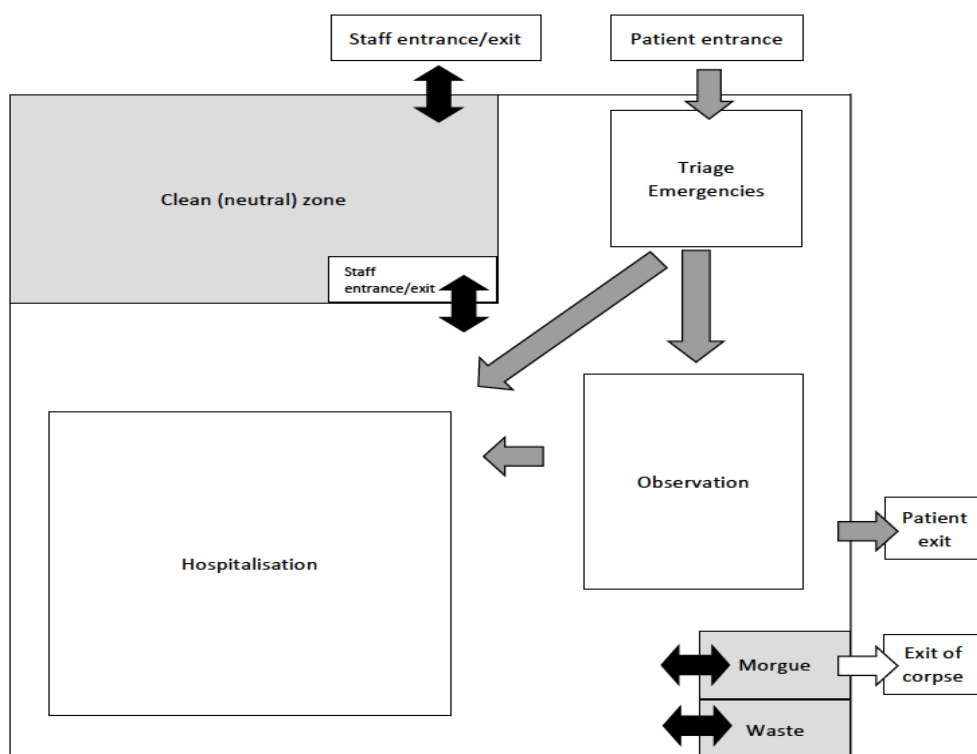
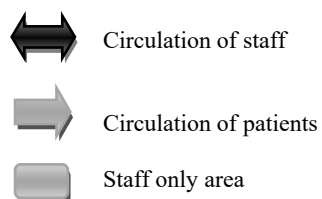


Figure 2. Circulation of patients, attendants and staff in the CTC (MSF) [12]



