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Strongyloides stercoralis in the Immunocompromised Population

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INTRODUCTION

Strongyloides stercoralis is an intestinal nematode of humans. It is estimated that tens of millions of persons are infected worldwide, although no precise estimate is available (42). Although most infected individuals are asymptomatic (43), *S. stercoralis* is capable of transforming into a fulminant fatal illness under certain conditions associated with a compromise of host immunity. Such conditions have commonly been summarized as "defects in cell-mediated immunity," although the specific circumstances under which *S. stercoralis* hyperinfection develops are not always predictable.

Given the increasing numbers of immunocompromised individuals throughout the world, a closer examination of the conditions under which *S. stercoralis* infection becomes dangerous is warranted. Better approaches to identifying, screening, and treating those at risk will likely decrease the morbidity and mortality associated with *S. stercoralis* infection.

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LIFE CYCLE

The *S. stercoralis* life cycle encompasses both free-living and parasitic stages. Adult female worms parasitizing the human small intestine lay eggs in the intestinal mucosa that hatch into rhabditiform larvae, which are shed in the stool. In the environment, under warm moist conditions that often characterize the tropical and subtropical areas where *S. stercoralis* is endemic, rhabditiform larvae can either molt into infective filariform larvae or develop through succeeding rhabditiform stages into free-living adults. Harsh environmental conditions are thought to be a stimulus towards development into parasitic stages. Sexual reproduction occurs exclusively in the free-living stage (80).

Humans are generally infected transcutaneously, although infection has also been experimentally induced by oral administration of water contaminated with filariform larvae (42). After dermal penetration, the filariform larvae, through undefined mechanisms, migrate to the small intestine. The most clinically relevant, though perhaps not the predominant (66), migration is the classic pulmonary route, in which organisms enter the bloodstream and are carried to the lungs, ascending the tracheobronchial tree to enter the gastrointestinal tract. Only female adults are detectable in humans, and subsequent reproduction occurs asexually (80).

Some rhabditiform larvae transform into invasive filariform larvae before being excreted. As such, they are capable of reinfecting the host by invading the intestinal wall or the perianal skin (42). This autoinfective cycle can occur at a low level throughout infection and allows subsequent generations to persist in the host indefinitely (80).

EPIDEMIOLOGY

Although *S. stercoralis* is often considered a disease of tropical and subtropical areas, endemic foci are also seen in temperate regions (5, 128). Low socioeconomic status (128), alcoholism (26), white race (24), and male gender (128) have been associated with higher prevalences of *S. stercoralis* stool positivity. Clusters of cases in institutionalized individuals with mental retardation (8, 93) suggest that nosocomial transmission can occur. Occupations that increase contact with soil contaminated with human waste, which may include farming (69, 98) and coal mining (127, 128) depending on local practices, increase the risk of infection. Swimming in or drinking contaminated water has not been proven to be a significant source of transmission, perhaps because larvae do not thrive when immersed in water (88). Different prevalences among ethnic groups (24, 128) may simply reflect behavioral or socioeconomic factors, but some have suggested that different skin types may be more or less resistant to larval penetration (128).

CLINICAL SYNDROMES

As the clinical syndromes of *S. stercoralis* encompass a spectrum and terms are used variably, it is necessary to set forth some definitions before proceeding further.

Acute Strongyloidiasis

From experimental human infections, it is known that a local reaction at the site of larval entry can occur almost immediately and may last up to several weeks (31). Pulmonary symptoms such as a cough and tracheal irritation, mimicking bronchitis, occur as larvae migrate through the lungs several days later. Gastrointestinal symptoms (diarrhea, constipation, anorexia, abdominal pain) begin about 2 weeks after infection, with larvae detectable in the stool after 3 to 4 weeks. Experimental human infections on which this description is based were initiated with many hundreds of larvae and most likely overestimate the severity and perhaps the tempo of naturally acquired infections.

