RISK FACTORS FOR STRONGYLOIDIASIS HYPERINFECTION AND CLINICAL OUTCOMES

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Abstract. Strongyloidiasis, caused by *Strongyloides stercoralis*, consists of various clinical syndromes. Strongyloidiasis hyperinfection leads to morbidity and mortality particularly in immunocompromized patients. This study aimed to determine the risk factors for strongyloidiasis hyperinfection and clinical outcomes. The medical records for hospitalized patients infected with *S. stercoralis* at Ramathibodi Hospital during 1994-2005 were retrospectively reviewed. Risk factors for strongyloidiasis hyperinfection were determined. There were 123 episodes of strongyloidiasis in 111 patients. The mean age was 46.8±17.8 years; 61% were males. Of 123 episodes, 37 (30.1%) had strongyloidiasis hyperinfection; the others had chronic strongyloidiasis. All the patients with strongyloidiasis hyperinfection and 88.3% of those with chronic strongyloidiasis were immunocompromized (p=0.032); 89.2% of the former and 55.8% of the latter had received corticosteroids (p<0.001). There were no significant differences in the type of immunocompromized host and the corticosteroid dosage between the two groups (p>0.05). The hyperinfection group had a lower mean serum protein (p=0.026) and albumin (p=0.027) but a higher frequency of sepsis (p=0.029), asthma-like symptoms (p=0.025), adult respiratory distress syndrome (p=0.026), and a longer duration of treatment (p=0.004). By logistic regression, corticosteroids use was a risk factor for hyperinfection (OR=6.5, 95%CI=2.1-20.0, p=0.001). Most of the patients were treated with albendazole or thiabendazole, with a cure rate of 76.9%, whereas other recent cases treated with ivermectin had an average cure rate of 83.3%. The overall mortality rate was 8.1%.

INTRODUCTION

Strongyloides stercoralis is an intestinal nematode with worldwide distribution, especially in tropical and subtropical areas. It is estimated that 50-100 million people are infected around the world (Genta, 1989). In Thailand, the overall prevalence of *S. stercoralis* infection was 23.5% in northeast (Jongsuksuntigul *et al*, 2003) and 7.6% in Bangkok and surrounding districts (Pitisuttithum *et al*, 1995). It is clinically important because *S. stercoralis* can persist and develop severe hyperinfection that causes morbidity and mortality in immunocompromized patients (Leelarasamee *et al*, 1978; Fardet *et al*, 2006).

The clinical manifestations of strongyloidiasis vary from asymptomatic to fatal illness. The life cycle of *S. stercoralis* starts with the filariform larvae of *S. stercoralis* penetrating the skin and migrating to the small intestine or lungs and ascending the tracheobronchial tree to the gastrointestinal tract. The autoinfective cycle occurs when an asexually reproduced larvae invades the intestinal wall or perianal area and enters the blood stream. This cycle is able to persist in the host indefinitely (Keiser and Nutman 2004). The clinical syndromes of strongyloidiasis are: acute strongyloidiasis,

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chronic strongyloidiasis, strongyloidiasis hyperinfection and disseminated infection (Keiser and Nutman, 2004).

Acute strongyloidiasis consists of local reaction, such as rashes and pruritic skin, occurring shortly after larvae entry. Pulmonary symptoms with eosinophilia develop several days later, with diarrhea and abdominal pain about two weeks after infection and just before the detection of larvae in the stool.

Chronic strongyloidiasis is often asymptomatic. Autoinfection occurs and the cell-mediated immune response of the host controls the number of larvae. Clinical manifestations include vomiting, diarrhea, constipation, recurrent asthma, and skin symptoms such as urticaria and larva currens.

Strongyloidiasis hyperinfection is a syndrome of accelerated autoinfection where the signs and symptoms are attributed to increased larval migration. Gastrointestinal and respiratory symptoms are presentation of chronic infection and the detection of increased numbers of larvae in the stool and/or sputum is the hallmark of hyperinfection.

Disseminated infection is often used to describe the presence of larva beyond the range of the respiratory and gastrointestinal systems but does not imply a greater severity of the disease (Keiser and Nutman, 2004).

