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COMMENTARY

Considering opportunistic parasitic infections in COVID-19 policies and recommendations

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The COVID-19 pandemic has led to a significant increase in the immunosuppressed population worldwide due to the disease pathology and extensive use of corticosteroids. This has subsequently increased the risk of opportunistic parasitic infections such as *Toxoplasma gondii*, *Strongyloides stercoralis* and other parasites in these patients. The reactivation of such parasites may remain unnoticed due to overlapping symptoms, the difficulty of diagnosis and lack of guidelines for opportunistic parasitic infections in COVID-19 management. Therefore, recommendations for systematic screening of high-risk patients in endemic regions and active research and surveillance to estimate the impact of these infections are required in COVID-19 policy guidelines.

Keywords: corticosteroids, COVID-19, lymphopenia, opportunistic infections, parasitic infections, SARS-CoV-2

The coronavirus disease 2019 (COVID-19) pandemic has posed several unprecedented situations for the global community due to an incomplete understanding of the pathophysiology of the disease, its association with risk factors and comorbidities, clinical complications and lack of effective treatment protocols. After several months into the pandemic, the RECOVERY trial produced evidence for the role of dexamethasone in reducing mortality in patients receiving either invasive ventilation or oxygen alone.[1] The guidelines of the WHO thus recommended systemic corticosteroids in patients with severe or critical COVID-19.[2] Subsequently, several patients have benefitted from corticosteroids worldwide. Further data from the RECOVERY trial showed the role of tocilizumab in improved survival in COVID-19 patients with hypoxia and systemic inflammation,[3] which has led to widespread use of tocilizumab in patients with severe COVID-19. It is important to realise, though, that it is a challenging task to maintain a risk-benefit balance for the use of immunomodulatory agents, especially with such extensive use. This is evident by the increased number of cases of mucormycosis in patients on high-dose corticosteroids with hyperglycaemia. The role of bacterial and fungal infections has been recognised in COVID-19 and their evaluation is included in the routine diagnostic workup. However, there are many opportunistic parasites such as *Toxoplasma gondii* and *Strongyloides stercoralis* that manifest with non-specific symptoms and require specific tests for their diagnosis, and thus may be missed. These parasites lie dormant in an otherwise healthy person, but may reactivate in an immunosuppressive state.

COVID-19 is associated with an overall exhaustion of the innate and adaptive arms of the immunity, viz., progressive lymphopenia (decreased CD4+ and CD8+ T cells, B cells, NK cells), increased immature neutrophils, impaired activity and depletion of monocytes, macrophages and dendritic cells.[4] Adding to this, corticosteroids cause global inhibitory effects on inflammatory responses. Also, the immunomodulatory role of parasitic infections in COVID-19 severity is not clear. In general, the helminthic infections polarise towards type-2 helper T cell (Th2) response and suppress the type-1 helper T cell (Th1) cytokine response along with amplification of the regulatory T cell (Treg) subsets.[5] This may lead to downstream effects on CD4+ and CD8+ T cells and increase the susceptibility to severe COVID-19. Notably, a significant reduction in Th1 and Th17 cells response with a dominant Th2 immune response has been associated with high mortality in COVID-19 patients.[6] Thus, the complex role of parasitic coinfections on the outcomes of COVID-19 is still elusive and must be focused upon in future studies.

Considering that a large number of patients with COVID-19 will have some degree of immunosuppression, it is expected that they may be at risk of reactivation of dormant/latent parasitic infections, especially in endemic areas. For instance, the protozoan *To. gondii* infects about 25–30% of the world's population, with a seroprevalence of 10–80% across countries.[7] The dormant tissue cysts that contain the bradyzoites of *To. gondii* are at a high

Table 1. Opportunistic parasites that may potentially complicate the clinical course of patients with COVID-19

Parasite	Strategies for rapid assessment/screening and treatment/prophylaxis[a]
Toxoplasma gondii	Serological screening may be considered for all COVID-19 patients with progressively depleting lymphocytes Trimethoprim-sulphamethoxazole chemoprophylaxis may be considered in selected seropositive patients
Strongyloides stercoralis	Serological screening of COVID-19 patients may be considered simultaneously when initiating corticosteroid therapy in endemic regions Stool examination to look for increased numbers of *Strongyloides* larvae Ivermectin may be considered in seropositive patients
Cryptosporidium species	Stool examination by modified acid-fast staining for diarrhoeas; coproantigen detection Nitazoxanide therapy may be considered; however, it is not much efficacious unless immune restoration occurs
Cyclospora cayetanensis	Stool examination by modified acid-fast staining for diarrhoeas Trimethoprim–sulphamethoxazole therapy may be considered; may require suppressive therapy until immune restoration
Cystoisospora belli	Stool examination by modified acid-fast staining for diarrhoeas Trimethoprim–sulphamethoxazole therapy may be considered; may require secondary prophylaxis until immune restoration
Microsporidia	Stool examination by modified trichrome stain for diarrhoeas or other symptoms Fumagillin may be considered for *Enterocytozoon bieneusi* and albendazole for other species; to be administered until immune restoration
Leishmania species	Rapid immunochromatographic tests may be considered for screening COVID-19 patients in endemic regions Pentavalent antimonial drugs, amphotericin B deoxycholate preparations or miltefosine may be considered, depending on the geographical region and disease presentation Prolonged treatment may be considered for PKDL
Trypanosoma cruzi	Serological screening of COVID-19 patients with depleting lymphocytes may be considered in endemic regions Benznidazole or nifurtimox therapy may be considered for acute disease

Abbreviations: PKDL, post-kala azar dermal leishmaniasis.
[a]When there is a high index of suspicion, it is ideal to carry out a complete diagnostic evaluation for specific parasites.

risk of reactivation with decreasing levels of CD4+ T cells, as in AIDS, and usually manifest as *Toxoplasma* encephalitis. Such a reactivation is also a likely scenario in COVID-19 with progressive lymphopenia, but may remain unnoticed because the presenting features of *Toxoplasma* encephalitis, such as altered sensorium, seizures and other neuropsychiatric symptoms, overlap with those of COVID-19.[8] It is also noteworthy that some of the neurological and psychological clinical features of long-COVID are also known to exist in toxoplasmosis,[8] and such patients who require additional post-COVID care may benefit from evaluation and management of *Toxoplasma*.

