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Occurrence and Risk Factors of *Cryptosporidium parvum* among Immunocompromised Patients in Ibb City- Yemen

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Abstract: *Cryptosporidium* parasite is causing opportunistic *Cryptosporidiosis* diseases among Immunocompromised patients that lead to acute and persistent diarrhea and health complications, especially in developing countries. This study **amid** to determine the occurrence of *C. parvum* among immunocompromised patients presenting at Al- Thawra hospital in Ibb city- Yemen. Sample of the study (87) stool specimens were collected between November 2016 and July 2017. The stool specimens were screened for the *C. parvum* by using formalin- ether concentration, Ziehl- Neelsen methods, and enzyme-linked immunosorbent assay (ELISA). The required data were obtained by a designed questionnaire. The result revealed that the overall rate of *C. parvum* was 62 (71.26%) observed among immunocompromised patients and both males and females had nearly equal frequency rates of infection. The highest rate of infection was 80% reported within age less than 10 years and 78.3% among patients who coming from the rural area. Also, it was found 83.33% of infected patients drinking from piped water with significant difference (P<0.05). In addition, 73.81% of individuals contacting animals were positive for infection. The most frequent rate of infection was 53.2% recorded for chronic renal failure, 42% for malignancy, and 4.8% for renal transplant patients. The clinical features most frequently presented were diarrhea, malaise, poor appetite, weight loss, abdominal pain, and fever. Similarly, 90.3% and 97.8% of cases were suffered from semi- liquid diarrhea and acute diarrhea, respectively. Recommendation as described in this study health education programs are needed for preventing and controlling the transmission of *Cryptosporidium* parasites among weak immune individuals.

Keywords: *Cryptosporidium*, Ibb City, Immunocompromised Patients, Occurrence, Yemen.

الحدوث وعوامل الخطورة لطفيل الأبواغ الخفية بين مرضى نقص المناعة في مدينة إب – اليمن

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المستخلص: يتسبب طفيلي خفيات الأبواغ في الإصابة بأمراض خفية الأبواغ الانتهازية بين المرضى الذين يعانون من نقص المناعة والتي يؤدي إلى الإسهال الحاد والمستمر والمضاعفات الصحية، خاصة في البلدان النامية. هدفت هذه الدراسة لتحديد نسبة الإصابة بطفيل الخفية الأبواغ بين مرضى نقص المناعة المترددين على مستشفى الثورة بمدينة إب- اليمن. طريقة جمع العينة (87) عينة من البراز تم جمعها من المرضي بين شهر نوفمبر 2016م ويوليو 2017م. تم فحص عينات البراز بحثًا عن طفيل الخفية الأبواغ باستخدام طريقة تركيز الفورمالين الأثير وطرق Ziehl- Neelsen ومقايسة الامتصاص المناعي المرتبط بالإنزيم (اليزاء) (ELISA). تم جمع البيانات المطلوبة من خلال استبيان مصمم. وأظهرت النتائج بأن المعدل الإجمالي للعدوى بطفيل الخفية الأبواغ كان 71.26% لوحظ بين المرضى الذين يعانون من نقص المناعة، وكان لكل من الذكور والإناث معدلات تكرار متقاربة للعدوى. تم تسجيل أعلى معدل للإصابة بنسبة 80% في الفئة العمرية أقل من 10 سنوات وبنسبة 78.3% بين المرضي القادمين من الريف. كما وجد أن 83.33% من المرضى المصابين يشربون من مياه الأنابيب مع وجود دلالة معنوية ($P<0.05$). بالإضافة إلى ذلك، وجد بأن الأفراد المخالطين للحيوانات مصابين بنسبة 73.81%. وجد بأن معدل الإصابة كانت أكثر بين مرضي الفشل الكلوي المزمن (53.2%)، وللأورام الخبيثة (42%)، وبنسبة 4.8% بين مرضى زراعة الكلى. كانت الآعراض السريرية الأكثر شيوعًا هي الإسهال والتوعك وضعف الشهية وفقدان الوزن وآلام البطن والحمى. وبالمثل، عانى 90.3% و 97.8% من الحالات من الإسهال شبه السائل والإسهال الحاد على التوالي. التوصيات هناك حاجة ماسة لتنفيذ برامج التثقيف الصحي لمنع ومكافحة انتقال طفيليات خفية الأبواغ بين الأفراد الذين يعانون من ضعف المناعة.