Chronic Strongyloidiasis

Chronic infection with *S. stercoralis* is most often asymptomatic (43). There are a number of signs and symptoms attributable to chronic strongyloidiasis that are unrelated to accelerated autoinfection. Chronic gastrointestinal manifestations, such as intermittent vomiting, diarrhea, constipation, and borborygmus, are common complaints. Pruritus ani and dermatologic manifestations such as urticaria and larva currens rashes are also common (89). Recurrent asthma (73, 109, 124) and nephrotic syndrome (133) have also been associated with chronic strongyloidiasis infection.

Complications such as intestinal obstruction (32), ileus (85), hemodynamically significant gastrointestinal bleeding, and acute worsening of chronic intestinal manifestations have occurred in the context of an increased larval burden. Even in the absence of pulmonary symptoms, such presentations could be considered a manifestation of hyperinfection when accompanied by large numbers of filariform larvae in the stool.

Hyperinfection

Hyperinfection describes the syndrome of accelerated autoinfection, generally — although not always (51, 120) — the result of an alteration in immune status. Parasitologically, the distinction between autoinfection and hyperinfection is quantitative and not strictly defined. Therefore, the diagnosis of hyperinfection syndrome implies the presence of signs and symptoms attributable to increased larval migration. Development or exacerbation of gastrointestinal and pulmonary symptoms is seen, and the detection of increased numbers of larvae in stool and/or sputum is the hallmark of hyperinfection. Larvae in nondisseminated hyperinfection are increased in numbers but confined to the organs normally involved in the pulmonary autoinfective cycle (i.e., gastrointestinal tract, peritoneum, lungs), although enteric bacteria, which can be carried by the filariform larvae or gain systemic access through intestinal ulcers, may affect any organ system.

Disseminated Infection

The term disseminated infection is often used to refer to migration of larvae to organs beyond the range of the pulmonary autoinfective cycle. This does not necessarily imply a greater severity of disease. Extrapulmonary migration of larvae has been shown to occur routinely during the course of exper-

imental chronic *S. stercoralis* infections in dogs (106) and has been reported to cause symptoms in humans without other manifestations of hyperinfection syndrome (57). Similarly, many cases of hyperinfection are fatal without larvae being detected outside the pulmonary autoinfective route.

As documenting disseminated infection may be more a matter of vigilance than a fundamental difference in disease mechanisms, the term hyperinfection will be used here to include cases with evidence of larval migration beyond the pulmonary autoinfective route.

HYPERINFECTION SYNDROME

General Features

The clinical manifestations of *S. stercoralis* hyperinfection vary widely. The onset may be acute (121) or insidious (135). Fever and chills are not uniformly present and should prompt a search for an associated bacterial infection. Other constitutional symptoms include fatigue (61), weakness (14), and total body pain (13). Blood counts performed during hyperinfection may show eosinophilia but more often show a suppressed eosinophil count. Patients who have increased peripheral eosinophilia during hyperinfection appear to have a better prognosis (54).

Gastrointestinal Manifestations

Gastrointestinal symptoms are most common but are nonspecific. Some case reports do not mention any gastrointestinal symptoms (97). Abdominal pain (12), often described as crampy (61) or bloating (20) in nature, watery diarrhea, constipation (61), anorexia, weight loss (61, 108), difficulty swallowing (136), sore throat (136), nausea (61), vomiting (61), and gastrointestinal bleeding (13), in any order or combination, are frequently reported. Ileus (76) and small bowel obstruction (83, 121) may result, with diffuse abdominal tenderness and hypoactive bowel sounds. Protein-losing enteropathy may give rise to acute or worsening hypoalbuminemia with peripheral edema (49) or ascites (61). Hypokalemia (53) and other electrolyte abnormalities may reflect these gastrointestinal disturbances.

Direct stool exam usually shows numerous rhabditiform and filariform larvae. Occasionally, adult worms (49) and eggs (3, 11) are also seen. Occult or gross blood is a common finding. Esophagitis and gastritis are reported, in addition to duodenitis, jejunitis, ileitis, colitis, including pseudomembranous colitis (53), and proctitis. Mucosal ulceration is most common in the small intestine, but can occur at any level from the esophagus (60) and stomach (135) to the rectum. Larvae may be seen in these ulcers on biopsy (38, 49, 135). Crypts are often distorted by the numerous larvae (135). Inflammatory infiltrates (76) and areas of necrosis (79, 136) in involved intestinal mucosa may (83) or may not (135) be present. The appendix may also be invaded by larvae (56, 108). Abdominal X-rays may show small bowel distension with air-fluid levels (12, 83). Mucosal edema (76, 79) and findings consistent with protein-losing enteropathy may also be demonstrated radiographically. Computed tomography scans can occasionally reveal intra-abdominal lymphadenopathy (121).