Another usually dormant opportunistic parasite, *S. stercoralis*, has been reported to infect 10–40% of the population in tropical and subtropical countries.[9] An immunosuppressed state may lead to a hyperinfection or disseminated strongyloidiasis with multiorgan system involvement, which may mimic COVID-19 presentation. A few cases of strongyloidiasis in COVID-19 patients following treatment with high-dose corticosteroids have been reported from various countries; however, it is likely that the majority of cases of stongyloidiasis may remain undetected due to a lack of awareness and the difficulties of diagnosis. A potential strategy to reduce the risk of *Strongyloides* hyperinfection/dissemination in COVID-19 patients has been suggested, which includes screening and treating patients in outpatient and presumptive treatment in inpatient settings,[10] but such practices are largely non-existent in most endemic regions of the world.

Many other parasites such as *Cryptosporidium*, *Cyclospora, Cystoisospora*, *Leishmania* spp., *Trypanosoma cruzi* and microsporidia may also complicate COVID-19 illness, especially in patients with depleted lymphocytes and on corticosteroids (Table 1). In a series of 375 patients with a diagnosis of COVID-19 from Egypt, evidence of parasitic infections including *To. gondii*, *Cryptosporidium*, *Blastocystis* and *Giardia* was reported in 72% of mild and 20% of severe cases.[11] Thus it is important to recognise the opportunistic pathogens as they can alter the course of the illness due to COVID-19.

Foremost, a high index of clinical suspicion is required by healthcare practitioners for timely intervention. A symptomatology of new onset, or involvement of multiorgan systems, should raise clinical suspicion and prompt evaluation. A serological screening approach for *To. gondii*, *S. stercoralis*, *Leishmania* spp. and *Tr. cruzi* may be considered for patients selected for corticosteroid therapy and/or with progressive lymphopenia for prophylaxis or treatment of these infections (Table 1). Nevertheless, there are many challenges in diagnosing superinfections during the course of a COVID-19 illness. There is a narrow window of opportunity between suspecting an additional aetiology and irreversible deterioration of a patient. Also, there is a gap in our understanding of the incidence and outcome of coexisting

opportunistic parasitic infections in COVID-19, which can be filled by focused research. It is noteworthy that the RECOVERY trial was conducted in the UK, which is a low-endemicity region for parasites; however, the situation is different in tropical countries, where parasitic infections are abundant. In these regions, the potentially increased risk of opportunistic infections needs to be considered when high-dose corticosteroids and/or tocilizumab are initiated in COVID-19 patients.

The likelihood of 'future waves' of the COVID-19 pandemic cannot be ignored in light of the evolving mutations in the spike protein, the associated immune escape and the circulation of several severe acute respiratory syndrome coronavirus 2 'variants of concern'. The pandemic has dealt substantial setbacks to the control of neglected tropical diseases, many of which are parasitic diseases that are now at a risk of resurgence back to preintervention levels due to the disruption in activities such as mass drug administration, case detection, treatment and vector control.[12] Such resurgence is likely to have an additional impact on the healthcare infrastructure. The long-term outcomes of the pandemic will depend on a holistic integration of various strategies, which not only include prevention by vaccination and management of risk factors and comorbidities, but also effective management of coexisting infections. Thus it may be a worthwhile task for policymakers to address the risk of opportunistic parasitic infections in their guidelines for COVID-19 management and research so that these infections do not take an unnoticed toll on human lives.

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References

1 TheRECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693–704.

2 World Health Organization. Therapeutics and COVID-19. March 31, 2021. WHO/2019-nCoV/therapeutics/2021.1.

3 TheRECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637–45.

4 Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. Lancet Respir Med.2021;(6): S2213-2600(21)00218-6.

5 Bradbury RS, Piedrafita D, Greenhill A, Mahanty S. Will helminth coinfection modulate COVID-19 severity in endemic regions? Nat Rev Immunol. 2020;20(6):342.

6 Gil-Etayo FJ, Suàrez-Fernández P, Cabrera-Marante O, et al. T-helper cell subset response is a determining factor in COVID-19 progression. Front Cell Infect Microbiol. 2021;11:624483.

7 Robert-Gangneux F, Dardé ML. Epidemiology of and diagnostic strategies for toxoplasmosis. Clin Microbiol Rev. 2012;25(2):264.

8 Roe K. The symptoms and clinical manifestations observed in COVID-19 patients/long COVID-19 symptoms that parallel *Toxoplasma gondii* infections. J Neuroimmune Pharmacol. 2021;16(3):513–6.

9 Schär F, Trostdorf U, Giardina F, et al. *Strongyloides stercoralis*: global distribution and risk factors. PLoS Negl Trop Dis. 2013;7(7):e2288.

10 Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related *Strongyloides* hyperinfection. JAMA. 2020;324(7):623–4.

11 Abdel-Hamed EF, Ibrahim MN, Mostafa NE, et al. Role of interferon gamma in SARS-CoV-2-positive patients with parasitic infections. Gut Pathog. 2021;13(1):29.

12 Toor J, Adams ER, Aliee M, et al. Predicted impact of COVID-19 on neglected tropical disease programs and the opportunity for innovation. Clin Infect Dis. 2021;72(8):1463–6.