

Fungal Infections among Returning Travelers

Anil A. Panackal,^{1,2,a} Rana A. Hajjeh,² Martin S. Cetron,³ and David W. Warnock²

¹Epidemic Intelligence Service, Epidemiology Program Office, ²Mycotic Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, and ³Division of Global Migration and Quarantine, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Endemic mycoses, such as histoplasmosis, coccidioidomycosis, and penicilliosis, have emerged as important health threats among travelers to regions of the world where these infections are endemic. Travelers have developed fungal infections as a result of a wide range of recreational and work activities, many of which have involved well-recognized risk factors for these diseases. In some instances, infections have been acquired during short trips, whereas, in other instances, infection has been acquired during a longer period of residence in an area where the infection is endemic. Travelers need to be made aware of the risks of acquiring mycotic diseases when visiting such regions. Health care providers need to consider these infections in their differential diagnosis among returning travelers with respiratory illness and should be familiar with the treatment and prevention of these diseases.

Endemic mycoses have a restricted geographic distribution. They are largely confined to areas of the world where the etiologic agents are found in nature. In recent years, however, increased domestic and international travel has led to an increase in the number of reported outbreaks and sporadic cases of mycotic diseases among individuals who normally reside in places far distant from the areas where mycotic diseases are endemic. The World Tourism Organization estimates that the number of international travelers was 595 million in 1997 and is expected to reach 1.6 billion by 2020. In 1998, US residents made 1.3 billion one-person trips of ≥ 100 miles away from home, and the number of visitors to the United States increased from 39.4 million in 1990 to 50.9 million in 2000 (Tourism Intelligence International; http://www.tourism-intelligence.com/travel_research.html). Travelers who developed fungal diseases were exposed during a wide range of leisure and work activities that often involved well-recognized risk factors for these infections. In some instances, infection was acquired during a short trip ("travel-related" infection), but in other instances, infection was acquired during a longer period of residence in an area where

infection is endemic, with subsequent migration to a region where infection is not endemic ("migration-related" infection).

In many cases of travel-related fungal disease, individuals present with nonspecific symptoms and signs of acute respiratory illness shortly after their return. However, in most migration-related infections, the disease may remain silent until months or years later. Because of surveillance limitations, more cases of travel-related fungal disease have been detected in outbreak settings, rather than in sporadic circumstances. Indeed, outbreak reports have served to heighten the awareness of health care providers with regard to fungal infections among returning travelers, who may be sentinels for outbreak events. Recently, some surveillance data on illness in returning travelers have become available from GeoSentinel (GS), a communications and data collection sentinel provider network consisting of 25 tropical and travel medicine clinics throughout the world [1]. Between April 1998 and March 2002, 32 cases of systemic mycoses were reported via the GS network (23 cases of histoplasmosis, 3 cases of coccidioidomycosis, 3 cases of cryptococcosis, 2 cases of blastomycosis, and 1 case of paracoccidioidomycosis). Among all ill returning travelers who visited GS clinics, the proportionate monthly morbidity due to these mycoses (per 100 travelers seen) ranged from 0% to 0.5% for sporadic disease, to a peak of 3% in June 2001, which represented an outbreak of histoplasmosis among US students returning from Nicaragua (figure 1). Although these data certainly underestimate the true magnitude of travel-related mycoses, they demonstrate that these diseases can result in mor-

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^a Present affiliation: University of Washington, Seattle-King County Department of Public Health, Wells Fargo Center, Seattle, Washington.

Reprints or correspondence: Dr. Rana A. Hajjeh, Centers for Disease Control and Prevention, 1600 Clifton Rd. NE, Mailstop C-09, Atlanta, GA 30333 (rhajjeh@cdc.gov).