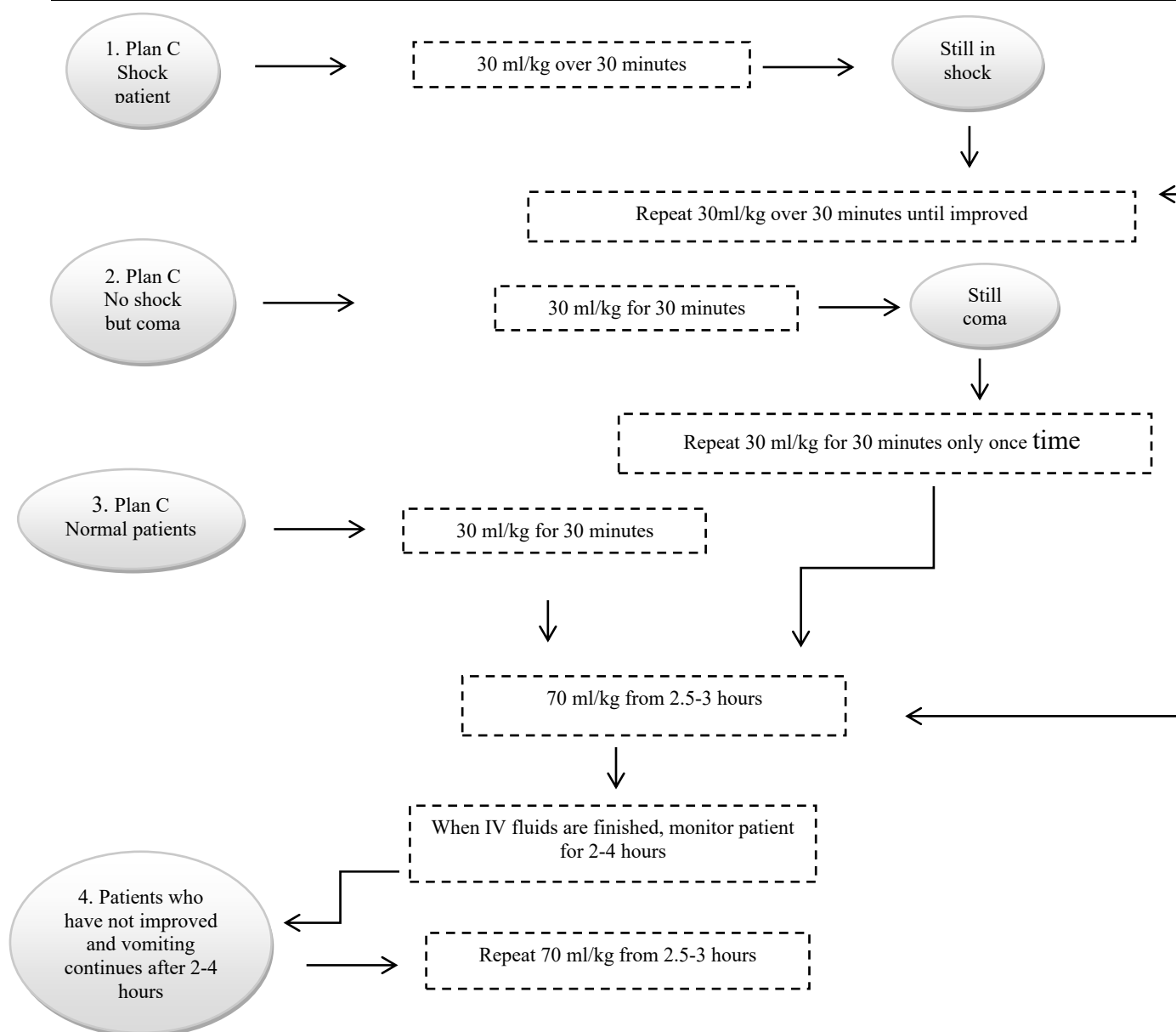


Figure 3. Flow chart of plan C – IV management [11]

2.5.4. Anti-microbial Therapy

Table 5 describes the antibiotic choices and dosing for the treatment of cholera that is fourth step in cholera management based on national guideline of Yemen [11]

Table 5. Antibiotic prescribed in cholera

Patient classification	First Choice	Second Choice
Adult (non-pregnant)	Doxycycline: 300 mg by mouth one dose	- Azithromycin: 1 g in a single dose. - Tetracycline: 500 mg 4times in a day for 3days - Erythromycin: 500mg 4times in a day for 3days
Pregnant Women	Azithromycin: 1gm in a single dose	Erythromycin: 500mg 4times in a day for 3days
Children who capable to swallow pills or tablets.	- Azithromycin: 20mg/kg in one dose - Erythromycin: 12.5mg/kg 4times a day for 3days - Doxycycline: 2-4mg/kg in a single dose	Tetracycline: 12.5mg/kg 4times in a day for 3days
Children < who unable to swallow pills or tablets.	- Azithromycin: oral suspension 20mg/kg in one dose - Erythromycin: oral suspension 12.5mg/kg 4times a day for 3days - Doxycycline: oral suspension 2-4mg/kg in a single dose	Tetracycline: oral suspension 12.5mg/kg 4times in a day for 3days
Note : Updating national guideline for acute watery diarrhea control (cholera) , 2024 , avoiding the prescription of azithromycin and erythromycin because the cholera resistance [13]		

Table 6. Adverse effects of the treatments [14]