الكلمات المفتاحية: طفيل الخفية الأبواغ، مدينة إب، مرضى نقص المناعة، الحدوث، اليمن.

1. Introduction.

Cryptosporidium parvum is a small pathogenic protozoan with global distribution and is considered to be the highest prevalence in developing countries in particular among the children. This parasite is an obligate intracellular protozoan parasite that is able to infect the gastrointestinal epithelium cells of vertebrates especially humans with cryptosporidiosis diseases **(Ryan *et al.*, 2016; Shrivastava *et al.*, 2017).**

The parasites mostly, transmit and infect humans by ingestion of the oocysts via contaminated food or water with fecal resulting from infected humans or animals **(Lima *et al.*, 2011)**. The *Cryptosporidium* infection considers one of the most significant causing diarrhea among humans worldwide that ranged from 1% to 3% in the US and Europe and between 10- 15% in developing countries. The *C. parvum* and *C. hominis* are mostly responsible for more than 90% of all cases caused by *Cryptosporidium* species **(Xiao, 2010; Lima *et al.*, 2011; Shrivastava *et al.*, 2017).**

The frequency rate of cryptosporidiosis among humans differs from one country to another around the world. It was ranged from 0.1–9.1% in developed countries and between 2.98–25.9% in developing countries **(Fletcher *et al.*, 2012; Kalantari *et al.*, 2018).** In the Arabic counties, the *Cryptosporidium* infection was recorded at 4.5% in Qatar (**Boughattas *et al.*, 2019)**, 58% in Najaf, Iraq **(Sayal, 2019).**

Few studies were conducted in different regions of Yemen that documented the frequency rate of cryptosporidiosis ranging from 24% to 78% among participated patients **(Al- Shibani *et al.*, 2009; Al-Shamiri *et al.*, 2010; Alyousefi *et al.*, 2013; Shamsan *et al.*, 2019).**

However, *Cryptosporidium* species are opportunistic gastrointestinal parasites that maybe lead to serious problems for patients having immunodeficiencies diseases **(Bouzid *et al.*, 2013).** *Cryptosporidium* species cause acute or chronic diarrhea syndrome among immunocompromised individuals that are frequently accompanied by abdominal pain, dehydration, mal- absorption, and weight loss **(De Oliveira- Silva *et al.*, 2007).**

Moreover, hemodialysis and cancer patients are well known to experience immune suppression, therefore they are more susceptible to acquire *Cryptosporidium* infection than any other patient **(Sulzyc-Bielicka *et al.*, 2012; El- Kady *et al.*, 2018).** In Saudi Arabia, the occurrence rate of *C. parvum* was 8.1% recorded among immunocompromised individuals **(Al- Megrin, 2010).** Also, in Sana'a- Yemen it was observed that the *C. parvum* was 27.5% recorded among immunocompromised individuals **(Al- Qobati *et al.*, 2018).**

At this time, there are no data determined the occurrence of *C. parvum* among immunocompromised patients in Yemen. So, the present study was designed to find out the incidence of *Cryptosporidium parvum* among immunocompromised patients in Ibb city, Yemen.

2.Materials and Methods.

2.1. Study Area and Period:

The current study is a cross- sectional descriptive was conducted in the Al- Thawra hospital in the Ibb city which is located about 194 km south of Sana'a, between the period of November 2016 to July 2017.

2.2. Study Population:

The participants in this study were immunocompromised patients, both male and female, aged between 5 to 65 years who recurrent at cancer and dialysis centers at the Al- Thawra hospital during the study period.