The immunocompromized conditions previously reported to be associated with strongyloidiasis hyperinfection are corticosteroid use, immunosuppressive drug use, hematologic malignancy, organ transplant, HIV infection, HTLV-1 infection, malnutrition and chronic alcoholism (Adedayo *et al*, 2002; Keiser and Nutman, 2004). However, some of these reports are small sample-size studies or were designed to study a particular risk factor. Strongyloidiasis can occur in any host and can progress to strongyloidiasis hyperinfection in an immunocompromized host. The particular type of immunocompromized conditions and their susceptibility to hyperinfection are unknown.

Thailand is endemic with a high prevalence of strongyloidiasis (Sithithaworn *et al*, 2003). There have been no large-scale clinical studies in Thailand to determine the risk factors for strongyloidiasis hyperinfection. We therefore conducted this study to determine the risk factors for strongyloidiasis hyperinfection and to assess the clinical outcomes of the disease. Knowing the risk factors can lead to early diagnosis and prompt treatment, which may prevent unfavorable morbidity and mortality.

MATERIAL AND METHODS

This was a retrospective cohort study. The medical records of patients infected with *S. stercoralis* in Ramathibodi Hospital between January 1994 and December 2005 were reviewed. Patients found with strongyloides larvae in the stool, sputum, bronchoalveolar larvage (BAL) fluid, or other tissues were included in the study. Since there were no patients diagnosed with acute strongyloidiasis, the study patients were classified into two groups, chronic strongyloidiasis and strongyloidiasis hyperinfection, according to site and number of larval specimens. Strongyloidiasis hyperinfection was defined as finding larvae in the sputum or BAL fluid or numerous larva in the stool or sites other than the gastrointestinal or respiratory tracts. Chronic strongyloidiasis was defined as finding only few larvae in the gastrointestinal tract or when the number was not described.

Possible risk factors and other data collected included patient demographics, underlying diseases, medications, signs and symptoms, laboratory data for the most recent tests prior to the diagnosis of strongyloidiasis (such as complete blood count, blood urea nitrogen, creatinine, total protein, albumin, hemoculture reports, stool, sputum, BAL fluid, and others pathological reports), treatment

and outcomes.

The clinical outcomes were defined as follows: Cure was defined as undetectable larvae in at least one specimen after treatment; relapse was described in patients with positive larvae in any specimens after successful treatment; unknown was used in patients who did not have repeated specimen examinations after treatment.

The primary objective of the study was to determine the risk factors for hyperinfection strongyloidiasis. The secondary objective was to compare mortality rates, treatment and outcomes between the two groups.

Mean (± standard deviation, SD), median (interquartile range, IQR) and frequencies (%) were used to describe the patient characteristics in each group. The chi-square test and Fisher's exact were use to compare categorical variables and *t*-test and Mann-Whitney *U* test were used to compare continuous variables between the two groups, where appropriate. The possible risk factors were entered into the model of binary logistic regression. All analyses were performed using SPSS program version 11.5. A p-value of less than 0.05 was considered statistically significant. The study was approved by the ethics committee of Ramathibodi Hospital.

RESULTS

There were 123 episodes of strongyloidiasis in 111 patients. The mean age was 46.8±17.8 years; 59.3% were males. The majority (71.5%) of the study patients resided outside Bangkok. More than half of the patients were farmers or labor workers. Twelve of 123 episodes (9.8%) were relapse episodes. There were 86 and 37 episodes of chronic strongyloidiasis and strongyloidiasis hyperinfection, respectively. There were no patients with disseminated strongyloidiasis or acute strongyloidiasis according to the above definitions.

The baseline characteristics of the patients who had chronic strongyloidiasis and hyperinfection are described in Table 1. There were no differences in demographics, address, domicile, or occupation between the two groups. All patients with strongyloidiasis hyperinfection were immunocompromized, whereas 11.6% of those with chronic strongyloidiasis were immunocompetent patients (p=0.032). The types of immunocompromized patients are shown in Table 1. There were no differences in the types of immunocompromized hosts between the two groups (p>0.05). Eighty-nine point two percent (89.2%) of those with strongyloidiasis hyperinfection and 55.8% of those with chronic strongyloidiasis received corticosteroids within three months before the diagnosis of strongyloidiasis (p<0.001). However, there were no differences in corticosteroids dosage or duration between the two groups. The therapeutic methods and details of corticosteroid therapy are described in Table 2. There were no statistically significant differences (p>0.05) between the two groups in the use of other immunosuppressive drugs *eg* azathioprine, cyclophosphamide or chemotherapy, radiotherapy or anti-secretary drugs.

