CRYPTOSPORIDIOSIS IN CHILDREN – CLINICAL FORMS AND CLINICAL CASES

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ABSTRACT
Cryptosporidiosis is one of the most common causes of diarrhoea worldwide, especially in the vulnerable groups of children between 0-5 years and immunocompromised individuals.

The purpose of the study is to estimate the prevalence of the Cryptosporidium infection in children from North-eastern Bulgaria and to determine the specifics of the clinical forms through the detailed description of several clinical cases.

Material/Methods: Stool samples of 458 children were investigated for the presence of Cryptosporidium spp. oocysts with specialized modified Ziehl–Neelsen staining and with an immunological test for detection of stool antigens. Prevalence estimates are presented in four groups - aged less than five years with or without symptoms and more than five with or without symptoms.

Results: The overall prevalence of cryptosporidiosis in children from North-eastern Bulgaria is 2.18% with the highest incidence (3.06%) in the age group between 0-5 years with diarrhoea. All different types of infestation of the gastrointestinal tract are observed, from an acute infection that requires hospitalization, through mild or persistent diarrhoea and asymptomatic invasion (1.53%). For each of the described forms, the details of the clinical presentation, laboratory and physical findings are presented as separate clinical cases.

Conclusions: Our findings demonstrate that the spectrum of clinical forms of Cryptosporidium-associated diarrhoea in children exist but up till this study are typically mis- or undiagnosed. The tendency that exists in Eastern European countries, including ours, to neglect or underestimate the impact of cryptosporidiosis, is particularly dangerous and should be changed especially in the risk groups of children and immunocompromised adults.

Keywords: Cryptosporidium, cryptosporidiosis, cryptosporidiosis in children, clinical forms, diarrhoea

INTRODUCTION
Cryptosporidiosis is a diarrhoeal illness that in humans is most commonly caused by Cryptosporidium hominis or C. parvum. It has a worldwide distribution facilitated by all routes of the fecal-oral mechanism– human to human, zoonotic, water- and foodborne. The clinical course of cryptosporidiosis includes varying in severity and duration diarrhoea, depending on numerous characteristics of the infected host: age, nutrition, co-infections and immunity [1–5]. The age of the host is the main factor in the pathophysiology of the cryptosporidiosis. The most vulnerable are children between the ages of 0 and 5 years, especially those younger than two years. The immature immune system (especially the mucosal immunity) and the increased chance for environmental exposure lead to a more severe course of cryptosporidiosis in infancy [1, 2].

The last Global Burden of Disease Study (2010-2015) estimates that infectious diarrhoea contributes approximately 1.3 million deaths globally [4,6]. The three leading causes in the most affected group of children up to 5 years are rotavirus enteritis, cryptosporidiosis and shigellosis [4,6]. Recent epidemiological studies using PCR and antigen detection tests show that Cryptosporidium spp. is identified in 15–25% of the children with diarrhoea, which renders this parasitosis severely underdiagnosed and probably even more prevalent than was previously estimated [2]. Cryptosporidiosis-associated involvement of the intestinal tract can be classified into several clinical forms. Acute diarrhoea with intoxication and risk of dehydration is mainly observed in newborns and small children (<two years). Persistent and chronic diarrhoea can be a significant problem in children with predispositions (malnutrition, comorbidity) or severely immunocompromised individuals. Especially in developing countries, it leads to weight loss and stunting in children’s development. Most common are the sporadic cases of mild and self-limited diarrhoea in children of all ages and immune-competent adults. The same groups are the ones where asymptomatic infestation with Cryptosporidium spp. is also described [1, 7]. These last two “undetectable” conditions enable the easy spread of the infection among the general population and the other susceptible individuals. In patients with primary or secondary immunosuppression Cryptosporidium spp. are commonly identified as opportunistic pathogens causing life-threatening atypical and extra-intestinal forms other than diarrhoea.[1, 3, 5, 8]

The aim of this study is to estimate the prevalence of cryptosporidiosis in children from North-eastern Bulgaria in two age groups – between 0-5 years and over 5 years. In addition, we aim to outline the specifics of the different
clinical forms of diarrhoea caused by *Cryptosporidium* spp. in children through the description of several clinical cases.

**MATERIAL AND METHODS**

A total number of 458 children (age between 0 months up to 18 years) were tested for cryptosporidiosis between 2014 and 2018 in one of the Parasitology laboratories in Northeastern Bulgaria. All patients included in the study submitted at least one stool specimen for morphological identification of intestinal parasites (IP). The specimens were collected in labelled plastic vials, transported to the laboratory and stained or fixed at the day of the collection. To maintain patient confidentiality, only demographic data (sex, age, and residence) was obtained. For the morphological identification of *Cryptosporidium* spp. oocyst, three slides per patient were prepared and stained with the modified Ziehl–Neelsen stain (mZNS) for selective identification of coccidian parasites according to a standardized staining protocol [9]. In a fraction of the samples (~30%) the morphological examination was aided by immunological detection of stool antigens using enzyme immunoassays (ELISARidascreen® *Cryptosporidium*) or immunochromatographic tests (RIDA® Quick *Cryptosporidium/Giardia* Combi).