2.3. Sample Size:

Samples sizes were calculated by Epi Info 2000- CDC using random sampling. The calculated minimum sample size was equal to 87 patients at a 95% confidence level with a high expected frequent rate of 5% and worst (least) the acceptable rate of 1%.

2.4. Data Collection:

That relevant data were collected before specimen collection, a pre- tested questionnaire was subjected for each participant in this work and filled via direct interviews with the patient. The demographic information such as sex, age, resident area, the clinical information regarding diarrhea diseases, and environmental factors like; the source of drinking water and the presence of animals inside the house.

2.5. Inclusion and Exclusion:

The inclusion criteria were patients who classified as an immunocompromised status and consented to participate in this study. Also, exclusion criteria were all patients didn't consented to participate.

2.6. Specimens Collection:

The stool specimen was collected under aseptic conditions from each patient in a dry, sterile, leak-proof container (60 mL). Each participant was given a labeled container and instructed with the correct way for collecting the stool specimen that immediately was transported to a medical laboratory for parasite identification.

2.7. Specimens Examination.

2.7.1. Microscopic Examination:

The collected specimens were independently examined by microscopic examination of prepared smear from formalin- ether fixed that stained by the modified Ziehl- Neelsen staining techniques according to Garcia (2007).

2.7.2. Serological Test (ELISA):

Enzyme- linked immunosorbent assay (ELISA) technique also was used to confirm the presence of the *Cryptosporidium* antigen in all collected stool specimens by using the ELISA DRG® *Cryptosporidium* Ag (stool) (EIA- 3467) (DRG international Inc, USA). The analysis procedure was followed according to the manufacturer's instructions.

2.8. Data Analysis:

The obtained findings were analyzed by using the SPSS program (20 version). The significance of the difference in proportion between the variables was analyzed by Pearsons Chi- square ($\chi 2$) which is equal to or greater than 3.84. Also, P- value ≤ 0.05 was considered statistically significant.

2.9. Ethical Statements:

The ethical statement of the current study was approved by the Ethical Committee of the College of Medical Science, Sana'a University and the Al- Thawra hospital in Ibb city. The purpose of this work was orally explained before the beginning of data collection to all healthcare staff and participants in this study. Research permissions were obtained from the health office and Al- Thawra hospital administration. Written consent was also obtained from all patient- participants.

3.Results.

In the present results, eighty- seven (87) collected specimens of immunocompromised patients were subjected in this work, 47 (54.02%) samples from males and 40 (45.98%) from females. The high specimens were collected from age group >50 (22.29%) who coming from the rural area 60 (68.97%), and drinking from piped water 48 (55.17%). Also, the high specimens were collected from poor personal hygiene (55.17%) poor food sanitation (55.17%), poor nutrition (58.62%), and contact with animals (55.17%) as listed in Table (1).

Table (1) Socio- demographic data of collected specimens

Variables		No. examined	%
Sex	Male	47	54.02
	Female	40	45.98
Age groups in years	<10	5	5.75
	11- 20	9	10.34
	21- 30	13	14.94
	31- 40	18	20.69
	41- 50	20	22.99
	>50	22	25.29
Resident area	Urban	27	31.03
	Rural	60	68.97
Sources of water	Piped water	48	55.17
	Wells	39	44.83
Personal hygiene	Poor personal hygiene	48	55.17
	Poor food sanitation	48	55.17
	Poor nutrition	51	58.62
	Family diarrhea	8	9.19
	Traveling	9	10.34
	Contact with animals	42	48.28

The present result showed that the overall rate of *C. parvum* was 62 (71.26%) among immunocompromised patients. The result according to sex found that the male and female had nearly equal frequency rates of infection with 70.21% and 72.50%, respectively. The highest incidence was (80%) among the age group less than 10 years and the lowest rate was 55% recorded among the group age 41- 50 years. Patients coming from the rural area showed (78.3%) higher with *C. parvum* infection than patients from the urban area (55.5%). Also, the highest rate of *C. parvum* infection was recorded among patients drinking from piped water with 83.33% with a significant difference ($P < 0.05$) in relation to the source of water and infection. Regarding personal hygiene, it was observed that patients with contact with animals were 73.81% more exposed to *C. parvum* infection that summarized in Table (2).