The diagnosis of strongyloidiasis was made by finding larvae in the stools, sputum, BAL fluid or tissue biopsies, as shown in Table 3. Ninety-four of 123 (76.4%) patients were found to have larvae in the first stool and twenty of 28 (71.4%) patients were found positive in the repeated stool examination. The total of 114 patients (92.7%) had positive stool examinations. Larvae were detected in the respiratory tracts of 59.5% (22 from 37) of patients with strongyloidiasis hyperinfection, and 40.5% of this group had numerous larvae in the stool. Fifteen (40.5%) patients with strongyloidiasis hyperinfection had larvae in both the stool and sputum or BAL fluid. Tissue biopsies that yielded *S. stercoralis* were from the gastrointestinal tract, such as on duodenal mucosal biopsy or chronic diarrhea

Table 1
Baseline characteristics of patients with chronic and strongyloidiasis hyperinfection.

Baseline characteristics	Chronic strongyloidiasis (n=86)	Strongyloidiasis hyperinfection (n=37)	p-value
Age, years, mean ±SD	47 ± 18.1	46 ± 17.4	0.755
Gender			0.842
Male	52 (60.5%)	21 (56.8%)	
Female	34 (39.5%)	16 (43.2 %)	
Address			1.000
Bangkok	25 (29.1%)	10 (27.0%)	
Outside Bangkok	61 (70.9%)	27 (73.0%)	
Domicile (Birth place)			0.753
Bangkok	10 (11.6%)	3 (8.1%)	
Outside Bangkok	76 (88.4%)	34 (91.9%)	
Occupation			0.283
Farmer	27 (31.4%)	8 (21.6%)	
Labor worker	28 (32.6%)	10 (27%)	
Merchant	5 (5.8%)	6 (16.2%)	
Government officer	4 (4.7%)	4 (10.8%)	
Housewife	14 (16.3%)	4 (10.8%)	
Student	3 (3.5%)	3 (8.1%)	
Soldier or policeman	5 (5.8%)	2 (5.4%)	
Host			0.032
Immunocompetent	10 (11.6%)	0 (0%)	
Immunocompromized	76 (88.4%)	37 (100%)	
Type of immunocompromized host			
Autoimmune disease	25 (32.5%)	17 (45.9%)	0.097
Hematologic malignancy	15 (19.5%)	5 (13.5%)	0.791
HIV infection	8 (10.4%)	3 (8.1%)	1.000
Malnutrition	2 (2.6%)	1 (2.7%)	0.364
Alcoholism or alcoholic hepatitis	9 (11.7%)	1 (2.7%)	0.627
DM	1 (1.3%)	0 (0%)	0.722
Solid tumor	12 (15.6%)	6 (16.2%)	0.784
Others[a]	5 (6.5%)	4 (10.8%)	0.450

[a]steroid abuse from herbal drugs that contain corticosteroids and HBV cirrhosis

with incidental finding in unexpected cases.

The clinical manifestations of chronic and strongyloidiasis hyperinfection are described in Fig 1. A higher frequencies of sepsis (p=0.029), asthma-like symptoms (p=0.025), pneumonia (p<0.001), adult respiratory distress syndrome (ARDS) (p=0.026) and vomiting (p=0.017) were found in the hyperinfection group. Asymptomatic and acute diarrhea were found more frequently in chronic strongyloidiasis but this was not significantly different (p>0.05). Laboratory results revealed only serum total protein and albumin were different between the two groups (p<0.05). The others, including hematocrit, white blood cell count (WBC), eosinophill count, blood urea

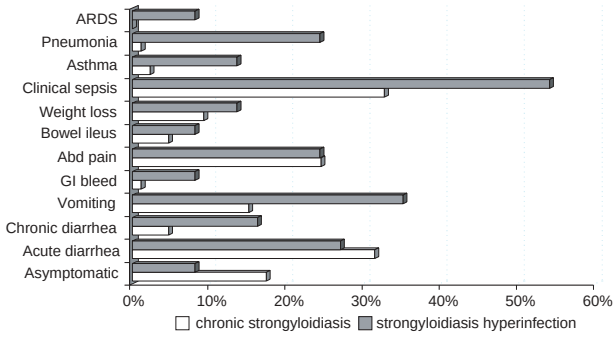

Fig 1–Clinical manifestations of strongyloidiasis.