Descriptive statistics and prevalence estimates are presented within the 95% confidence intervals.

**RESULTS**

The outcomes of the morphological and immunological tests for identification of *Cryptosporidium* spp. in children were pooled into single positive or negative result, one for each patient, regardless of the number or type of tests performed. The positive findings in the investigated groups (children ≤ 5 years with or without symptoms and 5+ with or without symptoms) are presented in Table 1 with the corresponding prevalence estimates. The overall prevalence is 2.18% ± 1.34% with the highest frequency (3.06% ± 2.24%) in children between 0-5 years with diarrhoea. The ratio of infestation with *Cryptosporidium* spp. in asymptomatic children (1.53% ± 2.11%) is another important result.

**Table 1.** Prevalence of cryptosporidiosis in symptomatic and asymptomatic children in different age groups.

|                     | Symptomatic |  | Asymptomatic |  | Total |  |
|---------------------|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                     | Tested /+/  | Prevalence (%)  | Tested /+ /  | Prevalence (%)  | Tested /+/  | Prevalence (%)  |
|                     | p=0.05      | ± CI, p=0.05    | p=0.05        | ± CI, p=0.05    | p=0.05        | ± CI, p=0.05    |
| Children 0-5 y.     | 229 7 3.06  | ± 2.24          | 79 1 1.27     | ± 2.49          | 308 8 2.60     | ± 1.78          |
| Children > 5 y.     | 98 1 1.02   | ± 2.01          | 52 1 1.92     | ± 2.77          | 150 2 1.33     | ± 1.84          |
| Children total      | 327 8 2.45  | ± 1.68          | 131 2 1.53    | ± 2.11          | 458 10 2.18    | ± 1.34          |

Numerous factors defining the severity of the clinical manifestation (age, number of stools daily, general condition, signs of dehydration, laboratory results, etc.) as well as the subsequent necessity for hospitalization were analyzed, and all cases with confirmed cryptosporidiosis were stratified into four specific clinical forms (Figure 1) - acute diarrhoea with a risk of dehydration that requires hospitalization (n=3), mild diarrhoea with ambulatory treatment (n=4), persistent diarrhoea (n=1) and asymptomatic invasion (n=2). Thorough information of the clinical presentation, physical signs, general laboratory and parasitology results and the treatment are presented on Table 2 with the detailed descriptions of four of our clinical cases, each for every one of the defined clinical forms. No atypical or extraintestinal forms were detected in the examined children with immunosuppression caused by malnourishment or oncohematological disorders.

**Fig. 1.** Clinical forms of cryptosporidiosis in children

![Clinical forms of cryptosporidiosis in children](https://www.journal-imab-bg.org/jimab/26/jimab2612986.jpg)
Table 2. Clinical features of four clinical cases with different clinical forms of cryptosporidiosis

| Clinical form | Acute diarrhearequiring hospitalization | Mild diarrheawith ambulatory treatment | Persistent diarrhea | Asymptomatic cryptosporidiosis |
|---------------|----------------------------------------|---------------------------------------|---------------------|-------------------------------|
| **Cases:** | **Patient 1.** | **Patient 2.** | **Patient 3.** | **Patient 4.** |
| **Age and sex:** | 2 years old / boy | 4 years old / boy | 6 years old / girl | 5 years old / girl |
| **Residency:** | Small village / Varna district | Small village / Varna district | Small town / Northeastern Bulgaria | Small village / Northeastern Bulgaria |
| **Background/ Epidemiology history:** | Frequent contacts with pets and other animals. | Frequent use of local water source (well) for drinking and household purposes. | Consumption of home-grown vegetables; contact with animals. | Contact with newborn pet (dog) and other animals (chickens, lambs). |
| **Clinical presentation:** | Acute onset with nausea, vomiting, stomach aches, watery diarrhea (> 5 stools/day) and fever (38°C) for 3 days before hospitalization. | Acute onset with nausea, stomach aches, watery diarrhea for 2 days (> 5 stools/day) and before outpatient examination. | Acute diarrheal episode for 2 days (> 4 stools/day) followed by intermittent stomach aches and/or loose stools 3 weeks of before examination. | No diarrhea. The stool sample is submitted for the required routine annual checkup for intestinal parasites of children between 2-7 years of age. |
| **Physical examination:** | Moderately impaired general condition. Fieberle (37.8°C), adequate but week. Skin: pale and dry, with reduced turgor, without exanthema. Tongue: dry. Heart: tachycardia. Lungs, liver, urinary and CNS: without significant changes. Abdomen: enhanced peristalsis and tenderness. | Mildly impaired general condition. Afebrile, adequate, irritable. Skin: without exanthema. Tongue: dry. Heart, lungs, liver urinary and CNS: without significant changes. Abdomen: enhanced peristalsis and tenderness. | Good general condition. Afebrile, adequate. Skin, tongue, throat: without significant changes. Heart, lungs, liver urinary and CNS: without significant changes. Abdomen: mild tenderness. | Physical status: without significant changes. Afebrile, adequate. Heart, lungs, liver urinary and CNS: without significant changes. Abdomen: without tenderness. |
| **Laboratory tests:** | CBC: HGB-126 g/l, HCT-0.344, RBC-4.61x10^12/l, WBC-8.42x10^12/l, PLT-382x10^9/l; CRP: 1.04 mg/l; Acid-base balance: moderate metabolic acidosis on admission, corrected on the second day. Electrolytes: K-3.1-4.87 (mild hypokalemia), Na-140-139, Cl-106-109 mm/l. Urinalysis: ketones – / -/+ positive on the first day: without changes of the other parameters. | CBC: HGB-139 g/l, HCT-0.390, RBC-4.61x10^12/l, WBC-10.97x10^12/l, PLT-352x10^9/l; CRP: 2.13 mg/l. Urinalysis: without significant changes. | CBC: without significant changes. Urinalysis: without significant changes. | CBC: without significant changes. Urinalysis: without significant changes. |
| **Parasitology tests:** | mZNS: high number of Cryptosporidium spp. oocysts | mZNS: Cryptosporidium spp. oocysts. ELISA: /+ positive for Cryptosporidium spp. coproantigens | mZNS: small number of Cryptosporidium spp. oocysts. Immunochromatographic tests: /+- copro- | mZNS: small number of Cryptosporidium spp. oocysts. Immunochromatographic tests: /+ positive. |
intestinal parasites as even higher than the prevalence of other more well-known infections (2.16%) is comparable or higher than the findings reported by similar research, those cases would have remained undiagnosed (as they usually do) and can persist as constant carriers of infection while in the children over 5 years the occurrence of cryptosporidiosis is almost halved (prevalence – 1.33%). This shows that one positive result in just one field of investigation doesn’t exclude the presence of other intestinal pathogens, thus requiring more specialized procedures as such for Cryptosporidium identification or multidisciplinary approach with microbiology and virology tests. Comorbidity of the GI tract with intestinal bacteria, viruses and parasites especially in the youngest children (<5 years) is a significant problem, demonstrated by numerous studies in the region [11, 15–18].

