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Productive role of *Vibrio cholera* in the generation of IL-1β and immunoglobulins in patients with diarrhea

Z. K. Khadur, A. A. Khadim, S. M. Mohsen

Middle Technical University, Diyala, Iraq

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Middle Technical University, Baquba Technical Institute, Diyala, Iraq. E-mail: zwidamicro69@mtu.edu.iq

Middle Technical University, Baquba Technical College, Diyala, Iraq. E-mail: alianwmicrbio81@mtu.edu.iq, sajamohammed@mtu.edu.iq

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The highly contagious diarrheal illness known as cholera, which affects millions of people globally, is caused by the bacterium *Vibrio cholera*. Cholera is a significant health problem that is most prevalent in insanitary nations and areas devastated by emergencies when access to clean drinking water is scarce. The present study aims to determine the role of *V. cholera* in stimulating the development of IL-1 beta and immunoglobulin (M, G, A) in diarrhea patients. The investigation was conducted in Baquba city, the governorate of Diyala Province, from 1/8/2023 to 1/11/2023. One hundred stool and blood samples were collected from diarrheal patients who were inpatients at Baquba Teaching Hospital/Internal Medicine Department after being examined by a specialist doctor to determine the positivity of *V. cholera* (stool samples) by culture and the levels of IL-1 beta with immunoglobulins (IgG, IgM, and IgA) (blood samples) by ELISA. SPSS version 20 was used to analyze the data. The current study reveals that 70% (n = 70) of patients with diarrhea had *V. cholera* with a significant variation. Most patients with *V. cholera* were 21–40 years old (54.3%) and 41–60 years old (28.6%), lived in a rural area (81.4%), had a fever ≤37 °C (78.6%), had watery stools (100.0%), had no blood in the stool (85.7%), had abdominal pain (72.9%), or had vomiting (88.6%). Significant differences in the levels of IL-1beta and immunoglobulin (IgM and IgA) were detected between *V. cholera* patients and healthy controls. Finally, these bacteria did not significantly affect the levels of human IgG. It has been concluded that the culture method is suitable for detecting *V. cholera* in stool samples. The incidence of cholera has increased in rural regions due to the loss of teaching about health and hygiene . Bacterial toxins play a significant role in inactivating macrophages that release IL-1beta via pyrin and the NLRP3 inflammasome.IL-1beta leads to increased inflammation due to its proinflammatory effect. The human serum levels of IgM and IgA immunoglobulins are more strongly affected by *V. cholera* than are those of IgG.

Keywords: diarrhea; *Vibrio cholera*; IL-1beta; immunoglobulin; IgG; IgM; IgA.

Introduction

Vibrio cholera is a Gram- negative bacterium shaped like a curved rod and movable bacterium that thrives in aqueous conditions. It causes copious, loose stools and often death if treatment for severe dehydration is delayed. Depending on the severity, antibiotics, oral rehydration and saline solutions can be used in treatment (Sit et al., 2022). The fecal-oral pathway is one pathway by which *V. cholera* acts. It spreads from person to person, and contaminated water and food also spread indirectly (Ganesan et al., 2020).

Cholera is prevalent in many parts of Asia and Africa, where epidemics can occur seasonally or irregularly (Zheng et al., 2022). These epidemics usually occur in nations with insanitary conditions, such as open defecation, contaminated food, and restricted access to clean water for drinking (Charnley et al., 2022; Ilic & Ilic, 2023).

One important cytokine that stimulates monocytes and proinflammatory signaling networks in the nervous system and peripheral organs is interleukin-1β (IL-1β). There is strict regulation of the production and release of IL-1β (Cheng et al., 2020). Pattern recognition receptors (PRRs), including NOD, TLRs, and RLRs are mainly produced by antigen-presenting cells, including dendritic cells and macrophages. However, PRRs, occurring throughout both immune and nonimmune cells, are what causes the development of pro-IL-1β (Cavalli et al., 2021). According to Escartín-Gutiérrez et al. (2023), *V. cholera* antigens significantly impacted the stimulation of IL-1beta generation from macrophages through heparin and NLRP3 in the inflammasome. It is recognized that human defense against *V. cholera* can be aided by certain antibodies; nevertheless, it is unclear which particular antibody isotype is most crucial for cholera immunization (Charles et al., 2020). Two isotypes, secretory IgA and serum IgG, have been demonstrated to provide autoimmune protection against *V. cholera* (Moor et al., 2017). In addition, LPS-specific IgA elevates the levels of sera and gastrointestinal fluids in patients as well as in vaccine recipients. Since the traditional complement pathway may cause complement-mediated bacterial lysis in response, it is impossible for IgM to provide safeguards against *V. cholera* (Chowdhury et al., 2022). In addition to exhibiting greater operational avidity than does monomeric IgG, it is possible that IgM performs complement fixation significantly better than does IgG (Vaillant et al., 2022).