nitrogen (BUN), creatinine, globulin, positive blood culture and positive stool occult blood were not different between the two groups (p>0.05). Blood cultures were positive in 15 (12.2%) patients. Gram-negative bacteria were the most common organisms (60%). Of the nine positive blood cultures with gram-negative bacteria, 5 were *Escherichia coli*; the others were *Salmonella* spp, *Klebsialla pneumoniae,* and *Pseudomonas aeruginosa. Staphylococcus aureus* and *Streptococcus* spp were found in

Table 2
Therapeutic methods and corticosteroid therapy in patients with strongyloidiasis.

Therapeutic methods	Chronic strongyloidiasis (n=86)	Strongyloidiasis hyperinfection (n=37)	p-value
Corticosteroids use	48 (55.8%)	33 (89.2%)	<0.001
Immunosuppressive drugs	30 (34.9%)	14 (37.8%)	0.838
Radiation	8 (9.3%)	4 (10.8%)	0.752
Anti-secretary drugs	27 (31.4%)	18 (48.6%)	0.102
Corticosteroids therapy			
Median daily dosage[a] of equivalent prednisolone, mg, (IQR)	30 (7.5-67.5)	40 (15-60)	0.453
Total duration of corticosteroid use	(n=43)	(n=31)	0.158
Less than 15 days	17 (39.5%)	7 (22.6%)	
15-30 days	3 (7.0%)	3 (9.7%)	
1-6 months	18 (41.9%)	16 (51.6%)	
more than 6 months	5 (11.6%)	5 (16.1%)	

[a]at the time of strongyloidiasis diagnosis

Table 3
Diagnostic specimen and types of strongyloidiasis.

S. stercoralis larva appeared in	Chronic strongyloidiasis (n=86)	Strongyloidiasis hyperinfection (n=37)
Stool	83 (96.5%)	15 (40.5%)
Sputum	0 (0%)	16 (43.2%)
BAL fluid	0 (0%)	7 (18.9%)
Sputum or BAL fluid	0 (0%)	22 (59.5%)
Stool, sputum or BAL fluid	0 (0%)	15 (40.5%)
Other (tissue biopsy or fluid cytology)	3 (3.5%)	3 (8.3%)

BAL=bronchoalveolar larvage

Table 4
Treatment and outcomes of strongyloidiasis.

Treatments and outcomes	Chronic strongyloidiasis (n=86)	Strongyloidiasis hyperinfection (n=37)	p-value
Treatment			0.056
Thiabendazole	15 (17.6%)	14 (37.8%)	
Albendazole	60 (70.6%)	13 (35.1%)	
Thiabendazole and Albendazole	1 (1.2%)	1 (2.7%)	
Ivermectin	4 (4.7%)	1 (2.7%)	
Albendazole and Ivermectin	5 (5.9%)	8 (21.6%)	
Duration of treatment, days, median (IQR)	7 (3-14)	11 (7-20)	0.001
Outcomes			0.059
Cured	62 (72.1%)	33 (89.2%)	
Relapsed	2 (2.3%)	2 (5.4%)	
Unknown results	22 (25.6%)	2 (5.4%)	
Death[a]	5 (5.8%)	5 (13.5%)	0.166

[a]all died from underlying diseases

5 positive cultures. *Cryptococcus neoforman* was found in an HIV-infected patient.

Treatment of strongyloidiasis varied depending on the available drug at each period of time. From 1994 to 1999, thiabendazole was the first line drug and albendazole was given in relapsed cases. From 2000 albendazole was the first line drug due to the unavailability of thiabendazole in Thailand. In refractory cases, prolongation of albendazole was used to eradicate this parasite until 2003 when ivermectin was available and was administered for intractable hyperinfection with strongyloidiasis. Since 2003, ivermectin has been increasingly used in both hyperinfection and chronic strongyloidiasis as single agent or combined with albendazole.

The treatment and outcomes for the two groups are described in Table 4. Outcomes in the ivermectin or ivermectin combined with albendazole groups were not significant (p=0.056). The median duration of treatment was longer in strongyloidiasis hyperinfection (p=0.001). Treatment with albendazole or thiabendazole had a cure rate of 76.9%, whereas treatment with ivermectin had a cure rate of 83.3%. There were no differences in cure rates between patients who received ivermectin and albendazole or thiabendazole and between patients with hyperinfection and chronic strongyloidiasis (p>0.05). Unknown treatment outcome, defined as lack of microscopic examination of any specimens after treatment, was higher in chronic strongyloidiasis (25.6% versus 5.4%).

