VIEWPOINT

COVID-19 and Dexamethasone
A Potential Strategy to Avoid Steroid-Related *Strongyloides* Hyperinfection

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A widely publicized press release and subsequent preliminary report of the RECOVERY trial, a randomized study conducted in the UK, noted a survival benefit with the use of dexamethasone in hospitalized patients with coronavirus disease 2019 (COVID-19).[1] The use of dexamethasone for management of COVID-19 has already increased, particularly given the recent National Institutes of Health COVID-19 Treatment Panel guidelines that recommend its use.[2]

Although clinicians are familiar with the most common adverse effects associated with dexamethasone, a corticosteroid, they may be less familiar with a potentially severe, but preventable, less common complication: *Strongyloides* hyperinfection or dissemination syndrome (hyperinfection).[3]

Strongyloidiasis is caused by a nematode (roundworm) infection, with most human disease associated with *Strongyloides stercoralis*. *Strongyloides* infection is predominantly acquired through contact with soil contaminated with free-living larvae, which penetrate the skin and migrate to the intestine, where they lay eggs. Eggs are excreted into the environment where they hatch. Larvae complete the life cycle by penetrating the skin of a new host. Unlike other soil-transmitted infections, eggs of *Strongyloides* may hatch into filariform larvae in the intestines and directly autoinoculate, reinfecting their human host (autoinfection) without an environmental stage. This unique characteristic perpetuates chronic infection, often lasting for decades.

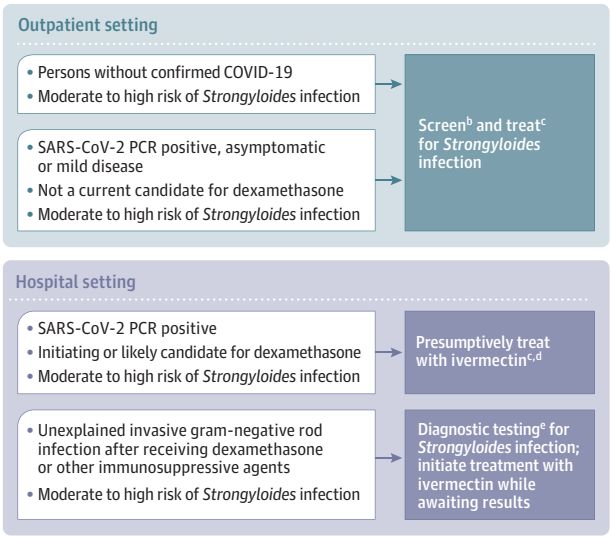
Although a majority of individuals with strongyloidiasis are asymptomatic, a severe disease manifestation is hyperinfection syndrome. This frequently fatal iatrogenic complication is usually associated with use of an immunosuppressive drug in persons with unrecognized chronic infection. The most common precipitator is use of a corticosteroid agent, which appears to be independent of dose or duration of treatment.[3-5] Coinfection with human T-lymphotropic virus type 1, which is disproportionately found in immigrant and refugee populations, is also associated with hyperinfection syndrome.[3,4]

Although prevalence data are lacking from many regions of the world, *Strongyloides* is estimated to infect hundreds of millions of people worldwide,[3,6] with studies suggesting that 10% to 40% of populations in tropical and subtropical regions may be infected.[6,7] A 2019 meta-analysis of studies involving migrants worldwide found a pooled strongyloidiasis seroprevalence of 12.2%; the prevalence was 17.3% among migrants from Asia, 14.6% among migrants from sub-Saharan Africa, and 11.4% among those from Latin America and the Caribbean.[8] The prevalence among certain populations of refugees from Africa and Asia arriving in the US is estimated to approach 50%.[9] Although there are no incidence or prevalence estimates of *Strongyloides* hyperinfection, there are hundreds of case reports, and the condition is likely underreported because of challenges in diagnostic testing and lack of clinician awareness of the syndrome.[3-7] Given the high prevalence rate in refugees, underrecognition of infection in the US, and a lifetime risk associated with *Strongyloides* infection, presumptive treatment of all at-risk US-bound refugees was initiated in 2011.[9] In 2016, the Committee to Advise on Tropical Medicine and Travel for Canada (CATMAT) issued similar evidence-based screening and preventive treatment guidelines for at-risk immigrant and refugee populations in Canada[5] and, in 2018, the European Centre for Disease Prevention and Control issued guidance.

