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# Potential impact of parasitic opportunistic infections on COVID-19 outcome: A review

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## Abstract

Treatment of COVID-19 remains a complicated challenge, especially among patients with severe disease. The illness by itself and the broad use of immunosuppressive agents for its management has increased the risk of opportunistic infections, including parasitic agents such as *Toxoplasma gondii, Strongyloides stercoralis* and coccidian parasites in these patients. The reactivation of such parasites may be overlooked due to the coincidental symptoms and the difficulty of identification. Diagnosis and treatment of COVID-19-associated opportunistic parasitic infections constitute major challenges in the management of COVID-19 patients. Strategies for systematic screening of high-risk patients and research to determine the impact of these infections on COVID-19 are needed. Herein, the current knowledge on the interaction of opportunistic parasitic infections and SARS-CoV-2 infection is summarized and analyzed.

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**Keywords:** COVID-19; SARS-CoV-2; Opportunistic infections; Parasitic infections.

**Abbreviations:** OPIs: Opportunistic Parasitic Infections; LMICs: Low- Middle-Income Countries.

## Introduction

Opportunistic Infections (OPIs) usually do not cause pathological effects in immunocompetent individuals. However, among immunocompromised patients, can produce severe diseases and death [1-4]. COVID-19 patients may be immunocompromised due to the illness itself, comorbidities or immunosuppressive therapy [5] and OPIs may be more prevalent in them. The increased case reports of OPIs in COVID-19 patients raise concern, particularly for those critically ill [6] with underlying illnesses or receiving immunosuppressive treatment and patients admitted to the Intensive Care Unit [4]. Fungal and bacterial infections have been recognized as important OPIs in COVID-19 patients [6]. However, information on OPIs co-infections is very scarce.

Worldwide, more than two billion people have intestinal parasitic infections, with predominance in low- middle-income countries (LMICs) [7-10]. Syndemics occur [11,12] with subsequent worse evolution than for either single infection [11]. In addition, COVID-19 pandemic has had significant impact on global health, particularly in LMICs [13,14] and it is of concern that, due to this effect the fighting of parasitic infections has decreased or disappeared which may cause an increase of these infections [15]. Therefore, OPIs should not be ignored among COVID-19 patients, especially in LMICs, where parasitic infections and multi-parasitism are frequent [16-19]. The aim of this article is to summarize the current knowledge on the relationship of OPIs and SARS-CoV-2 infection and make some comments.

## Parasitic infection immunomodulatory effects on COVID-19

It is unclear whether immunomodulation caused by parasitic infections is beneficial or harmful when hosts are co-infected with SARS-CoV-2 [20]. However, a compromised immune system could augment the pathogenic effects of parasites and the development of symptoms that could lead to death. The risk of

severe outcome due to co-infection could impact considerably the epidemiology of COVID-19 in LMICs [11].

Since COVID-19 can cause collapse of the innate and adaptive immunity, with increasing lymphopenia and reduction of monocytes, macrophages and dendritic cells [20,21], it is likely that patients with COVID-19 may suffer of reactivation of latent parasitic infections. Likewise, patients with severe disease receiving systemic steroids could have a constrained effect on the inflammatory response. In addition, parasitic infection-immunomodulatory effects can alter the evolution of viral diseases; helminths co-infections can induce a Th2 immune responsiveness and anti-inflammatory conditions, augmenting the susceptibility and severity of infectious diseases [20]. A dominant Th2 immune response with a major diminution in Th1 and Th17 cells has been associated with a high fatality in COVID-19 patients [22]. Helminths can also cause multiple adverse effects [23]. Therefore, the outcome of COVID-19 may be worsened in individuals with helminths co-infection [20,24,25], which could facilitate the OPIs.

The pandemic has produced a significant augmentation in the global immunosuppressed population because of the disease pathogenesis and broad usage of corticosteroids [4], which have been utilized to reduce hyper-inflammation and cytokine storm in COVID-19 patients [26]. As a result, this has enhanced the risk of OPIs and severity of COVID-19 [27].