Drugs	Common Side Effects
1- Erythromycin	- G.I.T. irritation: Nausea, vomiting, abdominal cramps, and indigestion. - Liver: Hepatotoxicity, jaundice.
2- Azithromycin	G.I.T. irritation: Nausea, vomiting, abdominal cramps, and indigestion.
3- Tetracycline	1-G.I.T. irritation: nausea, vomiting and diarrhoea 2-Hypersensitivity reactions (including rash, exfoliative dermatitis, Stevens–Johnson syndrome, urticaria, angioedema, anaphylaxis, pericarditis); - worsening of renal failure; - hepatotoxicity (rare); - discoloration and damage of the teeth and bones of the fetus if the mother takes tetracycline after the fifth month of pregnancy, and of children; they should therefore be avoided in pregnancy and children under 12 years.
4- Doxycycline	G.I.T. irritation: nausea, vomiting ,abdominal cramps and diarrhea

2.5.5. Nutrition status

In managing cholera, nutrition is vital for supporting recovery and reducing the risk of complications. Although rehydration is the primary focus of initial treatment, ensuring proper nutritional intake is key to maintaining overall health and strengthening the immune system [11].

2.6. Hemodialysis Therapy

The dialysis for cholera patients was done by hemodialysis (HD) machine and the procedure was as the following : HD time: 3 h/wk. HD bath: calcium 2.5 mEq/L, bicarbonate 35 mEq/L, potassium 2.0 mEq/L, magnesium 1.0 mEq/L, sodium 138 mEq/L and chloride 109.5 mEq/L. Adjust based on weekly measurements of electrolytes, calcium, and phosphorus. Hemodialysis therapy was carried out in Center of Renal Diseases and Dialysis, Hodedah city, Yemen [15-17].

2.7. Data Analysis

Statistical analysis was performed on the collected data to compare the outcomes between the three groups (plan A, plan B and plan C treatments). The analysis used to determine any differences in disease progression, severity, and patient outcomes based on type of treatment plan received.

3. Results

3.1. Gender distribution

Females represent 9,875 cases (55.4%), while males account for 7,946 cases (44.6%), showing a slight predominance of females. The male-to-female ratio is approximately 0.8:1, indicating an even gender distribution with a marginally higher number of cases among females.

3.2. Age distribution

The largest affected age group is ">20," accounting for 7,974 cases (44.8% of the total).The smallest age group is "5-10," with 2,244 cases (12.6% of the total).Children aged "1-5" represent 2,640 cases (14.8% of the total), emphasizing a significant burden on young children.

3.3. Plan of admission by dehydration severity

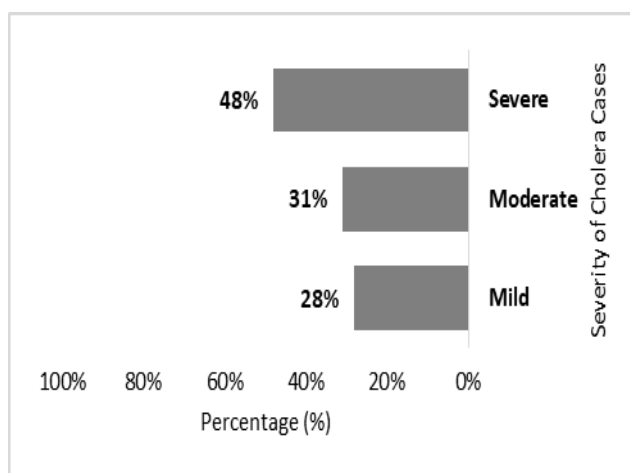
Table 7 and figure 3 categorizes the number of patients admitted under each treatment plan based on the severity of dehydration.

- Plan A (Oral Rehydration Only):** 4,995 cases (28%) were categorized as mild, 2,290 cases of males versus 2,705 cases of females. The cases were treated under this plan, reflecting minimal need for advanced intervention.