Table (2) Characteristics of immunocompromised patients infecting by *C. parvum*

Variables		No. examined	Positive cases No. (%)	OR	CI	χ^2	*P*
Sex	Male	47	33 (70.21)	-	-	-	-
	Female	40	29 (72.50)	-	-	-	-
Age groups in years	<10	5	4 (80)	-	-	0.8	0.3
	11- 20	9	7 (77.78)	-	-	0.34	0.55
	21- 30	13	10 (76.92)	-	-	0.22	0.63
	31- 40	18	14 (77.78)	-	-	0.11	0.7
	41- 50	20	11 (55)	-	-	1.5	0.2
	>50	22	16 (72.73)	-	-	0.08	0.77
Resident area	Urban	27	15 (55.5)	0.5	0.2- 1.4	1.9	0.16
	Rural	60	47 (78.3)	0.5	0.1- 1.4	2.3	0.1
Sources of water	Piped water	48	40 (83.33)	3.9	1.31- 1.7	7.6	0.005
	Wells	39	22 (56.41)	0.3	0.1- 0.7	7.6	0.005
Personal hygiene	Poor personal hygiene	48	33 (68.75)	0.04	0.1- 1.3	2.6	0.1
	Poor food sanitation	48	5 (10.42)	0.6	0.1- 3.7	0.3	0.5
	Poor nutrition	51	5 (9.80)	0.5	0.1- 2.5	1.2	0.3
	Family diarrhea	8	5 (62.5)	1.5	0.4- 5.4	0.5	0.47
	Traveling	9	4 (44.4)	0.66	0.2- 2.3	0.52	0.47
	Contact with animals	42	31 (73.81)	0.5	0.1- 1.4	2.3	0.1

OR= odds ratio, **CI**=Confidence intervals, χ^2 = Chi- square ≥3.84 (significant), ***P***<0.05 (significant)

The present result observed that the high- frequency rate was 53.2% recorded among chronic renal failure patients followed by malignancy patients (42%), and renal transplant with 4.8%. Also, there was no statistical significance with the types of immunocompromised diseases as listed in Table (3).

Table (3) Frequency rate of *C. parvum* among immunocompromised patients

Type of immunocompromised diseases	No. examined	Positive cases No. (%)	OR	CI	χ^2	*P*
Malignancy	35	26 (42)	1.3	0.5- 3.7	0.26	0.6
Chronic renal failure	49	33 (53.2)	0.9	0.7- 1.15	0.84	0.35
Renal transplant	3	3 (4.8)	1.42	1.24- 1.64	1.25	0.26

OR= odds ratio, **CI**=Confidence intervals, χ^2 = Chi- square ≥3.84 (significant), ***P***<0.05 (significant)

Table 4 shows that the clinical features accompanied by *C. parvum* infection among patients. It was found that 100% of patients presented with diarrhea, 90.3% with malaise, 83.9% with poor appetite, 80.6% with weight loss, 77.7% with abdominal pain, and the lowest rate was 30.6% reported for the presence of vomiting. Also, the result of the statistical analysis reported there was no statistical significance between the prevalence of *C. parvum* infection and clinical features as shown in Table (4).

Table (4) Clinical features among infected patients with *C. parvum*

The symptoms and signs	Positive cases		χ^2	*P*
	NO	%		
Diarrhea	62	100	-	-
Abdominal pain	48	77.4	0.47	0.49
Vomiting	19	30.6	1.01	0.3
Nausea	34	54.8	0.06	0.8
Fever	36	58.1	0.03	0.8
Weight loss	50	80.6	3.3	0.06
Poor appetite	52	83.9	0.19	0.66
Malaise	56	90.3	0.7	0.4

χ^2 Chi- square ≥3.84 (significant), ***P***<0.05 (significant)

The current findings revealed that semi- liquid diarrhea (90.3%) was the most reported among participated patients and no cases were with bloody diarrhea. Also, all patients were completely (100%) suffered from recurrent diarrhea followed by acute diarrhea at 97.8% while chronic diarrhea was the lower rate found among patients at 3.2% (Table 5).

