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Correspondence

Risk of Strongyloides Hyperinfection Syndrome when prescribing dexamethasone in severe COVID-19

Dear Editor,

Dexamethasone reduces mortality in patients hospitalized with moderate and severe COVID-19 infection [1]. In this context there is a need to consider asymptomatic *Strongyloides* infection in patients undergoing immunosuppression with dexamethasone, to avoid precipitating *Strongyloides* Hyperinfection Syndrome (SHS). There are now two published case reports of SHS in COVID-19 patients immunosuppressed with dexamethasone and tocilizumab [2,3] but this is likely to underestimate the incidence of this event.

Strongyloides stercoralis, a parasitic nematode infection endemic in tropical and subtropical regions, is estimated to infect 30 to 100 million people worldwide. There are also foci of *Strongyloides* endemicity in temperate regions including Japan, Italy, Australia and the USA. In high income countries, high risk populations include migrants, refugees, travellers and ex-prisoners of war. *Strongyloides* infection occurs when soil-dwelling filariform larvae penetrate the skin and migrate to the small intestine. There they mature to adulthood, embed in the submucosa, and produce eggs by parthenogenesis. Rhabditiform larvae, released from eggs, are passed in the stool, but can also develop into infective filariform larvae whilst still within the gut, resulting in autoinfection. It is this unusual property that allows infection to persist for decades and cause overwhelming infection if people become immunosuppressed later in life.

Strongyloidiasis is often asymptomatic in immunocompetent adults, but may present with mild gastrointestinal or respiratory symptoms, or with larva currens, a rapidly moving pruritic linear skin eruption. In patients proven to have strongyloidiasis by microscopy or culture, 77% of patients have eosinophilia and 81% have positive serology [4]. However, microscopy and culture are frequently negative in asymptomatic infection. If these patients become immunosuppressed, most commonly with corticosteroids, chemotherapy or HTLV1 infection, hyperinfection may occur. Uncontrolled proliferation and dissemination of the parasite presents with fever, respiratory and gastrointestinal symptoms as well as episodes of Gram-negative sepsis or meningitis. At this stage, eosinophilia is often absent, serology may be negative, but respiratory secretions and stools demonstrate larvae. SHS case fatality rate is reportedly 100% if untreated, reduced to 47% in those treated with ivermectin. Fatal hyperinfection has been reported following short courses of low dose glucocorticoid treatment and with single high doses of dexamethasone.

In the UK, admission to critical care with COVID-19 is most common in south Asian, Black and other ethnic minority groups. Severe *Strongyloides* infection is commonest in migrants from Asia and sub-Saharan Africa or other tropical regions. Clinically, it is difficult to distinguish between these conditions:

Severe COVID-19 produces cough (68.9%), fever (71.6%), dyspnoea

(71.2%) and diarrhoea (20%), whilst SHS results in cough, fever (80.8%), dyspnoea or wheeze (88.6%) gastrointestinal symptoms (71.2%) and disseminated larva currens (rash). They also share some important complications: Respiratory failure, secondary bacterial infection, renal failure and venothrombotic events in severe COVID-19 infection; shock, respiratory failure and Gram negative sepsis in SHS. Bilateral lung infiltrates are seen in both conditions.

Furthermore, post mortems are not routinely performed in COVID-19 patients; it is therefore quite possible that SHS has already been overlooked in fatal cases of COVID-19 infection.

To prevent this, we propose a risk assessment and screening algorithm for *Strongyloides*, in COVID-19 patients with risk exposures (Fig. 1). Patients deemed at high risk (migrants with high risk exposure) may need empirical treatment with ivermectin, which has an efficacy of 85% as a single dose [5]. Those at potential, but not high risk, should be monitored and if deteriorating on immunosuppression, urgent screening with microscopy of stool, respiratory secretions, and charcoal culture for *Strongyloides* larvae should be undertaken. Serology should also be performed, but results are not usually available within 24 hours.

Stauffer et al. recently proposed a screening and treatment protocol for *Strongyloides* in COVID-19 patients [6]. We welcome their proposal but suggest more focused screening and treatment for those at the highest risk of *Strongyloides* infection and SHS. The proposed broad screening of all SARS-CoV PCR positive patients including outpatients with mild infection; those not requiring immunosuppression; and even patients without SARS-CoV-2 infection would require significant resource and may overburden services and supplies of anti-parasitic agents.

