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Perspective Piece

COVID-19 and Corticosteroids: Unfamiliar but Potentially Fatal Infections That Can Arise following Short-Course Steroid Treatment

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Abstract. Corticosteroid use is increasing worldwide as recent studies confer survival benefit of corticosteroids in the management of patients with severe COVID-19. *Strongyloides* and amebic infections are neglected diseases that can progress to catastrophic complications in patients exposed to corticosteroids, even with short treatment courses. To prevent lethal outcomes, clinicians should be aware of the threat these two parasitic infections pose to at-risk patients receiving corticosteroids, especially in the era of COVID-19.

INTRODUCTION

Corticosteroids, such as prednisone, hydrocortisone, and dexamethasone, have powerful inhibitory effects on the immune system. Patients with COVID-19 may develop severe inflammatory-mediated disease with acute lung injury and multisystem organ dysfunction. Corticosteroids may improve outcomes in seriously ill COVID-19 patients by attenuating this inappropriate host immune response.[1–5]

Lower 28-day mortality was demonstrated in the large prospective, open-label controlled RECOVERY trial involving 6,425 participants admitted with COVID-19 in those randomized to 6 mg dexamethasone intravenously or orally once daily for up to 10 days than usual care.[3] In those receiving invasive mechanical ventilation, mortality among those treated with dexamethasone was one-third that in those receiving usual care and in those receiving oxygen without mechanical ventilation mortality was reduced by one-fifth.[3] Benefit was also seen in those treated more than 7 days after symptom onset with inflammatory lung damage, but not for those without respiratory support requirement at randomization, suggesting the timing of this intervention within the course of illness may be important.[3] On this basis, the use of corticosteroids, which are relatively inexpensive and readily available medications, has increased worldwide for the treatment of patients with severe COVID-19 disease, as recommended by several health authorities such as the WHO,[4] the NIH,[6] and the Infectious Diseases Society of America.[7] Similarly, evolving observational data also suggest that corticosteroids may be helpful in the management of the multisystem inflammatory syndrome, an uncommon but very serious complication of COVID-19 in children.[1,8,9]

Despite their utility, corticosteroids can be associated with significant adverse effects, often related to the dose and duration of administration as well as host-specific factors, such as underlying morbidities and concomitant medications. Prolonged systemic use of corticosteroids for more than 2 weeks can be associated with effects such as glaucoma, cataracts, adrenal suppression, hypertension, weight gain, psychologic effects, and gastritis. Shorter term use is better tolerated but can still lead to effects such as hyperglycemia and increased infection risk. Clinicians are likely aware of these common adverse effects of corticosteroids but may be unfamiliar with severe forms of potentially fatal parasitosis that can arise following even very brief courses. Frequently considered infections of endemic low- and middle-income countries, both *Strongyloides* hyperinfection syndrome and severe amebic colitis, are of global significance because of changing patterns in travel and migration. In the United States, for example, immigrants now account for nearly 15% of the population, with that percentage tripling over the past half-century.[10] Social and economic disparities make many of the 47 million immigrants residing in the United States particularly vulnerable to SARS-CoV-2 infection. Here, we bring attention to these potentially fatal infectious risks for COVID-19 patients, especially among at-risk vulnerable populations (Table 1).

STRONGYLOIDES HYPERINFECTION SYNDROME

Strongyloides stercoralis is a soil-transmitted nematode that infects tens to hundreds of millions of people worldwide.[11] Accurate estimates are limited, but studies suggest prevalence rates as high as 50% in some endemic areas, and 12% or more of immigrant populations may be infected.[11,12] The U.S. Appalachian region and rural Southern United States as well as the Spanish Mediterranean coast of Southern Europe are notable examples of temperate areas that are also considered endemic.[11,13–16] Infection arises when free-living filariform larvae found in human fecally contaminated soil penetrate the skin and migrate to the intestine.[11,16] Following maturation, adult females lay eggs that become rhabditiform larvae excreted in the feces or develop into infective filariform larvae within the lumen that autoinfect by penetrating the intestinal mucosa, propagating chronic infection.[11] A wide clinical spectrum is seen, ranging from mostly asymptomatic infection to hyperinfection syndrome with dissemination, as the larval form migrates throughout the body.[11] Gram-negative bacteremia and meningitis arise as the larvae carry enteric bacteria with them during migration.[11,16] Hyperinfection syndrome is associated with high mortality, approaching 90% in disseminated forms. Administration of immunosuppressive medications, such as corticosteroids, is

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TABLE 1
Suggested considerations to improve outcomes in patients with severe COVID-19 infection being treated with corticosteroids by decreasing the risk of *Strongyloides* hyperinfection and fulminant amebic colitis in at-risk patients