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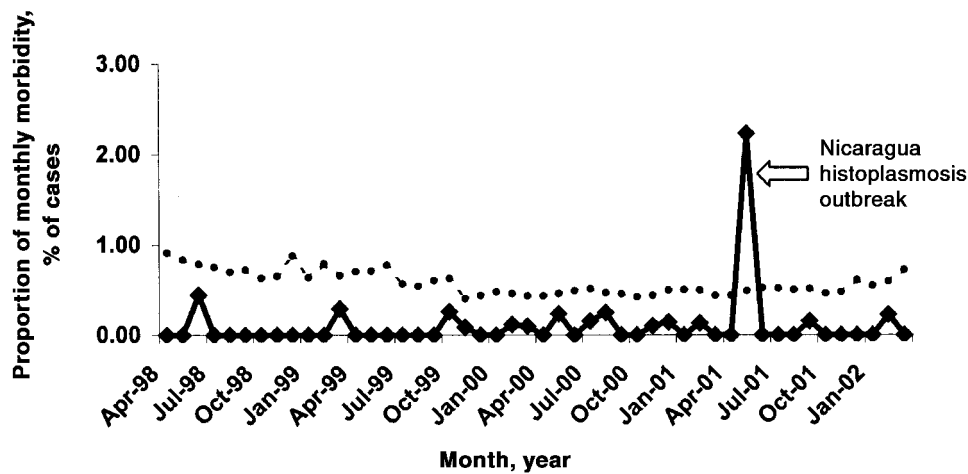


Figure 1. Cases of systemic mycoses as a proportion of all morbidity per month at GeoSentinel clinics among 21,292 returning ill travelers, April 1998–March 2002 ($n = 32$ cases). *Solid diamonds*, Cases of systemic mycoses as a proportion of morbidity in that month; *dashed line*, upper 3σ control limits from a Shewhart u -chart; *arrow*, outbreak of acute histoplasmosis among US travelers returning from Nicaragua.

bidity similar to other known travel-related illnesses, such as dengue, typhoid, or hepatitis A (GeoSentinel, unpublished data).

The most commonly reported travel-related mycoses have been histoplasmosis and coccidioidomycosis, but cases of penicilliosis were also described among travelers returning from Southeast Asia, and occasional cases of other diseases, such as lobomycosis, were associated with travel to South America [2]. The largest number of travel-related mycoses is reported among US residents, many of whom acquired an infection, such as histoplasmosis, during a visit to an area within North or Central America or, less commonly, in South America, Africa, or Asia, where mycoses are endemic. Travel-related mycoses were also reported among international visitors to North America or to countries in Latin America, Africa, and Asia. Most of these infections occurred among travelers returning to European countries, Australia, or Japan. However, with increasing numbers of visitors and immigrants from other Asian countries, travel- and migration-related mycoses are now being described in countries such as India [3, 4]. This review will focus on fungal infections acquired during recent travel abroad, rather than migration-related infections. It is intended to inform health care practitioners about the epidemiology, clinical manifestations, diagnosis, prevention, and treatment of the most common mycoses among travelers.

HISTOPLASMOSIS

Histoplasmosis, which is caused by the dimorphic fungus *Histoplasma capsulatum* var. *capsulatum*, is the most common endemic mycosis in the United States and has recently emerged as an important opportunistic infection among HIV-infected persons living in areas where it is endemic. In the United States,

histoplasmosis is most prevalent in the midwestern and central states; the disease has also been reported throughout Central and South America (figure 2). Histoplasmosis has also been reported from parts of southern and eastern Europe, parts of Africa, eastern Asia, and Australia [5]; however, these reports are usually limited to a single or a few cases that often have no clear source of exposure, and no outbreaks have been reported outside the Americas. All these factors make it very difficult to accurately map the worldwide distribution of this infection. *H. capsulatum* usually grows in soil enriched with accumulations of bat or bird droppings. Human infection commonly occurs after inhalation of dust generated from disturbance of such collections in the soil. Exposures may occur during activities such as construction, renovation, demolition, soil excavation, spelunking, and cleaning sites harboring the fungus [5]. The risk of infection depends on the activities performed and the duration and degree of dust or soil exposure. Longer and more-intense exposures usually result in more severe acute pulmonary disease.

