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Travel-Related Respiratory Infections

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Introduction

Respiratory tract infections are ubiquitous in developed and developing countries. Seasonal outbreaks of the common cold, pharyngitis, and influenza form a part of the medical landscape of everyday life, and pneumonia is one of the most frequent community-acquired infections in most countries. The importance of respiratory infections in travelers stems from their high frequency, pathogens that occur out of season, the possibility of less known but life-threatening pathogens, and other clinical pitfalls. The aim of this chapter is to consider the epidemiology of travel-related respiratory tract infections, to review certain less frequent pathogens, and to suggest a clinical approach to diagnosis.

Epidemiology of travel-related respiratory infections

Respiratory tract infections (RTIs) are the most prevalent infectious disease in humans. Surveys in the USA have established that RTIs affect more than 70% of the population yearly, with adults suffering at least two yearly episodes [1]. The incidence of respiratory disease in the UK usually peaks at about 600/100,000 or 0.6% during winter months, but may reach 1% of the population in some years [2]. Whether travel per se increases the risk for RTIs is unknown. The incidence of RTIs changes markedly throughout the year in all temperate countries; it may differ markedly from year to year, between regions, and

among different age groups. It is certain, however, that RTIs appear to be very frequent among travelers. In the USA, a prospective study has found that among internal air travelers during the winter season, 20% developed RTIs (3).

Several studies have reported on the occurrence of RTIs in travelers to developing countries using different methodologies. Only a few prospective studies have addressed this issue: Rack et al. have found among German travelers an RTI incidence of 13.8% [4], whereas among Israeli and American travelers, as many as 25–26% reported post-travel RTIs ([5, 6]. Several retrospective surveys on very large numbers of returning travelers have reported similar findings: in a seminal article 30 years ago, Steffen et al. reported that the incidence of respiratory symptoms was 12% among more than 10,000 travelers to developing countries [7]. Among nearly 5,000 Scottish travelers, 16.8% reported an RTI during travel [8]. In all these surveys, RTIs were second only to diarrhea as the most prevalent health event during travel.

Another set of data can be found in registries of ill returning travelers presenting at travel clinics or hospitals. These reports have an inherent selection bias toward more severe illnesses. Despite this, RTIs still figure high among travel-related infectious diseases. The most comprehensive registry of ill returning travelers is the multinational GeoSentinel registry. In this report, RTIs accounted for 77/1000 travelers, and were again second only to diarrhea in prevalence [9]. Other reports have focused on febrile illness in returning travelers. In another GeoSentinel study of febrile patients, RTIs accounted for 14% of all cases [10]. RTIs assume even greater importance among HIV-infected travelers, whereas among febrile patients, they were the leading diagnosis [11]. Hospital-based series from different countries show RTIs to be the diagnosis

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in 2.6–46% of febrile hospitalized patients [12]. These marked differences probably reflect local differences in hospitalization practices, rather than local differences in RTI incidence.

To summarize, although it is not known whether travelers to developing countries are more or less prone to RTIs, these conditions are highly prevalent among them, causing significant travel disruption and a significant number of post-travel hospital admissions.

Upper respiratory tract infections in travelers

Upper respiratory tract infection (URTI) is usually defined as an acute illness causing cough, with or without coryza, sore throat, and systemic symptoms such as fever and malaise [13]. As discussed previously, the true incidence of URTI in travelers is not really known, but is in all likelihood very high, second only to diarrhea in prevalence. Most cases are mild and therefore unreported. However, the burden of short-term morbidity, travel disruption, and cost is probably very considerable. The mode of transmission for most of the common viruses causing URTI is probably similar in travelers and the general population, with droplet infection and close contact accounting for most cases. Several viruses that cause RTIs can be transmitted orally, such as enteroviruses and adenoviruses, and may, therefore, be transmitted via food and water [14]. However, this mode of transmission is probably not important.

The spectrum of viral agents causing travel-related URTIs is similar to that seen in the general population. Camps et al. have diagnosed at least one virus from 56% of travelers with fever and respiratory symptoms [15]. The most frequent viruses detected were influenza virus (38%), rhinovirus (23%), adenovirus (9%), and respiratory syncytial virus (9%). Similar results were reported in German travelers, where again influenza was the most frequent isolate [16].