- Plan B (Oral and IV Rehydration):** 5,539 of moderate cases (31.1%) that included 3,101 cases of females versus 2,438 cases of males. Nearly all moderate cases. The cases were treated under Plan B, demonstrating the importance of combined oral and intravenous therapies.
- Plan C (Advanced IV Therapy):** 7,287 of severe cases (40.9 %) that included 3218 cases of males and 4,069 cases of females. Plan C was used almost exclusively for severe cases, managing. This highlights the necessity of advanced medical facilities for treating severe dehydration

Table 7. Plan of admission by dehydration severity

Dehydration Severity	Plan A (Oral Rehydration Only)	Plan B (Oral & IV Rehydration)	Plan C (Advanced IV Therapy)	Total
Mild	4,994	0	1	4,995
Moderate	5	5,534	0	5,539
Severe	0	2	7,285	7,287
Total	4,999	5,536	7,286	17,821

**Figure 4.** Severity of cholera (mild , moderate and severe)

3.4. Complication rate

In addition, 250/ 17,821 (1.40 %) cases complicated by acute renal failure (ARF) and 1595/17,821 cases (8.95 %) had shock. 728/17,821 cases (4.085 %) based on physical and radiological examination. 190 of mild cases were developed into moderate and transferred to plan B. 150 of mild cases were developed into severe illness and transferred to plan C.

3.5. Side effect of cholera medication

10 cases (0.06 %) of severe cases were developed to pleural effusion because the intravenous fluid overload (as the result of therapeutic side effect) (Figure 5).

3.6. Treatment outcomes

Table 8 and figure 5 presented the outcomes of patients based on the treatment plan they were admitted in DTC.

- **Cured:** most patients (17,782 cases, 99.78%) were successfully cured, reflecting the effectiveness of current treatment protocols. Significant effect of management intervention was reported ($\chi^2 = 17665.341$; p -value < 0.00001) (Table 8 and Figure 6)
- **Deaths:** 39 cases were recorded deaths, with the majority (37 cases) occurring among patients treated under plan C, indicating the high-risk nature of severe cases, where the case fatality rate (CFR %) was 39 /17821 (0.21 %),
- **Abandoned Treatment:** Only 11 patients abandoned treatment, representing a negligible portion of the total cases (Table 8 and Figure 3).
- **ARF :** A total of 250 patients, aged 5 to 92 years, developed acute renal failure (ARF) due to cholera. Serum creatinine levels ranged from 4 to 14 mg/dL, and potassium levels from 1.5 to 2.5 mg/dL. The case fatality rate was 18.4%, with 46 deaths out of 250 cases [15].

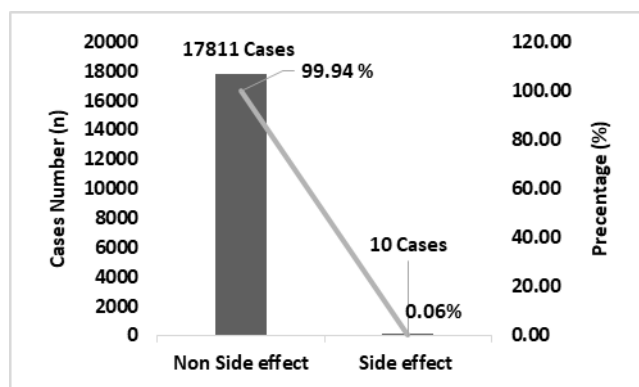


Figure 5. Side effect of cholera medication (n:10)

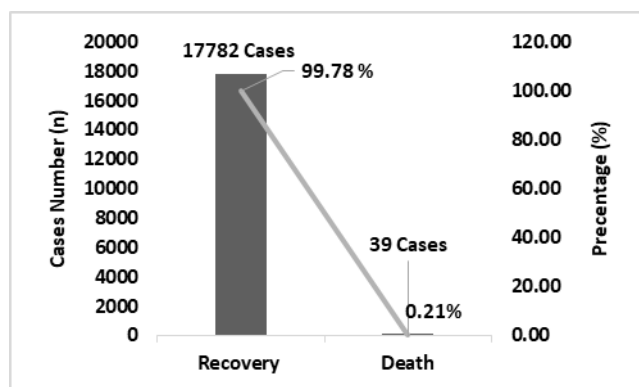


Figure 6. Impact of rehydration therapy on cholera outcome (n:39 death cases)

