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Review

The status of strongyloidiasis in the Mediterranean countries

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Abstract

Strongyloidiasis is considered one of the most serious parasitic infections globally, especially in tropical and subtropical regions. The disease's public health significance is substantial, as the infection can remain dormant for decades in the host and may be activated as hyperinfection after immunity dysregulation caused by immunosuppression. *Strongyloides stercoralis* infection is prevalent in tropical regions, whereas cases are usually reported sporadically in non-tropical countries and are estimated to cause asymptomatic chronic infection in 600 million people worldwide. Strongyloidiasis remains neglected in many Mediterranean countries, highlighting the urgent need for increased awareness among healthcare providers, especially regarding possible carriers returning from endemic regions.

This narrative review updates the status of *S. stercoralis* and its corresponding disease in the Mediterranean countries. This article searched internet databases such as PubMed, Science Direct, Google Scholar, and MEDLINE for Strongyloidiasis studies and cases published over the last ten years in the Mediterranean countries.

Strongyloidiasis remains neglected in many Mediterranean countries, highlighting the urgent need for increased awareness among healthcare providers, especially regarding possible carriers returning from endemic regions.

Key words: *S. stercoralis;* strongyloidiasis; Mediterranean; hyperinfection; non-endemic; immunocompromisation.

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Overview of *S. stercoralis* and Strongyloidiasis

Strongyloides stercoralis is a soil-transmitted intestinal parasitic worm that infects millions worldwide. *S. stercoralis* worm was first described in 1876 in the Mediterranean country, France, in soldiers returning from Vietnam, and who suffered from gastrointestinal symptoms [1]. *S. stercoralis* is a member of the Nemathelminths, class Nematoda, and the genus Strongyloides which comprise 52 species that invade the gastrointestinal tracts of mammals. Only *S. stercoralis* and *S. fulleborni* are known to infect humans, dogs, and cats [2,3].

The life cycle of *S. stercoralis* begins with an egg that hatches into a larva (immature worm), which then grows into a fully mature adult worm [4]. Female worms inhabit the tissue of the duodenum and jejunum of the humans' small intestine where they reproduce parthenogenetically (virgin birth) to deposit more than 100,000 eggs per day [5]. Most of these eggs are rarely seen in stool samples because they hatch in the intestine. The resulting immature rhabditiform larvae then move from the intestinal wall into the lumen and are passed with the stool, where they can be detected in fresh samples [5]. In the environment, the rhabditiform larvae may either mature into mature adult male and female worms; or develop into infective filariform larvae that can directly penetrate the skin of a new host [3]. Few rhabditiform larvae may remain inside the intestine and mature into filariform larvae that initiate a salient asymptomatic autoinfection cycle under restricted immune control and can stand in the infected host for decades [5].

The transmission of *S. stercoralis* within communities can be predominantly related to human habits of eating, personal hygiene, and activities, as well as environmental sanitation [6]. The infective filariform larvae in the soil can actively penetrate the skin of the palm and foot soles [5]. Herbs and vegetables that grow on fields with high humidity near the sewage serve as reservoirs for the infection, due to the increased chance of harboring viable parasites [6]. In non-endemic countries, the only route of infection relies on the introduction of the parasite by immigrants and travelers who got infected during their visit to the endemic countries [7]. Fortunately, no cases had been reported from person-to-person transmission of *S.*

stercoralis and thus no travel-related epidemics are expected for strongyloidiasis [8].

The incidence of strongyloidiasis varies widely among different countries, communities, and socioeconomic conditions with a prevalence that can be as high as 50% in endemic countries [9]. These countries are characterized by tropical, temperate, and heavy rainfall environments and include areas of Southeast Asia, Latin America, Northern Australia, Sub-Saharan Africa, parts of the Southeastern United States of America, and restricted areas in the temperate Southeastern Europe [9,10]. There are no comprehensive estimates available on the distribution of strongyloidiasis worldwide since the infection is occasionally misdiagnosed or difficult to detect from stool samples due to poor sensitivity of the applied laboratory diagnostic methods, as well as the absence of a gold standard diagnostic test. Thus, *S. stercoralis* is the most neglected parasite among soil-transmitted nemathelminths [1].