Pathogen	Epidemiologic risk factors of infection	Clinical features of severe disease	Evaluation in patients with epidemiologic risk factors	Strategies to treat and prevent severe disease
Helminth				
Strongyloides stercoralis	Skin contact with free-living filariform larvae in soil contaminated with human feces in endemic areas	Hyperinfection syndrome and disseminated infection: fever, dyspnea, wheezing, hemoptysis, pulmonary infiltrates, acute respiratory distress–like syndrome, anorexia, abdominal pain, diarrhea, eosinophilia, unexplained Gram-negative bacteremia or central nervous system infection, septic shock	In those with risk factors such as travel to or migration from an endemic area, or agricultural work, obtain serology. Consider stool studies for ova and parasite examination (submit multiple stools to improve sensitivity); stool PCR performs better but is not widely available	Treat established or suspected hyperinfection syndrome with ivermectin*
			Microscopic examination of body fluids, such as lower respiratory samples, can identify larvae	Consider preemptive therapy before the onset of hyperinfection syndrome with ivermectin* if no contraindication† in those with positive serology‡ or diagnostic stool studies, or at-risk patients not previously tested‡ or treated§ or those in hyperendemic areas
Protozoa				
Entamoeba histolytica	Ingestion of infective cyst in food or drink contaminated with human feces in endemic areas	Severe and fulminant amebic colitis: profuse diarrhea, bloody diarrhea, bowel necrosis, perforation, peritonitis, shock, toxic megacolon	In those with risk factors such as travel to or migration from an endemic area, obtain serology and antigen stool studies for *E. histolytica* or PCR when available	Treat established colitis or disseminated disease with metronidazole or tinidazole first; follow with paromomycin
	Sexual transmission		Stool microscopy lacks sensitivity and specificity so should be avoided if other modalities are available, whereas antigen tests have good specificity but may lack sensitivity	Treat intestinal carriage with paromomycin to prevent severe disease

* Albendazole is a second-line alternative.
† Contraindications to ivermectin generally include possible filarial coinfection such as Loa loa infection (endemic to West and central Africa), which may result in severe exacerbation of skin and eye involvement (Mazzotti reaction); age < 2 years or weight < 15 kg; consult an infectious diseases expert for further guidance.
‡ Or for those who previously tested negative by serology for *Strongyloides* without new risk factors, retesting or preemptive re-treatment may not be needed.
§ If no previous documented treatment for *Strongyloides stercoralis*.

the most commonly identified risk factor for the development of hyperinfection syndrome, which can occur in initially asymptomatic patients.[16,17] Hyperinfection may manifest as a range of gastrointestinal or pulmonary features, which are challenging to differentiate clinically from those of COVID-19 disease. About two-thirds with chronic infection may have eosinophilia. Stool and lower respiratory samples can be obtained for microscopic examination, but this method generally lacks sufficient sensitivity.[11,18] Stool PCR performs better than microscopy for diagnosis, but is not widely available. In non-endemic areas, serology helps identify patients with infection but may be less useful in endemic settings where positive serology can also indicate past infection.[11] *Strongyloides* infection should be suspected in patients with recent or remote travel history to endemic areas or those involved in agricultural work, regardless of time interval, as infection may be lifelong. Recent report of a 68-year-old immigrant from Ecuador with COVID-19 complicated by disseminated strongyloidiasis and polymicrobial septic shock following treatment including methylprednisolone exemplifies the risk.[17]

Ivermectin is the drug of choice for targeted treatment once the diagnosis is established.[16] Given that the diagnosis can be challenging, it is reasonable to consider preemptive therapy when strong suspicion exists before corticosteroids.[19] Although ivermectin may inhibit replication of SARS-CoV-2 in vitro, there are no data to support clinical use for COVID-19 treatment.[20]

SEVERE AMEBIC COLITIS

Amebiasis, caused by the protozoan parasite *Entamoeba histolytica*, infects millions of people worldwide, with multiple areas around the world continuing to observe prevalence rates exceeding 10%.[21] Transmission occurs via ingestion of infective cysts, most commonly by fecally contaminated food or water; however, sexual transmission is increasingly recognized.[21,22] Following transformation within the gut, the trophozoite stage can invade the intestinal mucosa, leading to inflammatory amebic colitis or disseminate with particular predilection to forming amebic liver abscesses.[21] The highest burden is among those residing in developing countries,

although changing patterns in immigration, travel, and sexual transmission are leading to re-emergence of amebiasis in developed settings.[21–31] Most cases are asymptomatic with approximately 10% of those infected developing amebic colitis, characterized by diarrhea which may be bloody.[21] Severe forms of amebic colitis, though less common, are associated with high mortality.[32] Colonic involvement may progress to bowel necrosis, perforation, peritonitis, shock, and toxic megacolon.[32] Corticosteroid use, even brief exposure, is a known risk factor for the development of severe amebic colitis, occurring even in initially asymptomatic patients.[32–37] Patients with diarrhea from amebic colitis are often misdiagnosed as having inflammatory bowel disease and inappropriately treated with steroids, prompting deterioration.[32] Microscopy, which lacks sufficient sensitivity and specificity, is unable to distinguish pathogenic and nonpathogenic amebae, so alternative methods should be used for diagnosis whenever possible.[18,21,38,39] A combination of serology, stool antigen, and/or molecular tests often help establish diagnosis, although serology is more difficult to interpret in endemic settings because it may indicate either past or active infection, and antigen tests may be of low sensitivity, particularly for cyst-containing stool and asymptomatic infection.[38,40,41] Stool PCR is highly sensitive but use is limited in resource-poor settings.[21,42] Those with symptoms should be treated with an amebicidal agent, such as metronidazole, followed by a luminal agent, such as paromomycin.[21,43] Asymptomatic patients only need to be treated with a luminal agent to prevent future development of colitis and spread to uninfected persons.[21]

CONCLUSION

Strongyloides hyperinfection syndrome and severe amebic colitis are two potentially devastating complications that can arise in patients receiving corticosteroids, independent of dose and duration. Clinicians should consider the possibility of these parasitic infections in at-risk patients, including those with a remote history of travel to endemic areas as these severe complications can arise even years later. Algorithms for screening may be problematic if access to diagnostic testing is not readily available for those at risk; hence, further work is needed to improve the prevalence estimates of these often under-recognized and misdiagnosed infections, as well as to develop and deploy rapid, widely available diagnostics to identify in advance those most likely to benefit from antiparasitic therapy to improve poor outcomes.

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