Most data regarding respiratory viruses among travelers relate to influenza. Large outbreaks of influenza have been reported among travelers, and the global fear of pandemic influenza and the spread of avian influenza have focused research on this field. Already during the pandemic of 1889–1890, the advance of pandemic influenza along lines of travel was well established [17]. Today, air travel is of great importance in influenza dissemination [18].

Influenza is not rare among travelers. The Hajj is probably the largest annual transit of persons in the world

and has presented an excellent opportunity to study influenza. In a large survey among Hajj pilgrims in 2003, RTIs accounted for 40% of all illnesses reported, and influenza virus accounted for half the respiratory viruses isolated [19]. In 2006, a detailed laboratory analysis for viral causes of URTIs in Hajj pilgrims found influenza to be second only to rhinovirus (11% and 15%, respectively) [20]. Apart from Hajj pilgrims, additional studies on Western travelers attest to the high incidence of influenza. Mutsch et al. have established in Swiss travelers an incidence rate of 1 case/100 travel months, with 2.8% overall incidence and 12.8% among travelers with a history of febrile illness. An important feature was that most cases occurred outside the usual North European influenza season [21]. Large outbreaks of influenza were also reported in cruise ships because the confined onboard conditions promote outbreaks [22].

Lower respiratory tract infections in travelers

Pneumonia is not a rare condition among returning ill travelers. Although it is significantly less prevalent than URTI in most series, it still accounts for many hospital admissions due to post-travel respiratory illness [12, 23]. Pneumonia is also an important cause of infectious mortality post-travel [9] and, in fact, was the only cause of mortality among 1106 ill Australian travelers over a 6 year period [24]. Due to its potential severity and associated mortality, post-travel pneumonia is a major medical concern in returning travelers. These concerns were accentuated after the SARS outbreak due to the fears of global spread of the disease and the attendant risks to healthcare personnel.

Most of the major causes of pneumonia have a global distribution. *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Staphylococcus aureus* are the dominant pneumonia isolates in developing countries [25–27]. Some agents of travel-related pneumonia have a global distribution, but are reported infrequently. Q fever, for example, is only rarely diagnosed in travelers, and in fact has more often been associated with a nonspecific febrile illness than with RTI, sometimes diagnosed only as part of an outbreak investigation [28, 29]. The majority of travel-related Q fever is reported from Africa. Whether African travel is indeed a risk factor for *Coxiella* infection or the disease is underreported from other locales (e.g., Southern Europe, where Q fever is quite prevalent [30]) is not known.

Some agents of travel-related pneumonia are rare in most developed countries and may, therefore, be missed by practitioners if the travel itinerary is not taken into account. These include most helminthic and some bacterial and fungal respiratory infections, which will be discussed below.

The etiology of travel-related pneumonia has in fact received scant attention. In a small study by Ansart et al., most cases of pneumonia were bacterial, with *Streptococcus pneumoniae*, *Mycoplasma*, and *Legionella* diagnosed in 38% of cases [31]. Three cases were caused by organisms not included in the “core organisms” covered by guidelines for the treatment of pneumonia, including one case each of Q fever, histoplasmosis, and schistosomiasis, and two cases were diagnosed with systemic infectious agents: dengue and leptospirosis.

In the following sections, several of these travel-specific agents of pneumonia are described in detail. However, one should keep in mind that even for mundane pneumococcal pneumonia, major differences in bacterial resistance patterns are encountered in different countries. For example, pneumococcal penicillin and multidrug resistance are very frequent in South Africa, the Far East, and even Spain, but very rare in the Netherlands [32]. These issues should all be addressed in the clinical approach to the patient with post-travel pneumonia and to empirical antimicrobial therapy.