The anti *V. cholera* LPS IgM was described by Yang et al. (2019) (Groza & Ewers, 2020). It has been shown to be strongly correlated with serum biocidal activity and may serve as an antibody isotype for antibodies that protect against *V. cholera.* Due to the scarcity of studies on the effect of *V. cholera* on the levels of IL-1beta and immunoglobulin (IgG, IgM, IgA), the current study intends to determine the role of *V. cholera* in stimulating the development of IL-1beta immunoglobulin (M, G, A) in patients with diarrhea.

Matherials and methods

The study was ethically approved by the Human Ethics Committee of the Al-Habbobi Teaching Hospital based on the Declaration of Helsinki under approval number 558, which was dated January 1, 2025. All the subjects received detailed instructions on the procedures of the study and signed informed consent. All patient data was kept confidential in the course of the research.

The current investigation occurred in Baquba city between 1/8/2023 to 1/11/2023. One hundred stool and blood samples were collected from diarrheal inpatients patients at Baquba Teaching Hospital/Internal Medicine Department after being examined by a specialist doctor to determine the positivity of *V. cholera* (stool samples) and the levels of IL-1beta with immunoglobulins (IgG, IgM, and IgA) (blood samples). In addition, forty blood samples were collected from a healthy population and used as a control group. A template flyer was written recording the following information from diarrheal patients: anthropometric and medical age groups, sex, living status,

fever >37.5, diarrhea > 3 days, watery stool, bloody stool, abdominal pain, and techniques as described below.

The blood from patients was placed in a centrifuge (6000 rpm for five min) and added to the serum. IL-1beta and immunoglobulins (IgG, IgM, and IgA) were concentrated using ELISA (Lubeck, Germany) after reading the leaflet that the company supplied.

Fresh stool specimens were collected within 24 hours of the onset of illness and before the administration of antibiotics. Fresh stool was collected in a clean dry container. Stool swabs were transferred to Cary-Blair transport tubes, which were labeled with patient information.

The sample was transferred to alkaline peptone water (pH 8.6) and incubated for 6–8 hours at 37 °C. Afterwards, the samples were cultured by plating on 3 basic media- blood agar, MacConkey agar, and thiosulfate citrate bile salt sucrose (TCBS) agar and then incubated for 18–24 hours at 37 °C. The growth of cholera on blood agar was characterized by beta hemolysis, colorlessness and non-fermentation on MacConkey agar, and golden yellow colonies on TCBS after 18–24 hours at 37 °C.

IL-1beta and immunoglobulin (IgM, IgG, and IgA) indicators, such as the mean, and SD tests were utilised to determine the statistical differences between *V. cholera* patients and healthy controls. Anthropometric and medical features, such as group frequencies with percentages and the differences among these percentages, were examined using the Pearson-Chi-square test. Indeed, $P \leq 0.05$ was considered to indicate a significant difference. The SPSS v. 21.0 program was used to organize the data from the current investigation.

Results

The findings on the prevalence of *V. cholera* among participants are presented in Table 1 and show that 70% of patients with diarrhea had *V. cholera* with a significant variation of $P < 0.05$.