Table 8. Treatment outcomes by plan of admission

Outcome	Plan A (Oral Rehydration Only)	Plan B (Oral & IV Rehydration)	Plan C (Advanced IV Therapy)	Total
Defaulter	1	7	3	11
Cured	4,998	5,527	7,246	17,771
Death	0	2	37	39
Total	4,999	5,536	7,286	17,821

4. Discussion

Early diagnosis and rapid management of dehydration are crucial for increasing positive outcomes. Most cholera cases are usually mild to moderate and easily managed with an ORS. The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) recommend low- osmolarity ORS, which contains sodium, chloride, potassium, citrate, and anhydrous glucose prepared in 1,000 mL of sterile water. This improved ORS recipe is safe, lowers hyper tonicity, and decreases stool output [18]. Severe dehydrating cholera can progress to hypovolemic shock due to the rapid loss of fluids and electrolytes, which requires a rapid infusion of IV fluids. The CFR exceeds 50% without proper clinical management but can be less than 1% with prompt rehydration and antibiotics [18]. Our study demonstrates that the application of rehydration therapy based on WHO guidelines significantly improved cholera prognosis, most patients (17,771 cases, 99.7%) across all plans (A,B,C) were cured, and only a few fatalities, the CFR was very low , less than 1 % namely (0.2 %), shows casing the effectiveness of the treatment protocols. This finding aligns with numerous studies that emphasize the effectiveness of rehydration, which remains the cornerstone of cholera treatment which said appropriate case management and especially the early use of ORS and rapid IV rehydration Fluids in patients with severe dehydration mortality rates can be reduced to close to zero [19]. Antimicrobial therapy should be given to moderately and severely ill patients [20]. Antimicrobial therapy shortened the mean duration of diarrhea by about a day and a half compared to placebo or no treatment, also reduced the total stool volume by 50% , and reduced the amount of rehydration fluids required by 40%. The mean duration of fecal excretion of vibrios was reduced by almost three days , the current recommended treatment for adults is a single oral dose of doxycycline 300 mg or tetracycline 12.5 mg/kg six hourly for three days). In children under eight years of age, co-trimoxazole, erythromycin or azithromycin are recommended . Tetracycline was the antibiotic most commonly compared to placebo/no treatment, and in indirect comparisons appeared to have larger effects compared to placebo than other antibiotics. However, in head-to-head comparisons tetracycline did not demonstrate significant benefits on either diarrhoea duration or stool volume compared to doxycycline (*low quality evidence*), or ciprofloxacin or norfloxacin (*moderate quality evidence*). Azithromycin has not been compared directly to placebo or tetracycline. However, single dose azithromycin shortened the duration of diarrhoea by over a day compared to ciprofloxacin (*moderate quality evidence*) and by half a day compared to erythromycin (*moderate quality evidence*). Quinolones in general were not more effective than other antibiotics [21]. As part of the 2024 update to the national guidelines for AWD control , including cholera, there is a critical revision to antibiotic treatment protocols. Specifically, azithromycin and erythromycin are no longer recommended due to emerging resistance patterns in *V. cholerae* . This change aims to enhance treatment efficacy and support antimicrobial stewardship. The national guideline recommends the use of doxycycline, tetracycline, and ciprofloxacin for the treatment of specific bacterial infections. These antibiotics are included due to their proven efficacy, broad-spectrum activity, and cost-effectiveness. The guideline's recommendation is based on local antimicrobial resistance patterns, therapeutic outcomes, and accessibility, ensuring optimal treatment while minimizing the risk of resistance development [13].

5. Conclusion

The study underscores the efficacy of rehydration therapy in cholera management, achieving a low overall CFR of 0.2% (less than 1 %) and the side effect was not reported . This emphasizes the critical role of prompt intervention and customized treatment strategies in outbreak situations. Therefore, the pharmacoepidemiological study provides valuable insights into optimizing cholera treatment protocols and highlights areas for improvement in outbreak preparedness and response strategies.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This work was conducted during our work at CTMID – Al Thawara Public Hospital Authority, Hodeidah, Yemen.

Ethical Approval

The studies involving human participants were reviewed and approved by Ethics Committee of Tropical Medicine and Epidemiology Studies of Hodeidah University (CTMES-HU) Hodeidah, Yemen.

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