A clinical approach to the returning traveler with respiratory symptoms

Acute and chronic respiratory symptoms are two common complaints, with the first being the most common presentation in general medical practice and the second being reported by up to 20% of the general population [33]. Clearly, therefore, in evaluating returning travelers, the first issue is to establish by a thorough medical history whether respiratory complaints are indeed temporally associated with travel. The majority of patients presenting with post-travel respiratory symptoms fall into one of two major categories: an acute febrile disease with respiratory symptoms or protracted respiratory symptoms post-travel, mainly cough.

Acute post-travel fever and respiratory symptoms

It is of primary importance for the physician to remember at the outset that respiratory symptoms are not rare in systemic febrile illnesses that are not commonly as-

sociated with the respiratory tract. In malaria, respiratory symptoms occur in up to half the patients and are not limited to cases of severe malaria with pulmonary edema/acute respiratory distress syndrome (ARDS) [34]. Similarly, cough is not rare in enteric fever [35] and leptospirosis [36], which are sometimes initially mistaken for URTI/pneumonia. Thus, if a thorough travel history reveals a stay in malaria-endemic areas, malaria must always be actively ruled out by repeated blood smears.

The acutely ill returning traveler with fever and respiratory symptoms may be suffering from either URTI or pneumonia. As recommended in practice guidelines in the general population, a chest radiograph (CXR) is needed to exclude pneumonia [37]. Radiological findings may include not only infiltrates of “usual” pneumonia, but other findings such as the infiltrates of acute respiratory distress/pulmonary edema in *vivax/falciparum* malaria or pulmonary nodules in acute histoplasmosis.

Among patients with URTI, an immediate issue is influenza: fever and cough with an acute onset are the definition of “influenza-like-illness” (ILI). Attention to influenza is heightened due to current concerns about avian influenza and pandemics because travelers are assumed to be the main force of pandemic spread [38]. Since early identification of influenza can provide benefits for the traveler (by instituting antiviral therapy) and the community (by limiting spread), travelers should be tested for influenza virus. The patterns of influenza seasonality in travel medicine reflect the transmission pattern in the destination countries. It should be remembered that in many tropical countries influenza transmission is continuous rather than seasonal [39].

Pneumonia

Guidelines for the assessment, triage, and treatment of pneumonia are well established [37]. We believe it is useful to consider three scenarios post-travel: usual pneumonia, severe pneumonia, and pneumonia with eosinophilia. The majority of travelers with pneumonia will not differ from routine cases of community-acquired pneumonia (CAP). Still, increased exposure to hotels requires heightened alertness to the possibility of legionellosis. Providing coverage for *Legionella* even in non-severe cases is probably merited (see discussion on legionellosis later in this chapter).

Among patients with severe CAP (SCAP), general CAP guidelines already address legionellosis. However, travelers to East and Southeast Asia may be exposed to *Burkholderia pseudomallei*—the causative agent of melioidosis. This disease can manifest as a severe necrotizing

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pneumonia and is not covered by usual treatment recommendations (see discussion on melioidosis later in this chapter).

Severe pneumonia can also be associated with viral infections. The most common worldwide is influenza. Primary influenza pneumonia is in fact underreported, but during pandemic years has accounted for 18% of all influenza-associated pneumonia [40]. Other rarely reported viral pneumonias in travelers include SARS and hantavirus pulmonary syndrome (HPS). No SARS activity has been recorded since the end of the 2003 epidemic. However, this situation may change, and for travelers from East and Southeast Asia with severe pneumonia, tests for possible SARS may be required. HPS, which is part of the viral hemorrhagic fever group, has been reported very rarely in travelers to South America (see Chapter 13).

Pneumonia with eosinophilia

Acute bacterial infections, including pneumonia, are usually accompanied by eosinopenia, and, therefore, even a high normal eosinophil count should be closely followed. Pneumonia with eosinophilia can be attributed to several causes; in developed countries exposure to various drugs or toxic substances is the more frequently established cause, but many cases remain idiopathic [41]. Among returning travelers, several unusual causes should be considered initially, mainly helminthic infections.