Table 1
Positivity of *V. cholera* among people with diarrhea ($N = 100$, $P < 0.05$)

Option	Number, %
Positive	70
Negative	30

The distribution of cholera patients referring to the social, demographic and medical characteristics is provided in Table 2. Table 2 shows a greater prevalence of *V. cholera* among females in comparison to males with $P > 0.05$. This in turn would elucidate that this difference is not statistically significant. Table 2 also depicts other effectual parameters. Most patients with *V. cholera* infection fell into the following age categories: 21–40 (54.3%) and 41–60 (28.6%). These results are demonstrated with a p-value of less than 0.001, which signifies a statistically significant association between age and the incidence of cholera, the younger adults being the more affected group. Table 2 also shows that most patients with *V. cholera* infection lived in rural areas (81.4%). In this aspect, a significant relationship between rural areas and incidence of *V. cholera* infection is ascertained, which can highlight the impact of environmental factors and lack of access to clean water in these districts. Table 2 shows that the majority of patients (78.6%) did not exhibit fever, with a significant association of of less than 0.001, indicating that fever is a less common symptom among cholera patients. Diarrhea is also assessed and shows that the existence of diarrhea for more than three days did not indicate a significant association of P-value more than 0.05 with the cholera diagnosis in this sample. However, all the tested patients had watery stools, confirming this symptom as a typical feature of cholera and highlighting a perfect association of P equal to 1.00. The majority of patients (85.7%) did not have blood in their stool, with a significant association of less than 0.001. Furthermore, Table 2 indicates that abdominal pain was widespread among the majority of patients with 72.9%. A considerable association of of less than 0.001 is deduced, which suggests that abdominal pain is a common symptom of cholera. In this aspect, vomiting was present in 88.6% of the patients. Thus, it can be said that vomiting is a common symptom in cholera cases with a statistical significance of $P < 0.001$.

Table 2
Distribution of cholera patients according to social, demographic and medical characteristics

Parameters	Variants	Number	Percentage	
Gender	males	30	42.9	>0.05
	females	40	57.1	
Age groups, years	1–20	3	4.3	<0.001
	21–40	38	54.3	
	41–60	20	28.6	
	>60	9	12.9	
Residence	rural	57	81.4	<0.001
	urban	13	18.6	
Fever >37.5 °C	yes	15	21.4	<0.001
	no	55	78.6	
Diarrhea>3days	yes	27	38.6	>0.05
	no	43	61.4	
Watery stool	yes	70	100.0	1.000
	no	0	0.0	
Blood stool	yes	10	14.3	<0.001
	no	60	85.7	
Abdominal pain	yes	51	72.9	<0.001
	no	19	27.1	
Vomiting	yes	62	88.6	<0.001
	no	8	11.4	

Table 3 introduces the comparison of IL-1beta concentrations between *V. cholera* patients and healthy controls. This indicates an increase in the level of IL 1β in *V. cholera* patients of (14.5 ± 6.6) compared to healthy controls (8.2 ± 2.9), with a significant important effect ($P < 0.01$).

Table 3
Comparison of IL-1beta concentrations (Pg/mL) between *V. cholera* patients and healthy controls

Groups	Numbers	Mean ± SD	P
V. cholera patients	70	14.5 ± 6.6	<0.01
Healthy people	40	8.2 ± 2.9	

This research reports significant amounts of IgM, IgG, and IgA in *V. cholera* patients in comparison to healthy controls. The associated statistical results are presented as follows. The mean IgM concentration was considerably greater in cholera patients (5.54 ± 2.03) in comparison to healthy individuals (1.92 ± 0.61). Indeed, the low signifies a statistically significant difference, suggesting that IgM levels can increase as a result of having the cholera infection. This would therefore reflect a severe phase immune response. The IgG concentrations in cholera patients (14.4 ± 5.0) were greater than in the healthy group (10.2 ± 3.3) with no statistical difference of greater than 0.05. This is an indication that the variation in IgG concentration would not be directly attributed to the cholera infection, and therefore other factors can have a direct effect. The IgA level (6.08 ± 2.28) was considerably raised in cholera patients compared to the healthy group (2.61 ± 0.81), with a statistical difference of of less than 0.01. This can signify that IgA level can have a serious role in the mucosal immune response of patients with cholera, helping to combat the infection.