Cardiopulmonary Manifestations

Pulmonary manifestations range from none at all to cough (84), wheezing (56, 136), a choking sensation (11), hoarseness (136), chest pain (11) (which may be pleuritic in nature (13), hemoptysis (in some cases massive) (61), palpitations, atrial fibrillation (39), dyspnea (84), and, rarely, respiratory collapse. Respiratory alkalosis is common (122). There is only one report of pneumothorax (73). If the diagnosis is not made and steroids are administered, symptoms may actually improve temporarily (113), although this experience is not universal (109).

Sputum may demonstrate filariform or rhabditiform larvae (15, 28, 37, 110) and even, occasionally, eggs (55). These findings suggest that filariform larvae develop into adults in the lungs and a new generation of rhabditiform larvae are produced locally (15). This hypothesis is supported by reports of adult parasites being expectorated posttreatment (72) and autopsy studies showing adult worms in lung tissue (11). Chest X-rays most frequently show bilateral (12) or focal (38) interstitial infiltrates. Lung tissues may show alveolar hemorrhage (11, 79). Petechial hemorrhage or hyperemia of the bronchial, tracheal (136), and laryngeal (11) mucosa has also been reported. Larvae seen on lung biopsy associated with inflammatory changes have been reported variably (13, 136).

Dermatologic Manifestations

Pruritic linear streaks of the lower trunk, thighs, and buttocks (larva currens) frequently accompany hyperinfection (49). Petechial (39) and purpuric (97) rashes of the same areas, in which larvae have been demonstrated on skin biopsy, are also reported. Skin manifestations of vasculitis (44), the underlying disease, and/or associated gram-negative sepsis (121) with disseminated intravascular coagulation (79) may, of course, also be present during hyperinfection.

Central Nervous System Manifestations

Meningeal signs and symptoms (56) are the most common manifestation of central nervous system involvement. Hyponatremia may accompany meningitis (44, 53). In patients with meningitis, spinal fluid may show parameters of aseptic meningitis (i.e., pleocytosis, elevated protein, normal glucose, negative bacterial cultures) (108, 126) or demonstrate characteristics of a gram-negative bacterial infection. Larvae have been found in spinal fluid (28), meningeal vessels (11), the dura, and the epidural, subdural, and subarachnoid (79) spaces.

Spinal fluid cultures in hyperinfection have grown *Escherichia coli* (56, 97), *Proteus mirabilis* (12), *Klebsiella pneumoniae* (61), *Enterococcus faecalis* (56), and *Streptococcus bovis* (53, 63), among others. Eosinophilic meningitis has not been reported.

Other Manifestations

Rare cases with liver dissemination may show an obstructive pattern in the liver enzymes, with elevations of the alkaline phosphatase and bilirubin (108) and, to a lesser extent, alanine aminotransferase and aspartate aminotransferase (59). Granulomata may be seen throughout the liver parenchyma, with

periportal inflammation occurring around degenerating larvae (108).

Organs to which larvae have disseminated include skin (77, 79), mesenteric lymph nodes (11), gallbladder (11), liver (59), diaphragm (79), heart (12, 59, 77, 79), pancreas (75, 79), skeletal muscle (75, 77), kidneys, ovaries (79), and brain (75). Chronic inflammation or necrosis (79) frequently surrounds the larvae, but tissue reactions, even in the same patient, are also frequently absent (79, 119).