The global incidence of strongyloidiasis was estimated to range from 30 to 100 million cases, with increased infection in immunocompromised patients [11]. However, recent studies concluded that the true prevalence of *S. stercoralis* would be as high as 600 million cases worldwide and was severely underestimated due to variations in the applied diagnostic schemes [12]. Moreover, most gastrointestinal parasitic infection surveys were designed to detect general parasite burden, rather than *S. stercoralis,* specifically [12]. The diagnostic test applied in those studies was conventional stool examination, but none of the applied techniques enhanced the detection of *S. stercoralis* larvae*,* such as the Baermann method or agar culture plate, and thus, previous data were mostly built on diagnostic methods of suboptimal sensitivity [12-15].

Strongyloidiasis in the Mediterranean Countries

The Mediterranean region comprises 26 countries across three continents: Asia, Europe and Africa. These countries are bound by immigration and travel history, geography, and culture and include countries of the Southern European coast, Western Asian coast, and Northern African coast.

Strongyloidiasis cases are usually reported sporadically in Mediterranean countries among immigrants and travelers (Table 1). In Italy, the seroprevalence of strongyloidiasis among human immunodeficiency virus-infected Latin American immigrants was 4.1% [16], whereas in another study it was 2.7% among Sub-Saharan migrants resettled in the same country [17]. In Turkey, the seroprevalence of strongyloidiasis among immunosuppressed patients reported by two different studies was 4% [18] and 0.92% [19], respectively.

A systematic review and meta-analysis were performed to provide information about strongyloidiasis prevalence among migrants coming from *S. stercoralis* -endemic areas who reside in Spain. The study has included all literature showing the prevalence of *S. stercoralis* among migrants from Africa, Latin America, Eastern Europe, Asia, and Oceania who reside in Spain. Twenty-four studies were included comprising 12386 screened individuals. Among them, 11 studies (comprising 7020 patients) evaluated the presence of *S. stercoralis* by stool

Table 1. Selected case reports on strongyloidiasis in the Mediterranean countries.

Country	Origin	Infection source	Age/gender	Risk factor	Primary clinical/laboratory remarks	Definitive diagnosis	Outcome	Ref
Portugal	Rural area	Local	69yr/female	Low socioeconomic, lack of sanitation	Gastrointestinal symptoms, ascites/eosinophilia, elevated CRP, ESR	ELISA	Cured	[25]
France	Rural area	Local	17yr/male	Lack of sanitation	Soft tissue/eosinophilia	Repeated stool microscopy, Baermann's method	Cured	[26]
France	Spain	Imported (traveller)	17yr/female	Lack of sanitation	Gastrointestinal symptoms/eosinophilia, Repeated stool microscopy	Concentration stool microscopy	Cured	[27]
Italy	Peru	Imported (immigrant)	35yr/male	HTLV-1	Abdominal pain, meningitis/repeated stool microscopy	Agar plate culture, ELISA	Cured	[28]
Greece	Ethiopia	Imported (immigrant)	33yr/male	HIV	Acute granulomatous appendicitis/eosinophilia	Repeated stool microscopy	Cured	[29]
Tunisia	Rural area	Local	45yr/female	Lymphoma	GIT symptoms/Histology	Concentration stool	Cured	[30]
Türkiye	Rural area	Local	65yr/female	Behçet's Disease	Gastrointestinal symptoms, ascites/eosinophilia, elevated CRP, ESR	Repeated stool microscopy	Cured	[31]

HIV: human immunodeficiency virus; HTLV: human T-lymphotropic virus, CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ELISA: enzyme-linked immunosorbent assay.

microscopy showing an overall prevalence of 1%. The overall prevalence was 14% in 13 studies (comprising 5366 patients) by serodiagnosis. Strongyloidiasis seroprevalence was 20% among migrants from Sub-Saharan Africa, 14% among migrants from Latin America, and 8% among those from North Africa [27].