The spectrum of illness is wide. Although asymptomatic infection is very common among persons who usually reside in areas where such diseases are endemic, outbreaks are known to have high attack rates of symptomatic disease, even among those previously exposed. Acute histoplasmosis in returning travelers usually presents as a flulike illness characterized by high-grade fever, chills, headache, nonproductive cough, pleuritic chest pain, and fatigue. Chest radiographs often reveal diffuse reticulonodular infiltrates and mediastinal lymphadenopathy. Symptoms typically occur 1–3 weeks after exposure, and most individuals recover spontaneously within 3 weeks, although the fatigue may persist longer. Disseminated infection is a rare complication but can occur in persons with severe immunodeficiency (e.g., persons with AIDS). Impor-



Figure 2. Geographic distribution of *Histoplasma capsulatum* (gray) and *Coccidioides immitis* (black) infections in the Americas (subject to limitations of surveillance and reporting). Although *C. immitis* is restricted in distribution to the Americas, infections due to *H. capsulatum* have been reported from parts of southern and eastern Europe, parts of Africa, eastern Asia, and Australia [5]; however, these reports are usually limited to a single or a few cases that often have no clear source of exposure, and no outbreaks have been reported outside the Americas, which makes it very difficult to accurately map the worldwide distribution of this infection.

tantly, individuals can be reinfected with *H. capsulatum* with sufficient exposure, and, in these individuals, the incubation period can be shorter.

Histoplasmosis has long been recognized as a common recreational disease among spelunkers (cavers) in North America, 60%–64% of whom have been found to have a positive skin test reaction to histoplasmin [6, 7]. Outbreaks of histoplasmosis were reported among traveling US residents after spelunking trips to bat-infested caves in Central and South America [8, 9] but recently have been reported increasingly among those engaging in other forms of adventure tourism and ecotourism, recreational activities that are on the increase. Recently, in May 2001, a class of 15 students, most of them from Georgia, went on a field trip to Nicaragua. Within 3 days of returning home, 12 (80%) developed symptoms consistent with acute histoplasmosis, later serologically confirmed, and 6 (40%) required hospitalization (figure 1). Their activities in Nicaragua included

visiting a silver mine that contained bat guano (Centers for Disease Control and Prevention, unpublished data).

Not all outbreaks of travel-related histoplasmosis are related to obvious exposures. In March 2001, a large outbreak of the disease occurred among US college students who developed an acute respiratory febrile illness within 1–2 weeks after they returned from Acapulco, Mexico [10, 11], where they spent spring break vacation (spring break for most US colleges usually takes place during the months of March or April each year) (table 1). More than 250 students from many colleges developed symptoms of acute histoplasmosis and 25 were hospitalized, and >150 persons tested had acute histoplasmosis serologically confirmed. Most ill students resided in or visited one particular hotel that was undergoing construction during the spring break period [11].

Histoplasmosis is the most common travel-related mycosis in patients from many European countries. Between 1970 and

Table 1. Selected outbreaks of travel-related fungal diseases.

Disease, date	Location infection acquired	Source of exposure	No. of case patients/no. of travelers examined	Reference
Histoplasmosis				
March 2001	Acapulco, Mexico	Hotel	193/290	[11]
March 2000	Belize	Cave	14/16	[12]
August 1995	Mato Grosso, Peru	Cave	4/4	[8]
January 1988	Santa Rosa National Park, Costa Rica	Cave	15/17	[13]
July–August 1982	Florida	Cave	5/6	[14]
Coccidioidomycosis				
October 2001	Kern County, California	Outdoor dust	5/344	[15]
January 2000	Hermosillo, Mexico	Construction	23/35	[16]
July 1996	Tecate, Mexico	Construction excavation	21/126	[17]
June 1970	Chico, California	Archeological dig	61/103	[18]

1994, 94 migration-related cases of *H. capsulatum* var. *capsulatum* infection were identified in France [19]. Of these, 41 cases were acquired in Central and South America, 25 in Africa, 13 in the Caribbean Islands, and 15 elsewhere. The mean duration of residence in a region where histoplasmosis is endemic ranged from 21 months among HIV-negative individuals to 10 years among those who were HIV infected. An additional 23 cases of *H. capsulatum* var. *duboisii* infection were reported, all of which were acquired in Central or West Africa [19].

Once suspected, the diagnosis of acute pulmonary histoplasmosis in returning travelers is usually made by serologic tests, such as immunodiffusion (ID) and complement fixation (CF), or by antigen detection. The CF test is more sensitive but less specific than the ID test. It becomes positive between 2 and 6 weeks after infection; a titer of $\geq 1:32$ or a 4-fold increase in titer between paired acute and convalescent serum samples is considered to be strongly presumptive evidence of infection [20]. Because low titers of CF antibodies can persist for years after acute histoplasmosis, acute and convalescent serum samples should be obtained whenever possible. The ID test is more specific but less sensitive than the CF test. When histoplasmin is used as the antigen, 2 major precipitin bands can be detected with the ID test. The M band can be detected in up to 75% of cases of acute histoplasmosis but can persist for many months after initial infection. The H band is specific for acute disease but only occurs in 10%–20% of cases.