Hyperinfections are often complicated and, rarely, preceded (63) by infections caused by gut flora that gain access to extraintestinal sites, presumably through ulcers induced by the filariform larvae or by virtue of being carried on the surface or in the intestinal tract of the larvae themselves. Blood cultures from patients with hyperinfection have grown *Escherichia coli* (3, 97), *Klebsiella pneumoniae* (12), *Proteus mirabilis* (12, 121), *Pseudomonas* (61), *Enterococcus faecalis* (63), coagulase-negative staphylococci (101), *Streptococcus bovis* (63), and *Streptococcus pneumoniae* (12). Polymicrobial infections can also occur (63). In addition to enteric gram-negative rods spreading systemically in this fashion, patients on immunosuppressive regimens may also develop systemic *Candida* infections by presumably similar mechanisms (86, 94, 101).

IMMUNOCOMPROMISED CONDITIONS ASSOCIATED WITH *S. STERCORALIS*

Immunosuppressive Drug Therapy

The largest category of immunocompromise consists of those conditions that are pharmacologically induced to treat autoimmune, allergic, and inflammatory disorders as well as to prevent rejection of transplanted organs.

Glucocorticoids. Of all the immunosuppressive drugs prescribed, glucocorticoids are the most widely used and the most specifically associated with transforming chronic strongyloidiasis to hyperinfection.

Hyperinfection has resulted from high-dose steroids (113), low-dose steroids (135), locally injected steroids (130), high levels of endogenous adrenocorticotropin (21), and pharmacologically administered adrenocorticotropin (25). Hyperinfection has resulted from steroids administered for diseases that themselves could be considered as having intrinsic immunological abnormalities, i.e., lupus (94), lymphoma (94), rheumatoid arthritis (20), leprosy (94), and polymyositis (73) and also for nonsystemic inflammatory conditions such as corneal ulcer (108, 130) and Bell's palsy (25). Signs and symptoms have begun as early as 20 days after the onset of steroid therapy (25) and as late as several years (94) without an obvious additional immunocompromising condition supervening.

One likely explanation for the ability of glucocorticoids to induce hyperinfection is their acute suppression of eosinophilia (34) and lymphocyte activation. Some have suggested that glucocorticoids may also have a direct effect on the parasites themselves, accelerating the transformation of rhabditiform to invasive filariform larvae (35) or rejuvenating reproductively latent adult females (67). As intriguing as this hypothesis is, little experimental work to support it has been reported apart from the identification of *S. stercoralis* cDNA encoding nuclear hormone receptors (112).

Vinca alkaloids. Vincristine use has been associated with a number of cases of hyperinfection (54, 94, 118). Although most of these patients also received glucocorticoids, it has been proposed that vinca alkaloids exert a toxic effect on myenteric neurons, decreasing intestinal motility and increasing the amount of time that rhabdtiform larvae have to molt to invasive filariform larvae. The first reported case of hyperinfection complicating lymphoma was a 63-year-old man with Hodgkin's who received vinblastin sulfate (but not glucocorticoids) and developed fecal impaction shortly thereafter (95). Two reports describe *S. stercoralis* in patients who received vincristine but not glucocorticoids: one was a case of hyperinfection that occurred in a patient with high endogenous adrenocorticotropin levels due to small cell lung carcinoma (21); the other was a case not of hyperinfection but of eosinophilic gastroenteritis and recurrent eosinophilia (99). Therefore, evidence for vinca alkaloids themselves causing hyperinfection remains anecdotal.

Cyclosporine. Given its widespread use, the absence of an association of cyclosporine with *S. stercoralis* hyperinfection is striking. In fact, one notes a decline in case reports of hyperinfection occurring in renal transplant recipients after about 1990, when cyclosporine became a standard part of the posttransplant regimen. There is some experimental evidence that cyclosporin A may actually have an anthelmintic effect on *S. stercoralis* (105). The one case of *S. stercoralis* hyperinfection in a patient on cyclosporine occurred after the drug was withdrawn and cyclosporine levels were declining (87). Resuming cyclosporine therapy alone was not sufficient to cure the hyperinfection, but the patient did well once treated with thiabendazole.

