Strongyloidiasis in immunocompromised migrants to non-endemic countries in the era of COVID-19: What is the role for presumptive ivermectin?

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Submitted to: Journal of Travel Medicine

Manuscript Category: Editorial

Keywords: migrants, *Strongyloides*, corticosteroids, dexamethasone, SARS-CoV-2, *Strongyloides* serology, hyperinfection

Word count: Text: 1200

Figures: 1

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Highlight:

The COVID-19 pandemic has led to widespread use of dexamethasone. Corticosteroid therapy is an important risk factor for *Strongyloides* hyperinfection. Challenges associated with the performance of *Strongyloides* tests, and the poor availability of high quality and timely diagnostic testing, makes the use of presumptive ivermectin reasonable in selected situations.

Strongyloides stercoralis is an intestinal helminth, present in tropical and sub-tropical regions worldwide as well as in temperate climates. Infection is acquired through direct contact with contaminated soil. An autoinfection cycle whereby infective stage larvae re-penetrate the host skin or bowel is responsible for the indefinite lifespan of *Strongyloides* in humans. Clinical disease is a lifelong risk unless treated. [1] Strongyloidiasis has a spectrum of clinical manifestations, it is often asymptomatic in immunocompetent hosts. In the immunocompromised host, the infection can present with an accelerated autoinfective cycle known as hyperinfection syndrome (HS) and disseminated strongyloidiasis (DS) resulting in a mortality rate of up to 85%. Specific types of immune suppression such as corticosteroid therapy, hematological malignancy, hematopoietic stem cell transplant, solid organ transplant and HTLV-1 infection are the most commonly identified risk factors for HS/DS. [1]

At the global level, there is uncertainty about the burden of strongyloidiasis. It is estimated that 613.9 (95% CI: 313.1-910.1) million people are infected throughout the world. [2] Migrant populations account for most cases of strongyloidiasis in non-endemic countries. A recent systematic review and meta-analysis demonstrated a pooled strongyloidiasis seroprevalence of 12.2% (95%CI: 9.0-15.9%) among migrants originating from endemic countries to non-endemic countries. [3] The highest risk regions of origin were East Asia, Sub-Saharan Africa, Latin America where the seroprevalence was >10% and intermediate risk in the Middle East, North Africa and South Asia with a seroprevalence of about 5%. In a recent survey performed in nine infectious and tropical diseases sentinel centres in Italy, strongyloidiasis was one of the most common neglected tropical diseases with an increasing number of cases diagnosed over a 7-year period. These numbers will likely continue to increase with the unabating rise in migration.[4]

The COVID-19 pandemic has led to widespread use of dexamethasone. Dexamethasone 6mg/day for 10 days is recommended for hospitalized patients with moderate and severe COVID-19 infection and has been shown to reduce mortality. However, in those with sub-clinical strongyloidiasis, this increases the risk for HS/DS. In non and low-endemic countries,

ethnocultural communities and migrants are most likely to harbour *Strongyloides* infection and several reports show them to also be at disproportionately high risk for morbidity and mortality from COVID-19. [5] To date, there are 5 published cases of *Strongyloides* complications following dexamethasone with or without tocilizumab treatment for COVID-19. However, this infection is likely both more common and underdiagnosed. [6]

Given the range of clinical manifestations together with lack of awareness, *Strongyloides* infection can be missed, often mistaken for another medical condition. This is well illustrated in two recent case reports in this journal. A 83-years-old female migrant from Venezuela on immunosuppressive therapy for rheumatoid arthritis and secondary Sjogren's syndrome presented with lower gastrointestinal bleeding.[7] A colonoscopy was performed and demonstrated erythematous mucosa and superficial ulcer leading to a working diagnosis of inflammatory bowel disease. The diagnosis of HS was made only from the histopathology showing granulomas surrounded by dense eosinophilic inflammation and *Strongyloides* larvae. *Strongyloides* hyperinfection was also initially missed in a 69-year-old migrant from Colombia presenting with abdominal pain and vomiting who developed progressive shortness of breath with diffuse bilateral infiltrates on imaging.[8] He was receiving immunosuppressive therapy as part of a clinical trial for stage IV prostate cancer with bone metastases. He was initially treated with broad-spectrum antibiotics, followed by methylprednisolone and gancyclovir for a suspicion of drug-induced toxicity and CMV viremia respectively. A diagnostic bronchoscopy was performed and microscopic examination of the bronchoalveolar lavage fluid revealed *Strongyloides* larvae. These cases reflect the lack of awareness of this neglected tropical disease and raise questions related to the best strategy to prevent severe strongyloidiasis in the migrant immunocompromised patients: systematic screening or presumptive ivermectin treatment have both been employed.

A recent systematic review provided indirect evidence supporting screening for strongyloidiasis in migrants from endemic areas and particularly in those who are, or are anticipated to become immunosuppressed because of the increased risk of HS/DS. [9] The most

cost-effective strategy to decrease morbidity and mortality due to strongyloidiasis in migrant is unclear. A recent cost-effectiveness analysis has showed that presumptive treatment of all immunosuppressed migrants from *Strongyloides* endemic areas to the European Union would generate cost savings to the health system. [10] Currently, screening for strongyloidiasis in migrants from endemic region who are immunocompromised, will undergo iatrogenic immunosuppression or have HTLV-1 infection is recommended. [1,11]

Despite the recommendations for screening, the diagnostic approach to strongyloidiasis is challenging and testing is not widely available, often requiring referral to a reference laboratory. The sensitivity of stool-based parasitological and biomolecular methods is low hence, infection can easily be missed. Serologic testing is the most sensitive modality and is the routine diagnostic method of choice, although specificity is difficult to define in the absence of a diagnostic gold standard. In immunosuppressed patients the sensitivity of serology may be reduced.