However, in Western Europe, endemic areas were restricted to rural areas of northern Italy, Portugal, the southern Valencian Mediterranean coastal region of Spain, and South-Western France. Clinical reports have been published from cases where the parasite was acquired locally. Moreover, possible autochthonous permanent transmission has been suggested in these regions. Autochthonous cases are usually reported in older male farmers who are diagnosed at advanced stages of disease [10,20-22,28,29]. A retrospective study was done in Spain to describe the prevalence of imported versus autochthonous strongyloidiasis for positive cases diagnosed by stool microscopy, agar culture, polymerase chain reaction, serology, and/or histology. Out of 36 patients, 21 were men with a mean age of 60.8 years; 15 cases were autochthonous, and 21 cases were imported from Latin America. Positive statistical associations ($p < 0.05$) were reported for autochthonous cases associated with older age, male sex, and agricultural activity. Fourteen cases were asymptomatic, three autochthonous cases presented with hyperinfection syndrome, and two patients died. Eosinophilia was reported in all cases [28]. Another retrospective study reported 11 out of 65 cases as autochthonous in Croatia [10].

Autochthonous strongyloidiasis is recognized in Western Asia, in particular, Palestine, and was diagnosed in adults and young children with prevalence ranges between 1.7 to 5.6% [30,31]. Another study reported the average annual incidence rate for strongyloidiasis at 1.7/100.000 population [32]. The major risk factors for strongyloidiasis in this country were poor sanitation, working on the farms, and contaminated vegetables [33].

Strongyloidiasis in non-endemic countries is usually diagnosed in its reactivation form after predisposition to certain risk factors. In addition, strongyloidiasis in these countries is usually unexpected by the treating physicians and is just identified after excluding illnesses with similar presentations and reviewing the patient's traveling history [7].

The identification of *S. stercoralis* in the laboratory needs an expert and well-trained technician with sufficient knowledge and suspicion for the reactivation of dormant infections that are led by the filariform larvae. Laboratory personnel in non-endemic Mediterranean countries most likely miss these skills which lead to misdiagnosis and thus the infection becomes under-reported [34,35].

Pathology, Pathogenesis, and Risk Factors for Strongyloidiasis

S. stercoralis is unique among other intestinal worms in its ability of life-long dormant persistence in humans causing asymptomatic or mildly symptomatic disease that may end with fatal hyperinfection and disseminated infection [4]. The filariform larvae are the infective stage of *S. stercoralis* that can initiate an infection accompanied by clinical signs and symptoms specific to every site and organ involved during its pathological cycle in the host [36].

Upon skin penetration, the filariform larvae pass through the dermis toward cutaneous blood capillaries. During this phase, larvae appear under the skin accompanied by transient itchiness, linear and urticarial rash, and skin lesions with edema at the site of its penetration [37,38]. After that, filariform larvae migrate into the bloodstream, are carried to the alveoli, and invade the bronchial epithelium which may cause some respiratory symptoms such as wheezing. However, in some cases, Loeffler's syndrome can occur following severe pneumonia which is manifested as dry cough, throat irritation, wheezing, bronchopneumonia, and eosinophilia [4,37]. Afterward, the worms are swallowed and reach the duodenum and jejunum where they mature into adults. The total incubation period of *S. stercoralis* is around one month before intestinal symptoms appear, such as diarrhea, abdominal pain, nausea, and anorexia [37].

In general, strongyloidiasis causes four clinical syndromes including acute infection, chronic autoinfection, hyperinfection syndrome, and dissemination syndrome [37]. In acute strongyloidiasis the early migrating filariform larvae throughout the body cause the above-mentioned non-specific symptoms in the skin, the lungs, and the intestine [39]. Chronic strongyloidiasis is considered when the symptoms continue to appear for more than three months and are developed when the primary acute infection is not completely eradicated. *S. stercoralis* autoinfection is a stage in which adult worms are sustained in a quite low and steady count in the intestine under strict immune control [37,39]. Autoinfection occurs when some rhabditiform form larvae stay in the intestine and transform into invasive filariform larvae that re-enter the bloodstream through penetration of intestinal mucosa or peri-anal skin [38]. Autoinfection allows the worms to build up in the host enabling them

to maintain their dormant persistence in the intestine. Autoinfection results in life-long sporadic recurrence of symptomatic episodes that persist for decades. Active infections of acute and chronic strongyloidiasis are usually seen in endemic countries [38].