Other immunosuppressive drugs. Numerous other drugs have contributed to immunosuppressive states associated with hyperinfection, including azathioprine (129), cyclophosphamide (29, 99, 118), antithymocyte globulin (74, 131), anti-CD3 (87), chlorambucil (94), 6-mercaptopurine (94), methotrexate (99, 118), bleomycin (118), adriamycin (99), doxorubicin (104, 118), daunorubicin (23), ifosfamide (118), melphalan (104), carmustine (104), VP16 (96, 118), and mitoxantrone (118), as well as total body irradiation (95). In all of these cases, glucocorticoids were administered contemporaneously. Attributing hyperinfection to any of these other drugs alone is therefore difficult.

Hematologic Malignancies

Glucocorticoids are employed in the treatment of many hematologic malignancies, but there are case reports of *S. stercoralis* hyperinfection developing in such patients prior to therapy (1, 132). In one case of small intestinal lymphoma, in which *S. stercoralis* larvae were seen in large numbers in the lymphomatous tissue itself; the authors suggest that chronic parasite-induced inflammation may have contributed to the development of the lymphoma in the first place (16).

Kidney Transplants

The majority of cases of hyperinfection that have occurred following organ transplant have occurred following renal transplant, and most of these cases seem to have been precipitated by increased glucocorticoid doses in response to rejection (9,

18, 27, 50, 58, 74, 87, 116, 125, 129, 131). The lack of reported cases following heart, lung, and liver transplants may simply reflect the fewer patients from *Strongyloides*-endemic areas receiving these transplants. As mentioned above, the number of reported cases of hyperinfection following renal transplant has declined with the use of cyclosporine.

One interesting feature of *S. stercoralis* in renal transplants is the number of cases in which invasive larvae have been found in the urine of these patients (29, 50, 74). One might speculate that a kidney in the peritoneal cavity is more likely to be encountered and invaded by migrating larvae. Larvae have been found in the urine of non-renally transplanted patients, as well (10, 14), so a peritoneal location is not a prerequisite for renal dissemination. In fact, some have suggested that the kidneys themselves may be capable of transmitting *S. stercoralis* from donor to recipient (50).

Bone Marrow Transplants

Relatively few cases of *S. stercoralis* hyperinfection following bone marrow transplant have been reported in the English literature. One intriguing case documented the presence of *S. stercoralis* eggs containing viable larvae on a urethral smear (114). A suggestion raised by the authors is that normal hatching of larvae from the eggs was prevented by drugs used for the bone marrow transplant (busulfan and cyclophosphamide), although no in vitro evidence has been presented to explore this possibility further. If some immunosuppressive drugs do indeed prevent egg hatching and therefore decrease the number of filariform larvae exposed to the intestinal mucosa, one would expect hyperinfection to be rare in individuals in whom pharmacologic immunosuppression is induced by those drugs.

HTLV-1 Infection

Infection with human T-lymphotropic virus type 1 (HTLV-1) is associated with increased prevalence of *S. stercoralis* infection (with direct stool studies as the criterion) (45), greater refractoriness to conventional treatment (102), and the hyperinfection syndrome (40).

S. stercoralis also appears to influence the natural course of HTLV-1 infection. HTLV-1-infected individuals with adult T-cell leukemia who are coinfected with *S. stercoralis* are significantly younger than patients with adult T-cell leukemia but without *S. stercoralis* infection, suggesting that coinfections shortens the period of latency prior to leukemogenesis (90). One reason for this may be that HTLV-1- and *Strongyloides*-coinfected individuals have an expanded population of HTLV-1-infected $CD4^+$ $CD25^+$ T cells and higher levels of circulating proviral DNA (103), which is associated with accelerated disease course.

From the parasite perspective, HTLV-1-infected hosts appear to be more tolerant because of a virally induced Th1 bias to their immune system. Peripheral blood mononuclear cells from HTLV-1-infected patients produce more gamma interferon at baseline (81), and these patients appear to make less polyclonal (81) and parasite-specific (92) immunoglobulin E.

HIV Infection

Although *S. stercoralis* hyperinfection was once considered an opportunistic AIDS-defining illness (134), the relative rarity of such case reports despite the vast numbers of people who must be coinfected is striking (64). In all, there are fewer than 30 cases of hyperinfection occurring in human immunodeficiency virus (HIV)-infected patients in the literature. A number of these patients had previously received steroids, either as adjunctive treatment for *Pneumocystis carinii* pneumonia (15, 65, 100) or as part of a chemotherapeutic regimen for non-Hodgkin's lymphoma (28). HTLV-1 infection is generally not commented on in these case reports. Therefore, a link between the two conditions is not solid.