Schistosomiasis manifests acutely as a combination of fever and respiratory symptoms, either with or without pulmonary infiltrates [42]. Other symptoms of acute schistosomiasis may include an urticarial rash, fatigue, and myalgia (see Chapter 24). Respiratory symptoms are at times the dominant symptom and may last for several weeks. Similarly, geohelminths—*Ascaris*, hookworms, and *Strongyloides*—can cause an acute febrile episode with cough, again with or without lung infiltrates. The presence of lung infiltrates in acute ascariasis defines the original Löffler syndrome.

Several dimorphic fungi may cause respiratory symptoms with pulmonary infiltrates. Among these, coccidioidomycosis in the western USA and paracoccidioidomycosis in Latin America are often associated with eosinophilia. The more frequent endemic fungal pneumonitis seen in travelers is histoplasmosis, which does not cause eosinophilia (see discussion later in this chapter and Chapter 29).

A simple algorithmic approach may be used to guide the diagnosis and therapy of acutely ill returning travelers with fever and respiratory symptoms (Figure 41.1). Clinicians are encouraged to make use of available inter-

national reporting systems (e.g., ProMed, available from <http://www.promedmail.org>) because these may present the earliest opportunity of recognizing an international common source outbreak (e.g., legionellosis).

Protracted post-travel respiratory symptoms

Unlike the data on the prevalence of chronic diarrhea among travelers and its etiology, there are few data on the prevalence and etiology of protracted post-travel respiratory symptoms—mainly prolonged cough. In the majority of cases of acute respiratory infections, respiratory symptoms persist well after fever has resolved, but will usually disappear or be greatly improved after 2–3 weeks [33]. In the general population, protracted cough is frequently ascribed to a few causes, including asthma, post-nasal drip, and gastroesophageal reflux. Among travelers, we have to consider several travel-related infections that may cause prolonged cough before applying the usual Western guidelines. Our approach is summarized in Figure 41.2.

A thorough medical history and physical examination are essential. An exact travel itinerary should be determined, as well as the types of exposures that have occurred (e.g., bathing in freshwater, exposure to contaminated soil, and types of raw food consumed). The geographical distribution of the major travel-related RTIs is described in Figure 41.3. Symptoms and signs that developed prior to the respiratory symptoms may suggest a specific diagnosis (e.g., ground itch, urticarial rashes, or gastrointestinal manifestations) [43]. In addition to history and physical examination, all patients with post-travel respiratory symptoms should undergo chest radiography and a complete blood count (CBC).

Persistent cough with eosinophilia

Helminth-associated respiratory symptoms can follow a protracted course, usually associated with marked eosinophilia. We have shown, for example, that among Israeli travelers with schistosomiasis, protracted cough was not rare, with the median duration of respiratory symptoms being 6 weeks (mean \pm SD 15.4 \pm 22.7 weeks) [44]. Therefore, regardless of the results of the CXR (in some patients granulomatous pneumonitis was not seen at all, or was discernible only after high-resolution CT), schistosomiasis needs to be actively excluded if exposure to infected waters may have occurred. Geohelminths can cause cough and eosinophilia [45]. Infiltrates can be fleeting, and, therefore, the diagnosis should be assessed in all patients, even when the CXR is normal.

