Cryptosporidiosis and the Ears of the Hippopotamus

A. Clinton White, Jr
Department of Internal Medicine, Infectious Disease Division, University of Texas Medical Branch, Galveston, Texas

(See the article by Mor et al, on pages 1366–1372.)

Despite the fact that Cryptosporidium was identified more than 100 years ago, the first human cases were only reported in 1976, and only a handful of cases were diagnosed before the discovery in 1982 of Cryptosporidium as a major cause of diarrhea in patients with AIDS [1]. During the next 5 years, Cryptosporidium was recognized as an important cause of waterborne episodes of diarrhea, childhood diarrhea both in wealthy and resource-limited countries, and sporadic diarrhea in adults. Among the causes of childhood diarrhea in resource-limited countries, cryptosporidiosis has been particularly linked to persistent diarrhea, which causes malnutrition, increased susceptibility to other pathogens, and chronic sequelae [2, 3]. Still, many physicians only associate cryptosporidiosis with diarrhea in AIDS. With the improvement of antiretroviral therapy, cryptosporidiosis has been disappearing from many physicians’ minds altogether, at least in wealthy countries.

By contrast, data suggest that illness due to Cryptosporidium in patients with AIDS accounts for only a tiny portion of the overall burden of illness due to Cryptosporidium. In fact, cryptosporidiosis in patients with AIDS may be like the ears of a hippopotamus, a small exposed area that warns of a larger and more dangerous problem lurking below the surface [4]. Between a quarter and a third of adults in wealthy countries have serologic evidence of prior cryptosporidiosis, but the number of diagnosed cases accounts, at most, for 1% of those potential cases.

There are a number of pieces of data that point to massive underdiagnosis as the cause of this discrepancy. For example, during the massive waterborne outbreak of diarrhea due to Cryptosporidium hominis that occurred in Milwaukee, Wisconsin, in 1993, <1% of cases were confirmed parasitologically [5, 6]. By contrast, serologic evidence supported an estimate of >400,000 infections [7]. The reason that only a small proportion of cryptosporidiosis cases are identified are numerous. Physicians do not routinely check for parasites in patients with watery diarrhea. When samples are sent for parasitologic studies, laboratories often do not uniformly perform tests to detect Cryptosporidium (which requires specialized techniques, including modified acid-fast or fluorescent staining, antigen detection, or polymerase chain reaction [PCR]) [8]. Indeed, the number of cases reported in the United States has more than doubled during the past few years, from <4000 to ~8000 cases per year, which appears to be mostly attributable to increased use of appropriate diagnostic tests [9].

Studies using PCR have documented increased rates of detection of Cryptosporidium. For example, Nair and colleagues noted Cryptosporidium in 6% of cases of traveler’s diarrhea [10]. In addition, PCR studies have documented increased rates of Cryptosporidium in diarrhea in people from wealthy countries [11]. Several studies have documented Cryptosporidium infection in 15%–25% of children with diarrhea in resource-limited countries (compared with rates of 5%–10% obtained using acid-fast staining) [12–14]. Clearly, better diagnostic tests that carry the sensitivity of PCR but do not require specialized procedures or technology are needed.

In addition to the role of cryptosporidiosis in diarrhea, there is some evidence of extraintestinal involvement with cryptosporidiosis. Biliary tract involvement is a well-recognized complication of Cryptosporidium infection in patients with AIDS (AIDS cholangiopathy). This complication is even more frequent in patients with hyper-immunoglobulin M syndrome. Respiratory cryptosporidiosis is also a rarely recognized complication of cryptosporidiosis in patients with AIDS. Although cough is a common concern of childhood cryptosporidiosis, few data are available on the cause and on whether it is due to respiratory tract infection.

In this context, Mor et al [15] studied children who presented with diarrhea to an acute care unit in Uganda. After excluding patients with vomiting who might have aspirated the organisms, the authors
induced sputum from 48 children with diarrhea and cryptosporidiosis and respiratory symptoms. Surprisingly, 17 (35%) of these samples had Cryptosporidium DNA according to nested PCR. In some cases, the respiratory symptoms preceded the onset of diarrhea. This is the first demonstration of respiratory cryptosporidiosis in apparently immunocompetent children. These data suggest that Cryptosporidium may be a respiratory pathogen, which raises a series of new questions. Is the cough in cryptosporidiosis due to respiratory tract infection? What is the route of infection: aspiration from a primary gastrointestinal infection, hematogenous spread, or primary respiratory infection? Does cryptosporidiosis present as a primary respiratory infection, as opposed to a complication of intestinal disease? Does Cryptosporidium alter pulmonary function? What is the effect of treatment on respiratory cryptosporidiosis? All of these questions have bearing on the burden of disease due to this organism. However, none of these questions would have been asked if novel techniques, such as PCR, were not being applied to an infection that we thought we understood.

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References