The number of cases of hyperinfection in AIDS patients that have occurred within a few weeks of treating chronic intestinal infection (38, 44, 59, 65, 123) is interesting. Whether anthelmintic therapy actually induces parasite migration, as occurs in filarial infections (30, 117), and is thereby the initiating event in hyperinfection is a matter for speculation. This "posttreatment hyperinfection" has also been observed in renal transplant recipients (108) in whom *S. stercoralis* infection was treated both before and after transplant. While these cases undoubtedly represent a tiny fraction of AIDS patients who have received anthelmintic treatment for positive stool exams, it does challenge the notion that screening HIV-positive individuals for *S. stercoralis* and treating coinfected individuals with conventional doses of anthelmintics will prevent hyperinfection (65).

Hypogammaglobulinemia

Cases of *S. stercoralis* hyperinfection have been reported with hypogammaglobulinemia (7, 110). Both of the patients in these reports were particularly refractory to prolonged anthelmintic therapy. The implication that antibody is important in controlling *S. stercoralis* infection is also supported by experimental animal models (48).

Malnutrition and Associated Conditions

Lung cancer has been associated with hyperinfection, both before (55, 96) and after (21, 96) administration of immunosuppressive chemotherapy. Hyperinfections complicating kala-azar (78) and other conditions of protein-energy malnutrition with wasting have also been reported. Whether these conditions predispose to hyperinfection through depressed immunity directly or through metabolic perturbations of endogenous cortisol were not investigated. Certainly malnutrition and the poor hygienic conditions associated with *S. stercoralis* infection frequently coexist, but, of course, these are the very areas where resources for studying the association are most limited.

DIAGNOSIS OF *S. STERCORALIS* INFECTION IN THE IMMUNOCOMPROMISED PATIENT

Parasitologic diagnosis of *S. stercoralis* hyperinfection is relatively straightforward, given the high numbers of larvae that exist in stool and, usually, sputum. Unexpected diagnoses have even been made from ascitic fluid (61) and blood smears (133).

The real challenge is screening patients prior to and during immunosuppressive therapy.

Screening At-Risk Individuals

Any individual with risk factors for acquiring *S. stercoralis* infection who is diagnosed with HTLV-1 or who is to undergo steroid therapy should be screened. Hyperinfection has occurred in patients on doses as low as 1 mg of dexamethasone daily for 8 weeks (121). Because of the longevity of the parasitic infection, even remote histories of travel, i.e., veterans of wars in the South Pacific (89) or southeast Asia (36) or residence in places where the disease was considered endemic decades ago, i.e., rural Appalachia (5), should prompt screening. In addition, peripheral eosinophilia or symptoms consistent with chronic *strongyloidiasis* should alert the clinician to the possibility of underlying *S. stercoralis*, although these are neither sensitive nor specific indicators of infection.

Diagnosis of Hyperinfection

Relying on stool studies alone for screening is inadequate, as evidenced by reports of hyperinfection developing in persons with negative screening stool exams. In chronic asymptomatic *S. stercoralis* infection, adult parasites may produce only 10 to 15 eggs per day (35). A single stool exam is said to be about 50% sensitive for making the diagnosis of *S. stercoralis* infection in someone with symptomatic chronic disease (111). In the asymptomatic individual, stool exams are probably even less sensitive.

The Baermann and formalin-ethyl acetate concentration techniques have been widely used to improve the sensitivity of stool exams. The Harada-Mori filter paper culture does not appear to be as successful for *Strongyloides* as it has been for hookworm (17). The blood agar plate culture method, in which the serpiginous tracks of bacterial growth along the paths of motile larvae become apparent after 1 or 2 days of incubation at room temperature, is a preferred method because of its high sensitivity and ease of implementation in standard microbiology laboratories (17, 111). Methods to sample duodenal fluid are more invasive and therefore less desirable.