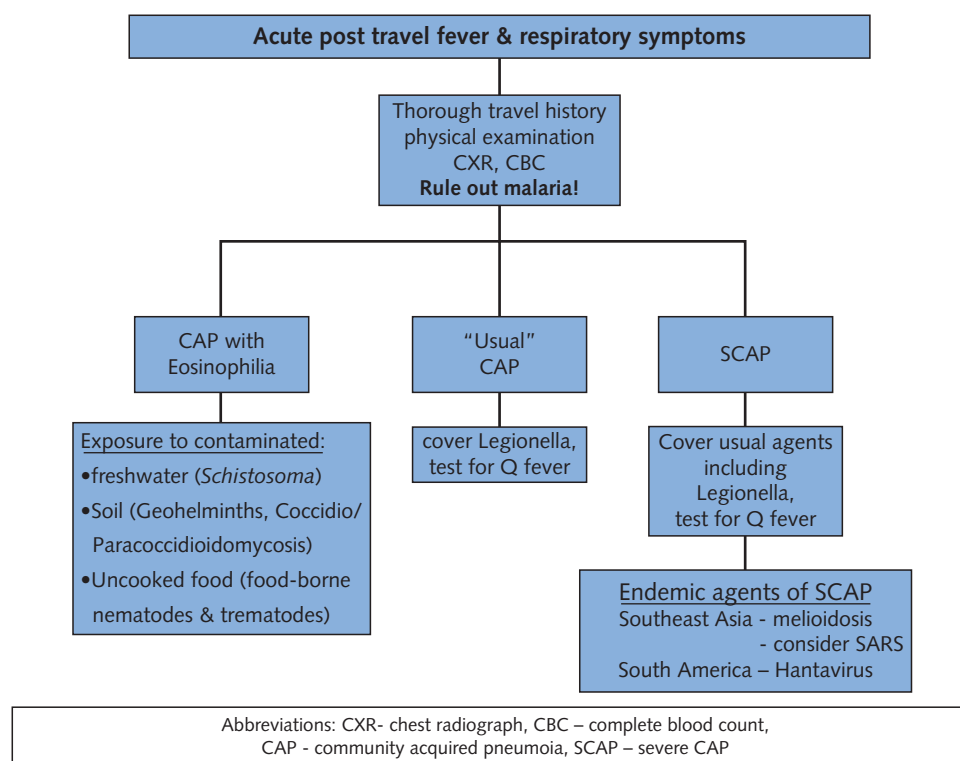


Figure 41.1 The clinical approach to the acutely ill returning traveler with fever and cough.

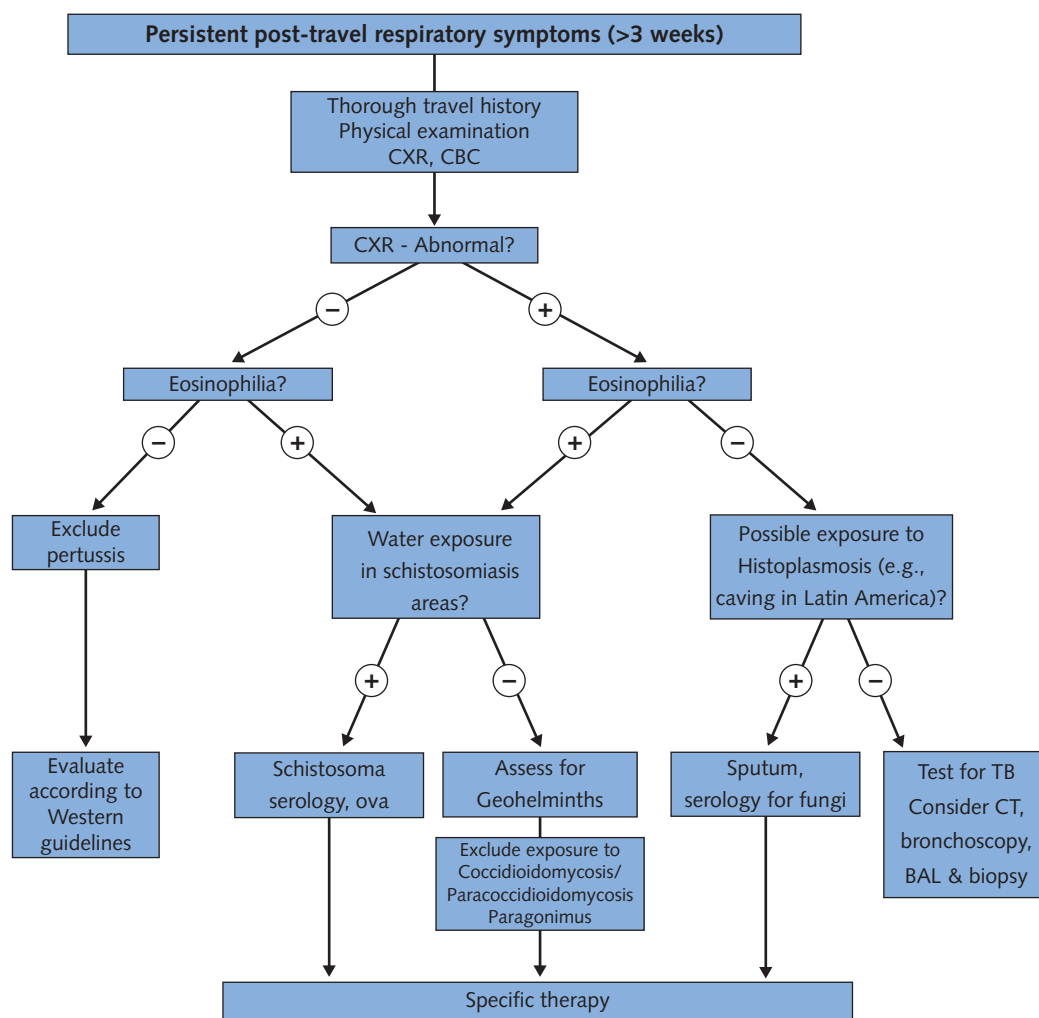
An additional pathogen that may present with protracted cough and eosinophilia is *Paragonimus*, which is rarely described in travelers. Paragonimiasis results from the ingestion by humans of the intermediary host of the helminth—usually by eating uncooked freshwater crabs. After an initial migratory phase, a chronic cavitory lung lesion develops, with productive cough, occasionally with hemoptysis and chest pain. The clinical–radiological picture closely mimics that of tuberculosis, for which it is often mistaken in developing countries. A careful history can sometimes reveal possible exposure. Also, some patients may recall a larva migrans like rash early in the disease course. The infection can be proven by demonstrating the ova in sputum and stool. Serological tests exist, but are not often available (see Appendix). Therapy, on the other hand is simple: a 2-day course of praziquantel. Paragonimiasis has mainly been reported from Southeast Asia and South America, but may occur in additional regions, including Africa.