Table (5) Type of diarrhea manifestation among infected patients

Type of diarrhea and diarrheal manifestation		No. examined	Positive cases No. (%)	χ^2	*P*
Type of diarrhea	Watery	6	6 (9.7)	2.6	0.1
	Semi liquid	81	56 (90.3)	2.6	0.1
	Bloody	0	0	-	-

Type of diarrhea and diarrheal manifestation		No. examined	Positive cases No. (%)	χ^2	*P*
Diarrheal manifestation	Chronic diarrhea	2	2 (3.2)	0.83	0. 36
	Acute diarrhea	85	60 (97.8)	0.83	0.36
Recurrent diarrhea		87	62 (100)	-	-

χ^2=Chi- square ≥3.84 (significant), ***P***<0.05 (significant)

This result showed the intensity presence of *C. parvum* parasite (oocysts stage) in the patient stool. The highest rate of slight infection was 51 (82.3%) recorded and the lowest was 1 (1.6%) reported for severe infection among immunocompromised patients with significant difference (*P*< 0.05) in relation to the intensity of infection (Table 6).

Table (6) *C. parvum* intensity among infected immunocompromised patients

Intensity of infection	Number of cases	Percentage	*P*
Slight infection	51	82.3	<0.00001
Moderate infection	10	16.1	
Severe infection	1	1.6	
Total	62	100	

Slight: 1- 5 oocysts, Moderate: 6- 10 oocysts, Severe: >10 oocysts, ***P***<0.05 (significant)

Table 7 shows the effective of technique used for detection the *Cryptosporidium* parasite. The M.Z.N stain technique showed 71.3% of specimens having a positive for *Cryptosporidium* infection while the ELISA technique showing the 93.1% of examined specimens were positive for *Cryptosporidium* antigen

Table (7) The positive rate of *C.parvum* by M.Z.N stain and by *Cryptosporidium* antigen (ELISA) methods

Methods of diagnosis	Positive cases	
	No	%
Modified Ziehl- Neelsen stain (MZ.N) n=87	62	71.3
Cryptosporidium antigen (ELISA) n=87	81	93.1

4. Discussion.

The current study revealed that the occurrence rate of *C. parvum* was 71.26% recorded among immunocompromised patients. This finding is higher than previous studies reported by **Baiomy *et al.* (2010)** in Egypt found that 7% of immunocompromised patients were infected with *C. parvum* parasite. Also, in Saudi Arabia, it was observed that the prevalence rate of *C. parvum* was 8.1% **(Al- Megrin, 2010).** A study by **Cengiz *et al.* (2017)** revealed that 11.3% of cases of immunocompromised patients in

Turkey were positive for *C. parvum* infection. Recently, it was observed that *C. parvum* was 27.5% recorded among immunocompromised individuals in the Sana'a city, Yemen **(Al- Qobati *et al.*, 2018).**

The high rate in the occurrence of *C. parvum* may be most likely to elucidate by many reasons such as the patients' immune state, personal habitats, environmental factors, and variation of the season.

The occurrence rate of *C. parvum* infection was 70.21% and 72.50%, respectively, recorded among the male and female immunocompromised patients on demonstrating both genders are equally susceptible to infection. These findings are on an agreement with the results of **Zali *et al.* (2004)** and **Al-Megrin (2010).**

The highest incidence was 80% recorded among age group less than 10 years and the lowest rate was 55% recorded among the age of 41- 50 years. This finding was in line with earlier studies that found the distribution of infection among the age groups was more common in less than 10 years old **(Al-Megrin, 2010; Al- Shamiri *et al.*, 2010; Sayal, 2019).** The children at age less than 10 years could be more susceptible to *Cryptosporidium* parasite due to many factors such as lack of hygiene awareness between them, stay for long- time outdoor plying in soil and sewage water, and their weak immune state **(Yu *et al.*, 2004; Samie *et al.*, 2006; Mogalli *et al.*, 2020).**

The present finding revealed that the cases coming from the rural area had the highest rate of *C. parvum* infection. Various earlier investigations have been documented the high rate of *Cryptosporidium* infection among cases coming from a rural area **(Al- Shamiri *et al.*, 2010; Elshahawy and AbouElenien, 2019).**

The high prevalence of *Cryptosporidium* parasites in rural areas could be due to many factors such as lack of hygienic practices, agriculture background, lack of clean drinking water, and contact directly with domestic animals.