## Opportunistic parasitic infections in COVID-19 patients

There is a gap in our knowledge of the prevalence and outcome of OPIs in COVID-19. The risk for *Toxoplasma gondii* and *Strongyloides stercoralis* infections has increased in COVID-19 patients [28]. Other parasites such as intestinal coccidia might also worsen the disease [29]. The reactivation of such parasites may be overlooked due to the similarity of symptoms and the difficulty of diagnosis. Therefore, OPIs should not be neglected among COVID-19 patients.

*Toxoplasma gondii* causes a worldwide zoonotic infection [30,31]. It often produces a chronic and latent infection in immunocompetent individuals but severe disease can develop in immunocompromised patients, such as those with AIDS [32,33], in who revitalization of latent infection can arise and cause encephalitis, systemic infection and death [34]; such scenario is likely in COVID-19 with growing lymphopenia. Reactivation of toxoplasmosis, often shown as brain or ocular alterations, has been evidenced in patients under immunosuppressive therapy [34-37]. A higher infection rate of *T. gondii* and *Cryptosporidium* spp. among COVID-19 patients was observed in a case-control study in Egypt [38]. The prevalence of toxoplasmosis was significantly higher in patients with COVID-19 than in healthy individuals and in the severe COVID-19 patients compared with the moderate disease patients [39]. A study reported that 84% of the patients with COVID-19 were positive for anti-*T. gondii* antibodies (IgG) [40]. In addition, toxoplasmosis enhanced the severity of COVID-19 [41]. These findings demonstrate that latent *Toxoplasma* infection is prevalent among SARS-CoV-2 patients. Therefore, reactivation of toxoplasmosis should be considered in COVID-19 patients, particularly those receiving immunosuppressive therapy.

*Strongyloides stercoralis* infection is predominantly endemic in LMICs [42]. However, the worldwide migration and chronic duration of the infection have favored its geographic dissemination [29]. An important burden of disease in global migrants has been documented [43]. In immunocompetent individuals, the infection is usually chronic and asymptomatic or slightly symptomatic. However, *S. stercoralis* can cause a life-threatening hyper-infection and systemic disease in immunocompromised patients [44,45] which may mimic COVID-19 [46]. The use of corticosteroids in patients with severe COVID-19 can provoke this clinical scenario. The symptomatology of meningitis is prominent, and implication of the central nervous system can produce mental symptoms alterations, stupor, coma and death. *Strongyloides* hyper-infection and dissemination usually occur in patients receiving treatment with steroids in whom a comorbidity has caused an earlier cellular immunity insufficiency [44,45,47]. A recent study detected 22 cases of strongyloidiasis in patients with COVID-19; 7 had hyper-infection and 15 had chronic infection [47]. It is likely that most of the cases of strongyloidiasis are not identified due to the difficulties of diagnosis. COVID-19 patients should be screened for *S. stercoralis.*

Among intestinal coccidia, the most identified are *Cryptosporidium* spp., *Cystoisospora belli*, and C*yclospora cayetanensis* which cause self-limiting acute diarrhea in immunocompetent individuals. However, immunodeficiency states lead to life-threatening severe disease [48-50]. The public health relevance of these pathogens is linked to their opportunistic nature with high morbidity and mortality in the immunocompromised population, particularly in AIDS patients with CD4+ T cell counts below 200 cells/µL [48-51]. These coccidia are the most detected opportunistic parasites associated with chronic diarrhea in this population and *Cryptosporidium* spp. have the highest opportunistic potential [2,48,50]. Diarrhea can lead to complications such as dehydration, malnutrition, weight loss and death [52]. In 375 COVID-19 patients from Egypt, parasitic infections including C*ryptosporidium, Blastocystis, Giardia and Toxoplasma gondii* were identified in 72% of moderate and 20% of severe cases [38], suggesting that COVID-19 may augment the incidence of OPIs that can alter the outcome of the illness. However, cryptosporidiosis was less frequent in patients with severe COVID-19 than in those with moderate disease, indicating a protecting role of *Cryptosporidium* spp. More studies are needed to clarify the relationship between coccidia and SARS-CoV-2 infection.