Table 4
Comparison of IgM, IgG and IgA concentrations between *V. cholera* patients and healthy controls

Parameters	Groups	Number	Mean ± SD	P value
IgM, g/L	*V. cholera* patients	70	5.54 ± 2.03	<0.001
	healthy people	40	1.92 ± 0.61	
IgG, g/L	*V. cholera* patients	70	14.38 ± 5.01	>0.05
	healthy people	40	10.23 ± 3.29	
IgA, g/L	*V. cholera* patients	70	6.08 ± 2.28	<0.01
	healthy people	40	2.61 ± 0.81	

Discussion

Cholera infection is an extended epidemic, which has probably been exacerbated by consuming unclean water, not washing hands frequently, not maintaining proper personal and environmental hygie-

ne, dining outdoors, and by lack of information information about health hazards. To stop disease outbreaks, safe water must be provided, sanitation must be improved, medical instruction must be given, and proper handling of foods must be followed. The current section focuses on appraising the obtained results of the current study and the reported results of the relevant studies provided in the open literature.

A total of 70 cases of (70%) *V. cholera* were detected in stool samples from 100 diarrhea patients by culture methods, and these results were high compared to those of Chowdhury et al. (2021), who reported that 56% of cases of *V. cholera* were detected by a rapid antibody test. In this aspect, Guillaume et al. (2023) showed that the percentage of *V. cholera* – positive stool samples was 17% by culture and 45% by polymerase chain reaction (PCR). Accordingly, these results are lower than the results of the current study.

The isolation and identification of *V. cholera* serogroup O1 or O139 by the culture of stool specimen remains the gold standard for the laboratory diagnosis of cholera due to its low cost, simplicity, high sensitivity, accuracy, and specificity compared to a rapid antibody test. The PCR technique is more accurate, sensitive, and specific than culture and rapid test methods for diagnosis. However, it is an expensive practice as it requires expensive equipment (Debes et al., 2022).

In a previous study, an increase was reported in cholera outbreaks in urban areas (79%) compared to rural areas in Bangladesh (21%). These results are consistent with the obtained results of the current study, which reported a greater incidence of this bacterium in rural areas (81.4%) than in rural areas (Das et al. 2023).

In 2022, Endris et al. (2022) showed that 100% patients with cholera had watery diarrhea and 84% vomiting. These findings are in agreement with the current results. In this regard, due to its flagellum, *V. cholera* may pass through the mucus and reach the intestinal wall. Within the mucosal barrier are the toxic bacteria *V. cholera.* As a result, adenylate cyclase constitutively promotes intracellular cAMP. Consequently, bicarbonate levels rise with noticable levels of potassium, sodium, and chloride. Diarrhea is caused by water being osmotically drawn from the intestine by the production of these chemicals. Potassium, sodium, and chloride are present. (Igere et al., 2022).

Previous contact with the pathogen can influence host vulnerability and even induce immunity, albeit this depends on the biotype and serotype of the pathogen encountered earlier. A high dose of immunization can affect health because of unstable acid bacteria. This explains why the level of activity required for bacteria can induce illness and be increased by reduced stomach acidity (Ahmed et al., 2022). The use proton pumping blockers and antihistamines may increase the possibility of infection and increase the likelihood of severe symptoms. The duodenum is usually the source of fluid distortions, while the colon is not affected by toxins. Most of the time, neutrophils are not detected in fecal collections because enterotoxin is noninvasive and only has a localized impact (Sousa et al., 2020).

The recent findings shown in Table 2 reveal red blood cell (RBC) counts in the stool of some patients with cholera, indicating the occurrence of bleeding in the intestine. A few patients with cholera had a fever >37.5 °C due to stimulation of the immune response in the host after invasion by the *V. cholera* pathogen.

Orimo et al. (2019) reported increased levels of IL-1beta in patients with cholera compared to healthy controls, and these outcomes agreed with the findings of the current study. Immune cells release the inflammatory cytokine IL-1β when infection or irritation occurs. Overall, IL1β stimulates inflammation, antigen-specific immune reactions, and extracellular matrix remodeling. This information indicates that people with diarrhea are more likely to produce IL1β when exposed to clinical strains of *V. cholera*.

The results of the present study reveal that CTB plays a key role in stimulating IL-1β synthesis in peritoneal macrophages through pyrin and the NLRP3 inflammasome (Orimo et al., 2019). A previous study revealed that inflammasome production in humans caused by *V. cholera* varies with different biotypes and is mediated through NLRP3-dependent and NLRP3-independent mechanisms (Queen et al., 2015). Queen et al. (2015) revealed that the cytotoxin of *V. cholera* (VCC) acts as a modulator of innate immunity, as this toxin binds to macrophages via the NLRP3inflammasome.