Moreover, the current work found that the high number of cases was 83.33% recorded among patients drinking from piped water and there are statistically significant. These results were in line with earlier reports that indicated an inadequate treatment of water considered as the most significant source for *Cryptosporidium* infection **(Antonios *et al.*, 2001; Hassl *et al.*, 2001).**

The unsafe water coming from piped water maybe referred to as inefficient coagulation, filtration, and poor disinfection during water treatment. Also, post- treatment contamination could be occurred and entered the piped distribution system **(Betancourt and Rose, 2004; Alshahethi *et al.*, 2020a).**

The present investigation noticed that 73.81% of individuals in contact with animals were positive for *C. parvum* infection. Also, poor hygiene practices were more contributed to the prevalence of *C. parvum* infection among studied cases. These results are in agreement with previous works that reported the most prevalence of intestinal parasitic infection was completely related to personal hygiene variables **(Alshahethi *et al.*, 2020b; Qasem *et al.*, 2020).**

The current study revealed that the frequency rate of *C. parvum* infection was 53.2% recorded for chronic renal failure, 42% for malignancy, and 4.8% for renal transplant patients. Similar results were obtained from many researchers. In Sana'a, **Al- Qobati *et al.* (2012**) found 30.1% of cancer patients infecting with *C. parvum*. Also, in Egypt, **El- Kady *et al.* (2018)** reported that the *Cryptosporidiosis* prevalent rate was 66% recorded among chronic renal patients. The lower rate of infection was 11% documented among also chronic renal patients in Jordan **(Zueter *et al.*, 2019).**

The current work observed that diarrhea, malaise, poor appetite, weight loss, abdominal pain, and fever were the most clinical features frequently encountered in the *Cryptosporidium* infection. Also, it was found that 90.3% and 97.8% of cases suffering from semi- liquid diarrhea and acute diarrhea, respectively. In addition, a complete of the cases were presented with recurrent diarrhea manifestation. These findings were in line with different reports that recorded that acute and persistent diarrhea, abdominal pain, fever, and weight loss were the most observed clinical features significantly associated with *Cryptosporidium* infection **(Sanad *et al.*, 2014; Elshahawy and AbouElenien, 2019).**

The association between *Cryptosporidium* infection and diarrhea has been documented. The infection by *Cryptosporidium* parasite causes fleeting destruction of microvilli and crypt hyperplasia with inflammatory cell infiltration and quickly recovered in individuals with a competent immune system. Whereas infections can lead to chronic diarrhea, water- electrolyte imbalances, malnutrition, and even death among underdeveloped or compromised immune systems **(Bouzid *et al.*, 2013; Widerström *et al.*, 2014).**

This result revealed that the highest rate of slight infection was reported among 82.3% of cases and only 1.6% of immunocompromised patients were reported as a severe infection. The high prevalence of diseases, especially intestinal parasites in Yemen, is due to or attributed to many factors that play a major role in the spread of these diseases. These factors representing living conditions, economic and environmental situations, lack of health awareness among the population, lack of health infrastructure and sanitation, and lack of clean drinking water.

5.Conclusion.

From this study, it was concluded that the high prevalence of Cryptosporidium infection among Yemeni immunocompromised patients exposes their life to high risks that including persistent diarrhea and health complications throughout their life. Many factors contributed greatly to the spread of this disease which was given us an understanding of some methods of controlling and preventing disease transmission. Therefore, health education programs are established between the community in general and patients in particular to avoid and prevent the transmission of the disease among them.

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