A significant number of individuals with COVID-19 displays gastrointestinal symptoms often prior to respiratory symptoms [53]. The presence of ACE2 receptor of SARS-CoV-2 in enterocytes, live virus in fecal samples, and SARS-CoV-2 in sewage and surface water has been documented [54,55]. Although the fecooral transmission of the virus has not been shown, there are reasons to believe in the existence of this route of transmission. This potential mode of spread could be significant, especially in LMICs where deficient sanitary facilities are frequent [54,56]. People with COVID-19 could be at a higher risk of developing enteric infections either due to shared epidemiology or immunity deficiency [5,54]. The depletion of the immune system in COVID-19 patients might favor the increase of OPIs [5,21]. In COVID-19, chronic diarrhea is associated with decreased diversification and abundance of gut microbiota, immunological deregulation and slowed viral clearance [57]. According to the shotgun metagenomics approach, the intestinal microbiome in COVID-19 patients has a generation of OPIs and a loss of favorable commensals, as compared to healthy controls [58].

Collectively, the findings suggest that intestinal coccidia can increase the likelihood of COVID-19 transmission, prevalence, and severity. This highlights the importance of preventive mea-

sures; in the presence of diarrhea, these pathogens should be considered, and fecal samples should be examined for coccidia to administer specific treatment to avoid complications. More studies are needed to find correlation between coccidian parasites and SARS-CoV-2 infection.

The present findings highlight the likely reciprocal effect between OPIs and COVID-19. This study suggests that COVID-19 patients have a higher chance of developing these infections which are more prevalent in critically ill patients. Numerous OPIs have been reported in COVID-19 patients [4,20,38]; this disease may enhance their occurrence due to reduction of the immune system facilitating the increase of these pathogens, which are difficult to identify due to coincidental symptomatology. Reactivation of latent infections following immunosuppression is the major cause of severe OPIs, such as strongyloidiasis, intestinal coccidiosis and toxoplasmosis [27,32,45,48]. Therefore, co-infection with these opportunistic pathogens could be an additional challenge for the management of COVID-19 patients.

The potential impact of co-infections on COVID-19 in LMICs is of concern due to the high prevalence rates of parasitic infections [59]. There is a gap in the knowledge of the clinical course and epidemiology of COVID-19 in these areas with considerable burdens of neglected tropical diseases; the investigations are just beginning [11]. Although studies have shown controversies, the evolution of COVID-19 patients may be worsened in individuals with helminth co-infections [20,24,25]. OPIs should not be neglected among COVID-19 patients, especially in LMICs. Reactivation of latent infections should be considered before the prescription of immunosuppressive therapy in these patients [41].

## Implications of parasitic opportunistic co-infections for COVID-19 management

The available findings have implications for COVID-19 management. Screening of OPIs should be performed in all patients with the disease. Early detection of these infections can lead to prompt treatment and consequently lower sequels and better outcomes of COVID-19 patients. Prophylaxis with specific therapy can reduce the risk of OPIs [4,27]. In this regard, given the recognized beneficial effects of melatonin as a potent antioxidant, anti-inflammatory, and immune-enhancing effects in viral and parasitic infections [5,60-62], it is an attractive choice to be used as an adjuvant treatment for COVID-19 and OPI co-infections. Developing vigilance platforms to monitor SARS-CoV-2 co-infection with parasitic pathogens is essential to understand their potential impact on the disease outcome and to prevent or alleviate potential worse consequences [11].

## Future perspectives

Large-scale studies to identify OPIs in COVID-19 patients and further investigations to evaluate the interactions between these infections and SARS-CoV-2 are required. Future studies for more reliable diagnostic procedures are highly needed for differential diagnosis in COVID-19 patients. More research to identify viral strains and viral load in stools, which are of concern as source for potential feco-oral transmission [29], is mandatory.

Mutated variations of SARS-CoV-2 decrease effectiveness of diagnosis, treatment, and vaccination as well as augment transmissibility and severity of the disease [63]. In this context, co-infection with opportunistic pathogens could be a further challenge for the management of COVID-19 patients.

## Conclusion

COVID-19 patients are at risk for OPIs. Understanding the potential interactions between the disease and these co-infections and their clinical impacts are critical for mitigating the worst outcomes. Strategies for prophylaxis, early diagnosis and treatment could reduce the risk of OPIs in these patients.

## Declarations

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