Skin testing for immediate hypersensitivity with parasite extracts has been tried experimentally, but this is not widely available (82). Coinfection with HTLV-1 has been shown to decrease the sensitivity of the skin test (81, 92), and it can be presumed that other immunocompromising conditions and antihistamine therapies would have a similar effect.

Serologic testing is now widely available and is sensitive although not specific. Infections with filariae or *Ascaris* spp. can lead to false-positives. Furthermore, the sensitivity of serologic tests may be decreased in HTLV-1 infection (92) and in hematologic malignancies (107). A single test does not reliably distinguish past from current infection, but given the persistent nature of *S. stercoralis* infection and the possibility that curative treatment may not completely eradicate every last organism, a positive serology test in a patient with a compatible clinical history preparing to undergo steroid therapy may be sufficient grounds for empirical treatment.

TREATMENT OF *S. STERCORALIS* IN THE IMMUNOCOMPROMISED PATIENT

As different immunocompromised states are associated with different degrees of refractoriness to therapy, the therapeutic regimen must be customized. Patients with hypogammaglobulinemia, for example, have been refractory to multiyear courses of thiabendazole (110) and ivermectin (4), while numerous cases of steroid-induced and AIDS-associated (123) hyperinfection have resolved with more conventional doses.

Anthelmintic Drug Treatment Options

Clinical trials assessing drug treatment of *S. stercoralis* infection have, for the most part, focused on patients with chronic strongyloidiasis, not hyperinfection. The criteria for success in these studies are improvement in symptoms and negative stool exams; however, it presumably takes only one viable worm to initiate hyperinfection under the right circumstances. The goal of treatment to prevent hyperinfection, therefore, is total eradication of the parasite, not just symptomatic improvement. The regimens necessary to accomplish this are not clearly defined.

Azole drugs. Thiabendazole was first introduced in 1963 and for many years was the treatment of choice for *S. stercoralis* infection. At a dose of 25 mg/kg twice a day for 3 days, its efficacy at clearing stool and improving symptoms in patients with chronic strongyloidiasis has ranged from 67% (41) to 81% (36). Side effects with thiabendazole occur in up to 95% of patients (33), with the majority reporting nausea and many complaining of foul-smelling urine, neuropsychiatric effects, malaise, or dizziness (41). Thiabendazole administered rectally was used successfully in treating a patient with *S. stercoralis* hyperinfection and bowel obstruction (6).

Mebendazole has been used successfully to treat a number of patients with *S. stercoralis* hyperinfection (115). It is poorly absorbed, however, and therefore decreased accessibility to migrating larvae may have played a role in cases where mebendazole was unsuccessful (19, 49).

Albendazole at 400 mg orally twice a day for 3 days has been shown to clear stool of *S. stercoralis* larvae in 38% to 45% of patently infected individuals (22, 70) and to normalize serologies in 75% of chronically infected individuals in whom larvae were not detectable, with few side effects reported (2). Albendazole has been used successfully in hyperinfection syndrome (78) and remains a viable treatment alternative to ivermectin (see below).

Ivermectin. In a small comparative study with thiabendazole, ivermectin given on 1 or 2 days cleared larvae from the stool at a rate comparable to that of thiabendazole (33). Ivermectin, however, was much better tolerated and has become the treatment of choice. Compared with albendazole, ivermectin has shown better rates of larval clearance from stool with a similarly favorable side effect profile (22, 70). It has been used successfully in hyperinfection (123), including cases that did not respond adequately to thiabendazole (84).

Clinical Scenarios

Treatment of hyperinfection. Optimal anthelmintic activity for both azoles and ivermectin requires an intact immune sys-

tem, as evidenced by refractory infections in patients with various immunodeficiencies (60, 83, 110). Therefore, treatment should continue until the clinical syndrome resolves and larvae are no longer detectable. The most practical detection methods only sample the intestinal compartment. Assuming that the autoinfective cycle requires at least 2 weeks, treatment and screening should continue until fecal cultures have been negative for at least this long. Patients who have had positive sputum or urine samples should continue to be examined as well. Decreasing the steroid dose has been advocated, but this may (20) or may not (122) be beneficial. Surgical blind loops may sequester organisms and require invasive methods to deliver anthelmintics at effective concentrations (108).