A final issue in the patient with persistent cough and eosinophilia is infection with coccidioidomycosis and paracoccidioidomycosis. Travelers to North and Latin

America may be exposed to these agents, but reports of infections mostly involve long-term expatriates rather than tourists. The diagnosis requires demonstrating the typical yeast in the sputum, but occasionally bronchoalveolar lavage and even lung biopsy are required. Serological tests are also available (see Chapter 29).

In the patient with persistent cough, lung infiltrates, and a normal leukocyte count, histoplasmosis should be considered. Chest CT may have a highly suggestive radiological pattern, which may direct clinicians to order specific diagnostic tests. Similarly, any traveler with a protracted cough and infiltrate should be evaluated for tuberculosis.

In a patient with a normal physical examination, a normal CXR, and without eosinophilia, pertussis should be considered. Even in developed countries, the level of immunity for *Bordetella pertussis* is inadequate in many adults [46], and travelers are not different in having little awareness of and little protection against the disease. Little is known about travel-related pertussis, but among Hajj pilgrims clinical pertussis occurred in 7.5% of travelers without immunity [47]. The disease is so underreported



Abbreviations: CXR - chest radiograph, CBC - complete blood count, TB - tuberculosis, CT - computerized tomography, BAL - bronchoalveolar lavage

Figure 41.2 The clinical approach to the returning traveler with protracted respiratory symptoms.

and unrecognized that testing the traveler with protracted cough is merited. Marked lymphocytosis on the CBC, an infrequent finding in the general population, is often a diagnostic clue.

In cases in which the diagnoses mentioned earlier are considered and excluded, the evaluation should generally follow established Western guidelines [33].

Following is a more detailed discussion of several pathogens that bear significant importance in post-travel pneumonia, including *Legionella*, melioidosis, fungal respiratory infection, and tuberculosis.

Specific agents of pneumonia in travelers

Legionella

Legionellae are a group of bacterial pathogens, whose usual habitat is aquatic environments, usually in close association with environmental amoebas. Colonization of air-conditioning systems, cooling towers, and water systems in hotels can result in aerosolization of the bacteria and outbreaks of severe pneumonia. Ever since the original