Ivermectin is the drug of choice for *Strongyloides* treatment. Limited availability and slow turnaround of diagnostic tests means that, in selected circumstances, it is reasonable to consider presumptive treatment in high-risk immunosuppressed patients prescribed additional urgent immunosuppression such as corticosteroids for SARS-CoV-2. Ivermectin has a very good safety profile and could be administered as a single dose for presumptive treatment. Presumptive treatment was recently recommended for patients with COVID-19 at moderate to high-risk for strongyloidiasis and who may become candidates for dexamethasone. [12] Ivermectin has been widely used in the context of SARS-CoV-2 pandemic given the reported inhibitory effect on viral replication in vitro, despite the absence of supporting clinical data. As a result, drug shortages have been widely reported with limited quantities available; targeting individuals at highest risk of *Strongyloides* infection for empiric treatment will be necessary. A simple and targeted presumptive treatment strategy for asymptomatic strongyloidiasis among COVID-19 positive patients or those with other conditions for which urgent corticosteroids need to be administered is proposed in Figure 1. For immunocompromised migrants from high and moderate-risk regions

who will be receiving urgent corticosteroids, presumptive ivermectin treatment should be given. Presumptive ivermectin should be considered in previously immunocompetent patients receiving tocilizumab with dexamethasone for the treatment of COVID-19. Currently, 200 micrograms/kg daily for one to two days is commonly recommended. [12] In the absence of symptoms, it is presumed that the burden of larvae in an infected patient is likely to be low, and therefore a single dose should be adequate while waiting for *Strongyloides* testing results. A positive test should trigger an infectious or tropical diseases consultation for further management. Screening despite presumptive treatment and follow-up if the screening is positive should be considered. Persons born or with prolonged residence in the rainforest regions of central Africa should have high microfilaremic loiasis excluded prior to administration of ivermectin given the risk of encephalopathy.

Detecting and treating occult or subclinical infections in the highest risk groups will be key to preventing morbidity and mortality from this infection. Challenges associated with the sensitivity and specificity of *Strongyloides* tests, and the poor availability of high-quality and timely diagnostic testing, makes the use of presumptive ivermectin reasonable in selected situations. Current shortages of ivermectin call for drug stewardship targeting individuals at highest risk for HS/DS. More cost-effectiveness studies of test and treat versus presumptive treatment strategies in the migrant populations are needed.

Declaration of interest

We declare no competing interests

Contributors:

Sapha Barkati designed the work and drafted the manuscript. Christina Greenaway and Michael Libman contributed to the drafting and revision of the manuscript. All the authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Figure 1 CAPTION

Algorithm for testing and initiating presumptive treatment for asymptomatic strongyloidiasis in SARS-CoV-2 positive migrants from endemic regions requiring hospitalisation and dexamethasone OR in a migrant requiring urgent corticosteroids for other medical conditions

Legend:

[a]Except Autralia, New-Zealand and New Caledonia

[b]Immunocompromised patients include: Primary immunodeficiency, hematologic malignancy on chemotherapy, oncologic malignancy on chemotherapy/radiation therapy, Hematopoetic stem cell transplant, solid organ transplant, COPD/Asthma/lung fibrosis on corticosteroids +/- immunosuppressive agents, Autoimmune/inflammatory disorder on corticosteroids +/- immunosuppressive agents, HIV with CD4 less than 200 cells/ul. Costicosteroids: Equivalent to 20 mg/day of prednisone for ≥2 weeks

[c]If *Strongyloides* serology and/or stool tests are positive, Infectious diseases consultation is recommended

[d]Patients who have been previously screened negative or who have already been treated with ivermectin should not be retreated or screened unless significant exposure occurred in the interval.

[e]Stool testing includes: *Strongyloides* culture techniques (e.g. agar plate culture, Baermann technique), stool Ova and parasites examination, *Strongyloides* nucleic acid amplification testing in stool

[f]In a patient co-infected with HTLV-1 or immunocompromised, optimal treatment for strongyloidiasis is unknown and screening despite presumptive treatment and follow-up if the screening test is positive should be considered

[g]Monitor patient for development of signs and symptoms that may suggest *Strongyloides* hyperinfection syndrome: non-specific abdominal pain, unexplained diarrhea, migratory rash, eosinophilia, enteric pathogen bacteremia/meningitis, new bilateral lung infiltrates. If those signs and symptoms occurs, examination for larvae (stool, sputum and other body fluid or tissue as appropriate (e.g. urine, cerebrospinal fluid)), presumptive ivermectin and infectious diseases consultation are recommended. If considering increasing immunosuppression, presumptive ivermectin and Infectious diseases consultation are also recommended.

[h]Consider presumptive ivermectin. Infectious diseases consultation is recommended

[i]Ivermectin adult dose: 200 mcg/kg per day x 1 day; Pregnancy category C

[j]Persons born or with prolonged residence in nations of the rainforest area of central Africa (e.g., Cameroon, Equatorial Guinea, Gabon, Central African Republic, Congo and the Democratic Republic of the Congo, Nigeria, Chad, South Sudan, and Angola) should have high microfilaremic loiasis excluded prior to administration of ivermectin given the risk of encephalopathy. Infectious diseases consultation is recommended.