The overall mortality rate was 8.1%. Patients with strongyloidiasis hyperinfection had a higher tendency toward mortality than the patients with chronic strongyloidiasis (13.5% versus 5.8%, p=0.166). Nine of 10 patients who died were cured from strongyloidiasis before death; one patient did not have a stool examination after treatment. The causes of death in these patients were from underlying diseases, such as lung cancer, germ cell tumor, acute lymphoblastic leukemia, systemic lupus erythematosus, nephrotic syndrome, cirrhosis, exogenous Cushings and AIDS. Some

Table 5
Logistic regression of risk factors for strongyloidiasis hyperinfection.

Risk factors	Univariate analysis			Multivariate analysis		
	OR	95%CI	p-value	OR	95%CI	p-value
Corticosteroids use	6.53	2.13-20.05	0.001	7.75	2.07-28.98	0.002
Anti-secretary drugs use	2.07	0.940-4.56	0.710	2.12	0.89-4.97	0.089
Radiation	1.18	0.33-4.20	0.796	0.77	0.21-2.88	0.698
Immunosuppressive drugs use	1.14	0.51- 2.53	0.754	0.61	0.25-1.49	0.278

OR=odds ratio; 95% CI=95% confidence interval

also had pneumonia, sepsis, acute renal failure or ARDS leading to death.

Results of univariate analysis indicate that immunocompromized patients who used corticosteroids were at risk for strongyloidiasis hyperinfection. The risk factors for strongyloidiasis hyperinfection, including immunocompromized host, corticosteroid use, use of other immunosuppressive drugs, use of anti-secretary drugs and radiotherapy, were assessed using multivariate analysis, as shown in Table 5. From multivariate analysis, only corticosteroids use was a risk factor for strongyloidiasis hyperinfection (OR=7.75, p=0.002, 95% CI=2.07-28.98).

DISCUSSION

In the present study, all patients with strongyloidiasis hyperinfection were immunocompromized, and the majority were corticosteroid users. Use of corticosteroids was the only independent risk factor for strongyloidiasis hyperinfection. Patients who used corticosteroids were 8 times more likely to have strongyloidiasis hyperinfection than patients who did not use corticosteroids. Previous studies demonstrated corticosteroid use is a risk factor for strongyloidiasis, with a lower odds ratio (Davidson *et al*, 1984; Nucci *et al*, 1995). These reports studied the risk factors for strongyloidiasis, but included both chronic and hyperinfection cases and were conducted in a non-endemic area with a low prevalence of strongyloidiasis. Hence, corticosteroid use markedly increased the risk for hyperinfection among patients who had strongyloidiasis. In clinical practice, we recommend looking for strongyloidiasis hyperinfection when caring patients using corticosteroids who have strongyloidiasis.

The median daily prednisolone-equivalent dosage at the time of diagnosis of strongyloidiasis hyperinfection was 40 mg (IQR 15-60), which is similar to a previous study (Fardet *et al*, 2006). However, with duration of corticosteroid therapy less than 15 days, hyperinfection was more frequent in the present study (22% versus 9%).

The pathophysiologic effects of corticosteroids on inducing hyperinfection include suppression of eosinophils (Genta, 1992; Keiser and Nutman, 2004), lymphocyte activation and a direct effect on the parasites that hastens their transformation from rhabditiform to invasive filariform larvae (Genta, 1992).

The present study demonstrated that other types of immunocompromized conditions, such as HIV infection, diabetic mellitus, chronic alcohol use, hypogammaglobulinemia and malnutrition were not risk factors for strongyloidiasis hyperinfection. Other therapeutic methods that have been reported as risk factors for hyperinfection were immunosuppressive drugs other than corticosteroids such as aza-

thioprine, cyclophosphamide, chemotherapy, radiotherapy and anti-secretary drugs (*eg* H2 blockers, proton pump inhibitors) (Keiser and Nutman, 2004). However, these were not risk factors in the present study.