In immigrants and travelers returning from endemic countries, *S. stercoralis* larvae exist as dormant sleeping enemies and are maintained in their hosts via continuous autoinfection cycles. Under normal circumstances, autoinfection does not seem to be a problem in these individuals and the infection may present as asymptomatic or mild symptomatic infection [38]. However, the host immunity is not protective against the auto-infective-stage larvae but still can control and minimize their pathogenic effect and this explains the presence of dormant *S. stercoralis* in the infected individuals in the Mediterranean countries, as well as the development of *S. stercoralis* hyperinfection syndrome in these individuals upon immune compromization [40].

S. stercoralis hyperinfection syndrome describes the status of hysterical accelerated autoinfection manifested with acute insidious symptoms. Hyperinfection emerges due to disruption in the controlling role of immune system elements that trigger and increase rhabditiform transformation rate into filariform larvae, which is followed by exacerbated pulmonary and gastrointestinal symptoms [41]. Hyperinfection syndrome is frequently seen in immigrants and travelers in non-endemic countries and mainly requires admission to the emergency department [42].

In the worst consequence of *S. stercoralis* hyperinfection, the filariform larvae may disseminate to organs outside the autoinfection cycle, such as the spleen, liver, gall bladder, and pancreas causing severe disseminated strongyloidiasis that is more severe and difficult to control [43]. Finally, hyperinfection and disseminated strongyloidiasis are usually accompanied by fatal secondary bacteremia [44]. Hyperinfection syndrome is frequently misdiagnosed in returning travelers and immigrants as gram-negative sepsis or acute respiratory syndrome [42].

As mentioned above, immune suppression is thought to be the leading risk factor of hyperinfection and disseminated syndromes development, despite the few case reports that documented disseminated strongyloidiasis in patients with intact immunity [45,46]. Immunocompromising conditions associated with hyperinfection and disseminated syndromes include hypogammaglobulinemia syndrome, human T-lymphotropic virus type-1 infection, HIV infection, malnutrition, alcoholism, and exposure to immune suppressive agents [43,45,47,48].

In Croatia, the epidemiological and clinical data of patients diagnosed and treated for strongyloidiasis over 9 years (2010-2019) were analysed. The diagnosis was confirmed by light microscopy and/or serological testing. Out of 65 strongyloidiasis cases, 60% were male, and 78% were aged between 50 and 79 years. Asymptomatic cases with unexplained eosinophilia were reported in 41.5%, acute infection in 18.5%, chronic symptomatic cases in 33.8%, and hyperinfection in 6.2%. Immunosuppression was noted in 30.8% of patients, four of whom developed hyperinfection, resulting in two deaths [10].

S. stercoralis Diagnosis

Strongyloidiasis is suspected in individuals suffering from clinical signs and symptoms typical to those observed in the skin, the lungs, and gastrointestinal tracts of acute strongyloidiasis [20]. In the Mediterranean countries, it is recommended to screen for dormant tropical infections in asymptomatic returning travelers and immigrants [35]. Laboratory diagnosis of strongyloidiasis is suspected with unexpected eosinophilia and positive serologic findings. In addition, similar screening panels can be performed in asymptomatic immune-suppressed patients in endemic areas [49,50].

Strongyloidiasis is one of the most difficult helminths to diagnose since the decisive diagnosis needs to detect the larvae in clinical samples. In addition, no agreeable gold standard test to investigate the parasite is currently available [37,49]. Several detection methods were applied to investigate strongyloidiasis, including microscopy, culture methods, specific antibody/antigen detection, and molecular techniques [49].

Microscopic examination of stool samples is routinely done as an initial screening procedure in symptomatic patients. Visualization of *S. stercoralis* rhabditiform larvae confirms acute, chronic, and autoinfection strongyloidiasis, while the recovery of filariform larvae and occasionally adult females, males and eggs, occurs in hyperinfection and disseminated syndromes [49,51]. However, stool microscopy is not sensitive in asymptomatic individuals due to decreased stool larval output and thus is not informative in non-endemic countries [37,49]. To improve microscopic sensitivity, it is advisable to examine three to seven consecutive daily stool samples, to collect alternative samples (duodenal fluids and respiratory samples such as sputum), to apply a combination of screening

methods, and to do additional processing procedures for stool, such as Harada-Mori filter paper culture technique, formalin-ethyl acetate concentration and Baermann funnel technique [52].