In summary, *Strongyloides* infection is common, in particular in tropical and subtropical regions and in travellers, migrants and prisoners of war who have spent time in these areas. Infection is often asymptomatic. COVID-19 patients with undiagnosed *Strongyloides* infection undergoing immunosuppression are at risk of developing SHS.

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Clinical guideline: Assessment and management of risk of Strongyloides Hyperinfection Syndrome (SHS) in hospitalised COVID-19 patients



COVID-19 positive patient
Requiring hospital admission and dexamethasone therapy

Assess all patients at risk of hitherto undiagnosed Strongyloides infection by taking thorough travel history, including travel or migration from high risk region (1) and high risk exposures (2)

1) Travel or migration from endemic areas:
Tropical and subtropical regions including: **Asia, Sub-Saharan Africa, South America, Caribbean***

*Particular high-risk areas: West Africa, South and Southeast Asia, South America, Caribbean. There are also foci of Strongyloides endemicity in temperate regions including Japan, Italy, Australia, Spain and the USA.

2) High risk Strongyloides exposure:
Migrants, refugees, travellers, farmers, miners, and military personnel

Rural travel or living; poor sanitation

Bare foot walking

Contact with human waste or sewage

Please note:
If additional signs or symptoms of SHS eg unexplained gastrointestinal symptoms or rash after tropical exposures **do not use this algorithm**, discuss with infectious diseases team for advice

Risk stratification and treatment algorithm

High risk for Strongyloides infection
Migration or travel from highly endemic region AND High-risk exposures

Non-high risk patients
Travel to endemic region but does not meet criteria for high-risk patient or has mild COVID-19 not requiring dexamethasone

Patient with moderate or Severe Covid-19 infection, requiring dexamethasone therapy: **Empirical treatment with Ivermectin (anti parasitic agent)**

Send Strongyloides serology

Send stool and sputum/Broncho Alveolar Lavage (BAL) specimen to parasitology laboratory for microscopy and Strongyloides culture

Contact the clinical parasitology service for further advice if pre-existing immunosuppression such as organ transplant recipients, biologics, immunosuppressant therapy, uncontrolled diabetes etc

*if treated for Strongyloides or has had negative Strongyloides investigations since high-risk exposure/migration, patient transferred to non high-risk

Ivermectin dosing information

Liaise with pharmacist prior to administration

Adult dose 200 micrograms/kg daily for 1 day

NB If Strongyloides larvae are detected in stool or BAL, additional doses of ivermectin will be required due to steroid-induced immunosuppression.

Pregnancy category C

Monitor patient for development of symptoms and signs suggestive of SHS:

- **Respiratory deterioration on immunosuppressive therapy**
- **Diarrhoea, rash**
- **Gram-negative sepsis; bilateral pulmonary infiltrates;**

If above occur or patient considered for additional immunosuppressant therapy:

Discuss with infectious diseases specialist regarding possibility of SHS and consider need for empirical ivermectin and:

- Send stool and sputum/BAL specimen to parasitology for microscopy
- Strongyloides serology

Fig. 1. Risk Assessment and Screening Algorithm.

Declaration of competing interest

The authors have no competing interests to declare.

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Angus De Wilton, Laura E. Nabarro, Gauri S. Godbole, Peter L. Chiodini*

Hospital for Tropical Diseases, University College Hospitals London NHS Foundation Trust, London, United Kingdom

Aileen Boyd, Katherine Woods
Homerton University Hospital NHS Foundation Trust, London, United Kingdom

E-mail addresses: aileen.boyd@nhs.net (A. Boyd), katherine.woods3@nhs.net (K. Woods).

* Corresponding author. Department of Clinical Parasitology, Hospital for Tropical Diseases, University College Hospitals London NHS Foundation Trust, London, United Kingdom.
E-mail addresses: angus.dewilton@nhs.net (A. De Wilton), laura.nabarro@nhs.net (L.E. Nabarro), gauri.godbole@nhs.net (G.S. Godbole), p.chiodini@nhs.net (P.L. Chiodini).