Another important presentation of cryptosporidiosis is the persistent (>two weeks) and in some cases chronic diarrhea, especially in children with predispositions. In our case (Patient 3), we can attribute the prolonged infection to the comorbidity with other intestinal parasites (B. hominis and G. duodenalis). This shows that one positive result in just one field of investigation doesn’t exclude the presence of other intestinal pathogens, thus requiring more specialized procedures as such for Cryptosporidium identification or multidisciplinary approach with microbiology and virology tests. Comorbidity of the GI tract with intestinal bacteria, viruses and parasites especially in the youngest children (<5 years) is a significant problem, demonstrated by numerous studies in the region [11, 15–18].

Most common among the investigated children were the cases with mild diarrhea (3-5 stools daily) that does not require hospitalization (n=4). Alongside with the asymptomatic infections, those clinical forms comprise 60% of the confirmed cases. At first glance, both conditions that lack significant physical and laboratory signs of the infection may include physical and laboratory signs of dehydration - pale and dry skin, tachycardia, impaired general condition, metabolic acidosis, hypokalemia, etc., as demonstrated by the first clinical case (table 2).

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tious Cryptosporidium oocyst for a prolonged period, in some cases even over 2 months [1]. Furthermore, some studies demonstrate that even an asymptomatic infection can sometimes lead to stunt weight and growth in children [2].

**CONCLUSIONS**

This first epidemiological study and revealed cases of cryptosporidiosis in children of Northeastern Bulgaria demonstrate several important problems.

All possible clinical forms of cryptosporidiosis (from asymptomatic infection to the acute, severe diarrhoea with dehydration) occur in the population. This contradicts with the general approach in the clinical practice in the country where, in contrast with bacterial and viral agents, parasites are rarely considered by physicians as a potential cause of diarrhoeal disease. This tendency to underestimate cryptosporidiosis is especially hazardous in both risk groups of children and immunocompetent adults. Thus, it is necessary the examination for cryptosporidium infection to be mandatory in any type of diarrhoeal episode in the following risk groups:

- Children between 0-5 years with acute, persistent or chronic diarrhoea, particularly if it requires hospitalization.
- Children of all age groups (especially between 0-5 years) living in risk - poverty, malnutrition and growth retardation, minorities or immigrant populations, institutionalized etc.
- Children of all age groups with immunodeficiencies - primary immune deficiencies syndromes, acquired immune deficiency (HIV/AIDS), oncological diseases (lymphomas, leukemias and other oncohaematological disorders), bone marrow or solid organ transplant recipients, on hemodialysis etc.

Cryptosporidiosis is a disease that requires mandatory reporting from all European countries. However, in both the official information and systematic regional overviews the data conveyed from the Eastern European countries, including Bulgaria, comprise of only single accidentally discovered cases. Our proactive research demonstrates that cryptosporidiosis occurrence in children is much higher than previously reported. This translates erroneously into the lowest morbidity as compared to other parts of the continent and undoubtedly underestimates the burden of the infection in children.

**Abbreviations (in text and tables):**

- IP - intestinal parasites
- mZNS - modified Ziehl–Neelsen stain

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