Macrophages trigger the release of IL-1 beta, a proinflammatory cytokine that increases inflammation. Vidakovic et al. (2023) revealed that cholera bacteria play a major role in producing biofilms for human cells, especially encapsulated immune cells such as neutrophils. NK cells, CD4+ T cells and macrophages inhibit their functions. Subsequently, these cells become unable to produce cytokines (IL-1 beta, TNF-a, and IFN-y) that mediate the inflammatory response against this bacterium, which leads to disease progression. These results agree with the findings of the current study as presented in Table 3.

Yang et al. (2019) showed increased levels of immunoglobulins (M, A) in cholera patients compared to healthy control patients, and these findings were compatible with current outcomes against cholera toxin established by Escartín-Gutiérrez et al. (2023).

Yang et al. (2019) showed that the anti-*V. cholera* LPS IgM is strongly correlated with serum biocidal activity and may serve as a stand-in antibody isotype for antibody protection against this bacterium. Referring to activating the traditional complement system, IgM is more potent than IgG. According to the current findings, monoclonal IgM is the strongest immunoglobulin isotype known to be biocidal. It was shown to have at least 20–200 times the effectiveness of IgG for both high-binding monoclonal antibody forms, with identical binding strengths. Combining biocidal analysis with measurements of all and particular serum IgG and IgM vibriocidal antibodies might be helpful in analyzing the development of the immune system's reaction and its relationship to safeguarding, especially in light of findings highlighting the extraordinary strength of the IgM isotype (Kauffman et al., 2021).

In stage 1–2 clinical studies of cholera immunizations, antiviral antibody titers were used by Iyer & Harris (2021) as a surrogate to predict vaccination efficacy, and there is a recognized relationship between immunogenicity and *V. cholera.* The idea that antiviral immunoglobulin is the strongest predictor of defense against cholera has been called into question by previous observations that several markers (IgM, IgG, and IgA) either separately or together appear to be more predictive of contamination prevention .

Bahroudi et al. (2021) ascertained that a novel vaccination method lipopolysaccharide mesenchymal stem cell-cultured medium (LPS-MSC-CM) may be a suitable medicinal alternative for treating infections caused by *V. cholera.* By increasing the levels of vibriocidal immunoglobulins (IgM, IgG, and IgA), the vaccine modifies inflammation and anti-inflammatory reactions and induces strong preventative humoral immune reactions that guard against *V. cholera* disease in newborns.

Human antibody reactions were previously studied, and the results suggest that IgM and IgA mucosal antibodies are crucial adaptive reactions during *V. cholera* illness. It was discovered by Farr et al. (2021) that in diarrheal people who had O antigen induced cholera, the gene expression of IgM and IgA increased. Furthermore, Farr et al. (2021) demonstrated that human IgD likely has little impact on immunization against *V. cholera.*

In their recent investigation, Clutter et al. (2023) revealed that young children had considerably lower levels of *V. cholera* LPS-specific IgG and no additional functional antibodies in comparison to older children as well as adults.

A prior investigation by Aung et al. (2016) reported that in the examined human blood samples, there was an unexpectedly elevated titer of IgG toward the OmpU antigen of *V. cholera*. The identification of the homolog of *V. cholera* OmpU, the IgG-recognizing OmpC protein of *E. coli*, suggested that these types of antibodies originated in response to the outer layer of membranes of the symbiotic *E. coli* bacteria. These results are consistent with those reported in the current study as shown in Table 3.

Conclusion

The current study investigated the influence of *Vibrio cholera* on the production of IL-1β and immunoglobulins (M, G, A) in patients experiencing diarrhea. It has been concluded that the culture method is perfect for the detection of *V. cholera* in stool samples. The incidence of cholera was higher in rural regions due to the lack of teach-

ing about health and hygiene. Bacterial toxins play a significant role in activating macrophages that release IL-1β via pyrin and the NLRP3 inflammasome. IL-1β leads to increased inflammation due to its proinflammatory effect. Compared to those of IgG, the serum levels of IgM and IgA immunoglobulins proved more effective against *V. cholera*.

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