Antigen detection in urine may be useful for the diagnosis of acute pulmonary histoplasmosis, provided that samples are obtained within 2 weeks after exposure [12]. The histoplasmin skin test can detect previous exposure to the fungus, becoming positive 2–4 weeks after a person has been infected; however, the

reagent is currently not available in the United States. Nonetheless, all diagnostic tests for histoplasmosis require cautious interpretation, because cross-reactivity can occur with other endemic mycoses, such as blastomycosis and coccidioidomycosis.

The Infectious Diseases Society of America (IDSA) has developed guidelines for the management of histoplasmosis [21]. Antifungal treatment is not usually indicated for healthy, non-immunocompromised persons with acute, localized pulmonary infection, because this form of the disease is self limited, often resolving within 3 weeks. For persons with severe symptoms who do not improve after 1 month of observation, itraconazole (200 mg once daily) can be given for 6–12 weeks. In our recent experience during outbreaks, more physicians opted to treat acute pulmonary histoplasmosis at an earlier stage; however, no clinical trials have been conducted to assess whether such treatment is effective in reducing the intensity or duration of symptoms. For those with underlying immunodeficiency or chronic disease, itraconazole should be administered for longer periods. All persons with severe disease, including diffuse pulmonary and disseminated histoplasmosis, should be treated with either amphotericin B or itraconazole.

Prevention of sporadic exposure to sources of *H. capsulatum* in areas where it is endemic is difficult. Nonetheless, individuals who are at increased risk for severe infection, especially immunocompromised persons, should be advised to avoid situations in which contaminated material can become aerosolized. If exposure cannot be avoided, however, travelers should be advised to wear masks and special protective equipment [5]. After engaging in high-risk activities, such as cave exploration, it may be prudent to hose off boots and place clothing in airtight plastic bags to be laundered. Transportation of soil,

guano, and other potential fomites should be avoided. Public health authorities should place warning signs at known high-risk locations.

COCCIDIOIDOMYCOSIS

Coccidioidomycosis (Valley fever) is caused by the dimorphic fungus *Coccidioides immitis*, which is found in the soil of certain arid semidesert regions of the southwestern United States (Arizona, central and southern California, New Mexico, western Texas, and parts of Utah). The disease is also endemic in parts of Central and South America (figure 2). Human infection occurs after inhalation and has been associated with ground-disturbing activities, such as building construction, landscaping, farming, archaeological excavation, and numerous recreational pursuits [22]. Natural events that result in the generation of dust clouds, such as earthquakes and windstorms, also increase the risk of infection and have resulted in large outbreaks.

Approximately 40% of infected persons develop an illness, usually 1–3 weeks after exposure, typically characterized by fever, headache, rash, muscle aches, nonproductive cough, weight loss, and malaise. In rare instances, individuals can develop severe lung disease (e.g., cavitary pneumonia), and <1% of infected persons develop dissemination to the CNS (e.g., meningitis), joints, bones, and skin [22]. Persons who are at increased risk for disease dissemination include African Americans, Filipinos, persons with immunodeficiency (e.g., persons with AIDS and those receiving immunosuppressive medications), pregnant women in the third trimester, and patients with diabetes [23]. In contrast to histoplasmosis, once individuals are infected with *C. immitis*, they are usually immune to reinfection.

Coccidioidomycosis has long been recognized as a travel-related mycosis associated with visits to endemic areas in southern California, Arizona, and other neighboring states. Several reports recently documented the extent of the problem, especially with the recent increase in seasonal migration within the United States to the endemic regions of the Southwest. Between 1980 and 1998, 23 cases of coccidioidomycosis were diagnosed among patients at the Cleveland Clinic (Cleveland, OH) [24]. Between 1992 and 1997, 161 individuals in New York State were discharged from hospitals with the diagnosis of coccidioidomycosis; all patients for whom travel information was available had reported travel to areas where the disease is endemic, most notably the southwestern United States [25]. With increasing domestic and international travel to such areas, an increase in the number of cases of coccidioidomycosis throughout the United States seems almost inevitable. For instance, in 2000, 27 million US travelers visited Arizona, and nearly 1

million visitors from abroad visited this state (Arizona Office of Tourism; http://www.azot.com/research/resource_links.asp).