Coincident infection with enteric organisms is very common. Empirical or culture-driven antibacterial (or antifungal) coverage is warranted in those with evidence of additional infecting organisms. Adult respiratory distress syndrome may also occur during the course of hyperinfection (77, 122), often requiring mechanical ventilation.

It should be borne in mind that hospitalized patients with hyperinfection are infectious and should be placed on contact isolation. Use of gloves, masks, and aprons and diligent hand washing are effective measures that will prevent spread to health care workers (68) and other patients. Screening family members, particularly spouses (62, 88) and those with shared risk factors (105), should be considered in some circumstances, because person-to-person transmission is hypothetically possible.

Primary prevention of hyperinfection. Individuals initiating steroid therapy who have positive serologic tests and an exposure history but no history of *S. stercoralis* hyperinfection should have baseline stool examinations. Regardless of the results, it could be argued that they should receive a course of treatment (ivermectin, 200 μg/kg/day for 2 days, repeat after 2 weeks). Subsequent decisions about screening and prophylactic ivermectin must be individualized, but at the very least, a low threshold for performing stool exams should be maintained.

Patients with HTLV-1 who have positive results on serologic testing or stool examinations should receive a course of treatment and be followed for decreasing titers and/or clearance of larvae from stool culture.

Persons residing in strongyloidiasis-endemic areas or in high-risk occupations need to be educated about modes of parasite transmission to avoid recurrent infection.

Secondary prevention of hyperinfection. Given the reported cases of hyperinfection that have occurred following treatment and apparent clearance of *Strongyloides* (27, 29, 125), some clinicians have continued anthelmintics in individuals with a history of hyperinfection for extended periods. Two-day courses of thiabendazole given every two weeks have been successful (108), although there are reports of patients that continued to shed larvae (60) and developed symptomatic disease (45) on this regimen. If multiple courses of anthelmintic treatment are to be given for an extended period, ivermectin is better tolerated and should be the drug of choice. If secondary prophylaxis is not pursued, patients with a history of *S. stercoralis* hyperinfection should at the very least be screened periodically as long as their underlying predisposing condition persists.

CONCLUSIONS

Our understanding of *S. stercoralis* infections in normal and immunocompromised hosts continues to evolve. Relatively recently, it was thought that any defect in cellular immunity could tip the equilibrium of chronic strongyloidiasis toward hyperinfection. Although various immunocompromising conditions have been associated with hyperinfection, steroids and HTLV-1 infection are the most consistent. What these two conditions have in common is an effect on that arm of the immune system that controls many helminthic infections, the so-called Th2 response. This represents a complex interaction of antibody, particularly immunoglobulin E and immunoglobulin G4, T-cell-derived cytokines (notably interleukin-4 and -5), and peripheral and tissue eosinophils. While steroid treatment acutely suppresses eosinophilia and T-cell activation, HTLV-1 infection increases basal gamma interferon production by T cells and reduces immunoglobulin E levels (91). The importance of Th2 cytokines in controlling *S. stercoralis* infection has also been demonstrated in animal models (47, 48). The altered cytokine milieu in cases of hematologic malignancies may also explain how these conditions could result in *S. stercoralis* hyperinfection.

Although AIDS and malnutrition have both been associated with hyperinfection, the number of reported cases is much less than the overlapping endemicities of these conditions would predict. AIDS does not specifically impair Th2 immunity, and individuals in malnourished communities often have other chronic infections that maintain a Th2 bias. In fact, relatively few cases of *Strongyloides* hyperinfection have been associated with other concomitant helminth infections (38, 78), although the area of endemicity and modes of acquisition overlap considerably. Animal models support the notion that chronic infection with other helminths improves host resistance to *S. stercoralis* (71).

Practical issues regarding diagnosis, treatment, and primary and secondary prophylaxis of *S. stercoralis* hyperinfection are far from resolved, but the development of sensitive screening serologic tests and well-tolerated anthelmintic drugs represent significant advances in the past decade. Clinicians with an awareness of the possibility of hyperinfection are better equipped to diagnose, treat, or prevent altogether the fatal consequences of this lethal nematode.

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