The clinical manifestations of strongyloidiasis hyperinfection were more severe than chronic strongyloidiasis. Clinical sepsis was the most frequent manifestation, and accounted for more than 50% of patients with strongyloidiasis hyperinfection. The frequencies of sepsis, asthma-like symptoms, pneumonia, and ARDS were higher in patients with strongyloidiasis hyperinfection, which is in agreement with previous reports (Keiser and Nutman, 2004). The manifestations of hyperinfection are attributed to increased larval migration and exacerbation of gastrointestinal and respiratory symptoms. The numbers of eosinophils in this study were not different between the two groups and were within normal range, which is different from previous studies that found strongyloidiasis was associated with eosinophilia (Berk *et al*, 1987; Roman-Sanchez *et al*, 2003). This may be explained by the fact that these previous studies were performed in non-endemic areas. In a report from Brazil, an endemic area, eosinophilia was not associated with strongyloidiasis (de Messias *et al*, 1987). Lower total protein and albumin, which were associated with strongyloidiasis hyperinfection in the present study, can be either a cause of or result in strongyloidiasis hyperinfection. Several reports have demonstrated that malnutrition and hypogammaglobulinemia are associated with strongyloidiasis hyperinfection (Scowden *et al*, 1978; Brandt de Oliveira *et al*, 1981; Keiser and Nutman, 2004).

The majority of positive blood cultures in the present study revealed gram-negative bacteria. This finding corresponds with other studies that found enteric bacteria can follow the larva from gastrointestinal tract to systemic infection (Keiser and Nutman, 2004; Pornsuriyasak *et al*, 2004; Lam *et al*, 2006). However, there was no difference in bacteremia between the two groups in the present study. Strongyloidiasis has an autoinfective cycle. Larva can invade the intestinal wall, migrate to the lungs and introduce enteric bacteria into the blood stream in both chronic and strongyloidiasis hyperinfection. The use of antibiotics to inhibit bacterial growth in both study groups resulted in no difference in bacteremia between the two groups.

The cure rates for thiabendazole and albendazole against strongyloidiasis in previous reports ranges from 38% to 81% (Grove, 1982; Keiser and Nutman, 2004), in which thiabendazole had a higher cure rate than albendazole. The cure rates for ivermectin were 78-100%, and it had fewer side effects. Thus, ivermectin is the treatment of choice for strongyloidiasis (Naquira *et al*, 1989; Toma *et al*, 2000; Igual-Adell *et al*, 2004; Keiser and Nutma, 2004). In the present study, the cure rate of thiabendazole or albendazole was 76.9% and for ivermectin was 83.3%. However, strongyloidiasis hyperinfection needed a longer duration of treatment than chronic strongyloidiasis in order to prevent relapse. Side-effects of ivermectin found in the present study were confusion in a patient with accidental overdose of ivermectin at 2,000 µg/kg/dose. The patient recovered within one day after discontinuation of ivermectin.

There were some limitations in the present study. First, the study was retrospective. The diagnosis of strongyloidiasis hyperinfection could have been underestimated in many ways, such as a lack of sputum examination in some patients with chronic strongyloidiasis and different methods for the detection of the larva. We did not use the agar plate culture method, which is a standard laboratory method with a high sensitivity (Siddiqui and Berk, 2001; Keiser and Nutman, 2004). Second, the number of immunocompromized patients other than those who used corticoster-

oids was too small. This may lead to a discrepancy between our results and those of previous reports which showed an association between other types of immunocompromized hosts and strongyloidiasis hyperinfection (Scowden *et al*, 1978; Adedayo *et al*, 2002; Carvalho and Da Fonseca Porto, 2004; Keiser and Nutman, 2004). Third, HTLV-1 infection, which has been reported to be associated with strongyloidiasis hyperinfection, was not investigated in this study because HTLV-1 is not an endemic disease in Thailand (Urwijitaroon *et al*, 1997; Ishida *et al*, 2000). The results from the present study may provide clinical data for clinicians who care for patients at risk for or having strongyloidiasis hyperinfection.

In conclusion, the use of corticosteroids is a major risk factor for strongyloidiasis hyperinfection. Strongyloidiasis hyperinfection is associated with a higher incidence of sepsis, pneumonia, and ARDS. A future study of the cost-effectiveness of routine screening for strongyloidiasis hyperinfection in this population is needed to confirm the benefits of screening for this in clinical practice.

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