Travelers from the United States to endemic areas in Central America have also experienced coccidioidomycosis. In recent years, Mexico has become the country most frequently visited by Americans, and several outbreaks of the disease have been reported among returning travelers. In 1996, 21 (17%) cases of coccidioidomycosis occurred among members of a church group from Washington State who had recently returned from a 6-day stay at an orphanage near Tecate, Mexico [17]. Members of the group assisted with construction projects that required excavation, but the trip's organizers were unaware of the potential for *C. immitis* infection. Symptomatic patients saw 19 health care providers, only one of whom correctly diagnosed coccidioidomycosis. More recently, 35 church group members from Pennsylvania traveled to Hermosillo, Mexico, to assist with a church construction project [16]. Within 2 weeks of returning home, many travelers developed a flulike illness, and 8 (23%) had serologically confirmed disease. These 2 outbreaks illustrate the importance of informing travelers about regions where *C. immitis* is endemic and the risk of developing coccidioidomycosis and its clinical manifestations. Health care providers—especially those in nonendemic areas—also need to be familiar with coccidioidomycosis, its diagnosis, and the need to obtain a detailed travel history.

Visitors from other countries have developed coccidioidomycosis after trips to the southwestern United States. In the past, most of these infections occurred among travelers returning to European countries [26], Japan [27], or Australia [15, 28]. More recently, however, changing migration patterns have resulted in several cases of coccidioidomycosis among Indian citizens who had previously resided and worked in Arizona [3, 4]. In addition to these sporadic cases, an international outbreak of the disease was recently reported [29]. In October 2001, >300 individuals from 30 countries participated in the World Championship of Model Airplane Flying in Lost Hills, California, an area where coccidioidomycosis is highly endemic. One week after returning home, a participant from the United Kingdom developed flulike symptoms but was not diagnosed with coccidioidomycosis until culture of bronchoalveolar lavage specimens was performed. Cases among participants have since been confirmed in Finland, Australia, and New Zealand [29]. Again, this outbreak illustrates the need for clinicians to have a high index of clinical suspicion for travel-related mycoses and their areas of endemicity so that appropriate serologic tests, which may afford an earlier diagnosis than culture, may be performed.

The diagnosis of acute pulmonary coccidioidomycosis can be made by direct microscopic examination of lower respiratory tract specimens for *C. immitis* spherules or by culture of such specimens. Serologic tests are the most common diagnostic

method. The immunodiffusion tube precipitin (IDTP) test, which uses heated coccidioidin as antigen, detects IgM antibodies to *C. immitis* and is most useful for diagnosing recent infections. These antibodies can be found within 1–3 weeks after the onset of symptoms but disappear within a few months among persons with acute pulmonary disease [30]. The sensitivity of the IDTP test can be improved by first concentrating the serum. The CF test measures IgG titers, but these antibodies do not appear until 4–12 weeks after infection and may persist for long periods in patients with chronic pulmonary or disseminated disease. High ($\geq 1:32$) or increasing CF titers suggest spread beyond the respiratory tract. A latex agglutination test, which is more rapid than the IDTP test, is also available but has a >5% false-positive rate [31].

The IDSA has developed guidelines for the management of coccidioidomycosis [32]. Most patients with acute symptomatic infection do not require antifungal treatment, because the illness is self limited. However, treatment may be indicated for persons who are at increased risk of dissemination. The drug of choice is fluconazole (400 mg daily for 3–6 months). Patients with bilateral reticulonodular or miliary infiltrates and pregnant women should be treated with amphotericin B.

Prevention of exposure to sources of *C. immitis* in areas where it is endemic is difficult. Nevertheless, travelers should be advised to decrease their risk by limiting their exposure to outdoor dust. Wearing well-fitted masks or driving in vehicles with enclosed air-conditioned cabs can provide some protection [33]. Groups undertaking construction work or other dust-generating activities should be informed about dust-control measures, which include wetting soils before disturbing the earth. Travelers should also be warned to avoid transporting soil and other potential contaminated fomites (e.g., geologic specimens).