With more than 44 million first-generation immigrants residing in the US, many of whom work essential jobs and live in environments less conducive to social distancing, the convergence of risk for both chronic strongyloidiasis and COVID-19 infection could be common and is concerning. In addition, it is likely that dexamethasone use will increase for COVID-19 in *Stronglyoides*-endemic low- and middle-income countries because corticosteroids are inexpensive and widely available. The most proactive approach to avoid the risk of iatrogenic *Strongyloides* hyperinfection is to address infection in asymptomatic persons prior to the use of immunosuppressant therapy, particularly corticosteroids. Most patients with chronic strongyloidiasis are asymptomatic. Peripheral eosinophilia may be associated with parasitic infection and is commonly believed to be a good clinical marker for *Strongyloides* infection. However, eosinophilia has poor sensitivity, specificity, and predictive value, particularly in predicting hyperinfection syndrome.[3,4] Therefore, suspicion of underlying chronic infection must be made independent of signs and symptoms and instead based on factors such as country of origin and long-term residence. Additionally, risk should be weighted for patients by demographic risk factors associated with transmission (eg, history of rural residence, labor associated with exposure to soil) and duration of exposure. Because infection may be lifelong, suspicion should not be based on duration outside an endemic area; fatal cases have been reported more than 50 years after leaving an endemic area.

How should clinicians evaluate and manage the risk of *Strongyloides* hyperinfection among patients with COVID-19 with increased use of dexamethasone? The current recommended dexamethasone dose from the COVID-19 Treatment Panel is 6 mg/d (≈40 mg of prednisone) for 10 days.[2] A study that reviewed 133 individuals with *Strongyloides* hyperinfection found that hyperinfection was associated with corticosteroid administration in 83% of cases, with an average dose of 40 mg per day of prednisone.[10] In addition, cases have occurred within 5 days of administration of the first dose of corticosteroids,

Figure. Approach to Reducing Risk for *Strongyloides* Hyperinfection/Dissemination in Persons at Moderate to High Risk of Infection[5] During the Coronavirus Disease 2019 (COVID-19) Pandemic[a]



[a] This strategy has not been evaluated in patients with COVID-19 who are candidates for corticosteroid therapy.

[b] Serologic testing is preferred. When testing is not available, presumptive treatment is acceptable if there are no contraindications to ivermectin.

[c] If the patient previously tested negative for strongyloidiasis or has documented treatment with ivermectin, no screening or treatment is needed.

[d] Ivermectin 200 µg/kg once per day orally for 1 or 2 days. Possible contraindications include possible *Loa loa* infection (endemic to West and Central Africa), pregnancy, and weight <15 kg.

[e] Generally includes testing of multiple specimens for ova and parasites or pathologic examination of other sites of suspected infection.

following doses as low as 20 mg of prednisone and following a single dose of dexamethasone, leading experts to assert that the occurrence is independent of dose, duration, or route of administration.[3]

Based on the available data, it is likely that the benefit of dexamethasone outweighs the risk of possible *Strongyloides* hyperinfection, an uncommon complication. However, due to the high mortality associated with this syndrome and the availability of inexpensive and effective therapy, ivermectin could be used as a preventive strategy for at-risk patients. Ivermectin is considered extremely safe and is used in many settings for parasite control programs (mass treatment) because of a low adverse event profile. In vitro data suggest that ivermectin has direct activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), although no current data are available to support its use for management of COVID-19, and no group has recommended its use.

A possible strategy to avoid hyperinfection syndrome for patients at moderate to high risk for strongyloidiasis in anticipation of widespread use of dexamethasone during the COVID-19 pandemic is presented in the **Figure**. The 2016 CATMAT recommendations has stratified risk categories into high, moderate, and low, which may be used for this purpose.[5] A test-and-treat strategy is suggested for the outpatient setting and for patients with mild COVID-19 when serologic testing is available. For patients with COVID-19 who are, or may become, candidates for dexamethasone, it is reasonable to consider presumptive treatment with ivermectin for moderate- to high-risk patients not previously tested or treated for *Strongyloides*. When serologic testing is unavailable or delayed and when treatment with steroids is imminent, waiting for serologic results to guide treatment decisions is not advisable. Although this suggested treatment approach has not been formally studied, many clinical experts advocate a similar approach for select patients (eg, before organ transplant).

In patients at risk of strongyloidiasis who receive dexamethasone without being tested or treated for *Strongyloides*, clinicians should include *Strongyloides* hyperinfection syndrome on the differential diagnosis for patients who experience acute clinical decompensation, especially if gram-negative rod bacteremia or central nervous system infection is detected.[3]

Strongyloides hyperinfection syndrome is potentially catastrophic to patients. It is possible that as dexamethasone becomes more widely prescribed for individuals with COVID-19, a substantial number of patients may be at risk. This iatrogenic potentially fatal complication is avoidable. Clinicians and health care systems should consider implementing a strategy to prevent hyperinfection syndrome in patients with COVID-19 who are at risk for strongyloidiasis and are candidates for dexamethasone therapy.

ARTICLE INFORMATION

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