Absolute eosinophil count is requested for patients with uncomplicated chronic strongyloidiasis or for returning travelers and immigrants. Unexpected eosinophilia is considered at an absolute eosinophil count of 0.4-1.5 × 10^3 cells/μL and is regarded as alarming to proceed with further strongyloidiasis diagnosis [53].

S. stercoralis serodiagnosis correlates the level and types of elevated antibodies with the infection stage, which means acute, chronic, hyper infection, treatment follow-up, and cure [54]. Several serological schemes were applied and have shown satisfactory results. Labeled immunoassays, such as enzyme-linked immunosorbent assay (ELISA) and immunofluorescent assays for IgG and its subclasses and IgE are routinely applied due to their reliability and accepted running cost [55]. However, the specificity of immunoassays in endemic countries might be compromised due to background false seropositivity throughout the community that was acquired from the antigenic cross-reaction between different helminth types other than *S. stercoralis*. On the contrary, serodiagnosis can represent the gold standard in the Mediterranean countries due to increased test specificity since no other helminths are endemic in these countries [56]. A study evaluated the performance of microscopy and serology on clinical samples collected from travelers and immigrants returning from endemic regions. Serology showed a sensitivity of 100% and a specificity of 97%, with positive and negative predictive values of 67% and 100%, respectively. In contrast, stool microscopy demonstrated a sensitivity of 45% and a specificity of 100% [57].

In summary, an informative screening test panel for Strongyloidiasis consists of stool microscopy, absolute eosinophil count, and serology which is usually applied to returning travelers and immigrants in the Mediterranean countries [56]. Molecular assays such as PCR and its variants, as well as genotyping schemes, are applied to confirm the positive results during acute and reactivated strongyloidiasis [58,59]. However, despite its superior performance, PCR is not included in the screening test panel in Mediterranean countries due to its expensive running cost [60].

Ivermectin has been registered as the drug of choice in the World Health Organization's list of essential drugs for the treatment of *S. stercoralis* and was recommended for treating strongyloidiasis as the first-choice therapy, while albendazole and thiabendazole are the second therapeutic options [61].

Conclusions and Recommendations

Data on strongyloidiasis in the Southern European coast of the Mediterranean countries are insufficient and, on the other hand, are rare in the Western Asian coast and Northern African coast. Additionally, the issue of dormant *S. stercoralis* infection and asymptomatic carriers remains overlooked, with the actual incidence largely unknown and in need of further investigation. This is especially important as more individuals are travelling between endemic and non-endemic tropical countries. For instance, in Jordan, there is a significant demand to travel to endemic countries for purposes such as education, tourism, and United Nations peacekeeping operations, thus increasing the chance of infection importation. In addition, since autochthonous strongyloidiasis is prevalent in Palestine, more efforts should be conducted to uncover the presence of this parasite in neighbouring countries on the seaboard, including the Jordan Valley, Syria, Lebanon, and Egypt.

It is crucial that every traveler, immigrant, or worker arriving from endemic countries be screened for any dormant infections. Thereafter, if any of these individuals require immunosuppressive therapy to treat conditions like diabetes, autoimmune disorders, or cancers, or if they are infected with immunosuppressive viruses, their physicians must be informed of their travel history before starting treatment. In addition, the performance of screening laboratory tests must be improved to increase the sensitivity of detection and avoid nonspecific results.

Greater focus is needed on refugees displaced among Mediterranean countries due to wars and geopolitical shifts. These individuals often experience poor health outcomes in host countries, driven by language and communication barriers, cultural differences, limited access to healthcare services, and, at times, institutional discrimination [62]. Healthcare providers and policymakers in host countries could benefit from establishing a universal healthcare framework for migrants, focusing on proactive measures such as early testing and management through comprehensive multi-disease screening, including latent tropical infections such as strongyloidiasis.

Authors' Contributions

All authors have participated equally in this review, data collection, and manuscript drafting.

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Conflict of interests

No conflict of interests is declared.

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