PENICILLIOSIS

The first natural human infection with *Penicillium marneffei* was reported in a 61-year-old man, a US citizen who had traveled to Southeast Asia. The infection was diagnosed when the patient, who had Hodgkin's disease, presented with a splenic abscess [34]. More than a decade elapsed before a second case was reported [35]. This patient also was a man, a US citizen, who had traveled throughout Southeast Asia. Between 1988 (when the first cases of AIDS-associated penicilliosis were described) and 1994, 14 cases of the disease were reported among HIV-infected individuals returning to their native countries after visits to Southeast Asia [36]. Members of this group included residents of Australia, France, Italy, The Netherlands, the United Kingdom, and the United States. Although it is now clear that the greatest impact of penicilliosis has been felt by the populations of Southeast Asia, particularly persons living

with AIDS in northern Thailand, the disease continues to be diagnosed among returning travelers.

The most common clinical features of penicilliosis include fever, marked weight loss, nonproductive cough, lymphadenopathy, hepatosplenomegaly, and anemia. Many patients present with multiple papular skin lesions, some of which show a central necrotic umbilication, resembling molluscum contagiosum. These are often found on the face, neck, trunk, and upper limbs [37]. The diagnosis can be made by direct microscopic examination or culture of specimens from the bone marrow, lymph nodes, skin, and other infected sites. Culture of these lesions is important, because other fungal infections, such as histoplasmosis, may have similar clinical manifestations in immunocompromised persons. Chest radiographs may reveal cavitary lesions or infiltrates. There are no widely available serological tests for this disease.

Amphotericin B is the drug of choice for severe cases of *P. marneffei* infection. The usual regimen is 1 mg/kg once per day for 2 weeks, after which itraconazole (200–400 mg daily) or ketoconazole (400 mg daily) should be given for a further 6 weeks. For milder infections, an azole agent can be used from the outset.

Prevention of exposure to sources of *P. marneffei* in the environment is difficult. There is evidence of seasonal variation in the incidence of the infection in Thailand, with the highest number of cases occurring during the rainy season from May to October [38], which suggests that the infection may be acutely acquired. To date, however, no definite environmental source or route of transmission has been identified. Individuals with a compromised immune system should be advised to avoid travel to areas of Southeast Asia (e.g., Vietnam, Laos, Singapore, Malaysia, Burma, Thailand, Indonesia, Hong Kong, and the southern part of China, Guang Xi province) where *P. marneffei* is known to be endemic.

OTHER INFECTIONS

In addition to the 3 mycotic diseases so far described, migration-related cases of a number of other subcutaneous and systemic fungal infections were reported from a number of countries. In most instances, these infections occurred months or years after a period of residence in area where the fungus is endemic. Paracoccidioidomycosis, which is caused by *Paracoccidioides brasiliensis* and is endemic to the subtropical regions of Central and South America, has a prolonged incubation period that can be many years long [39]. The chronic progressive adult form with dissemination is the most common presentation, with clinical manifestations such as fever, weight loss, anorexia, and pulmonary, mucosal, and cutaneous lesions. With such a long incubation period, clinicians may overlook the significance of a patient's history of travel or stay in an

area where mycotic disease is endemic when attempting to generate a differential diagnosis. Clearly, it is essential that remote, as well as recent, patient travel history be obtained.

CONCLUSION

With increasing international travel, a number of mycoses are now emerging as important infections outside their previously restricted areas of endemicity. It is becoming more important to ensure that travelers, especially immunocompromised ones, are made aware of the risks of acquiring such diseases and of measures that can be taken to minimize the risk of infection. Health care providers need to be aware of the presenting features, diagnostic tests, and management of these diseases. With latent periods ranging from a few weeks to several years, it is essential for clinicians to be aware of a patient's short-term and long-term history of travel or residence, as well as the geographic distribution and risk factors for these diseases. Recently, histoplasmosis and coccidioidomycosis have been included as travel-related illnesses in the Health Information for International Travel Yellow Book (<http://www.cdc.gov/travel/diseases.htm>).

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