

Consensus document

Imported infectious diseases after returning from foreign travel: Consensus document of the Spanish Society for Infectious Diseases and Clinical Microbiology (SEIMC)

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ABSTRACT

In a global world, knowledge of imported infectious diseases is essential in daily practice both for the microbiologist-parasitologist and the clinician who diagnoses and treats infectious diseases in returned travellers. Tropical and subtropical countries where there is a greater risk of contracting an infectious disease are among the most frequently visited tourist destinations. The SEIMC considers it appropriate to produce a consensus document that will be useful to the primary care doctor, as well as the specialists in internal medicine, infectious diseases and tropical medicine who help treat travelers returning from tropical and sub-tropical areas with infections. *Preventive aspects* of infectious diseases and infections imported by *immigrants* are explicitly excluded here, since they have been dealt with in other SEIMC documents.

Various types of professionals (clinicians, microbiologists, and parasitologists) have helped produce this consensus document by evaluating the available evidence-based data in order to propose a series of key facts and information about individual aspects of the topic. The first section of the document is a summary of some of the general aspects to do with the overall evaluation of travelers who return home with potential infections. The main second section contains the key facts (causative agents, diagnostic procedures and therapeutic measures) associated with the major infectious syndromes affecting returned travelers [gastrointestinal syndrome (acute or persistent diarrhea); febrile syndrome with no obvious source of infection; localized cutaneous lesions, and respiratory infections] are indicated. Finally, the characteristics of special types of traveler, such as pregnant women and immunocompromised travellers, are described. Accompanying this document is an extensive bibliography that forms the basis of these recommendations.

ARTICLE INFORMATION

Keywords:

International travelers

Imported infectious diseases

Enfermedades infecciosas importadas tras el regreso de viajes en el extranjero: documento de consenso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC)

RESUMEN

En el mundo global, el conocimiento de las enfermedades infecciosas importadas es esencial en la práctica diaria, tanto para el microbiólogo-parasitólogo como para el clínico en enfermedades infecciosas que atienden a viajeros internacionales. Entre los destinos turísticos más visitados se encuentran muchos países tropicales o subtropicales, donde el riesgo de contraer una enfermedad infecciosa es más elevado. La SEIMC ha considerado pertinente la elaboración de un documento de consenso que sirva de ayuda tanto a médicos de Atención Primaria como a los especialistas en Medicina Interna, Enfermedades Infecciosas y Medicina Tropical que atienden a viajeros que regresan con infecciones tras un viaje a zonas tropicales y subtropicales. Se han excluido de forma explícita los *aspectos de prevención* de las mismas y las infecciones importadas por *inmigrantes*, objeto de otros documentos de la SEIMC.

Varios tipos de profesionales (clínicos, microbiólogos y parasitólogos) han desarrollado este Documento de Consenso evaluando los datos disponibles basados en la evidencia para proponer una serie de datos clave acerca de este aspecto. Inicialmente se revisan los aspectos generales acerca de la evaluación general del viajero que regresa con una potencial infección. En un segundo bloque se señalan los datos clave (agentes causales, procedimientos diagnósticos y medidas terapéuticas) de los síndromes infecciosos principales en el viajero que regresa [síndrome gastrointestinal (diarrea aguda o persistente), el síndrome febril sin foco aparente, las lesiones cutáneas localizadas y las infecciones respiratorias]. Finalmente se describen las características en viajeros especiales como la viajera embarazada y el viajero inmunodeprimido. Este documento se acompaña de la bibliografía correspondiente que fundamenta estas recomendaciones.

INFORMACIÓN DEL ARTÍCULO

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Introduction

Justification

According to the World Tourism Organization, there were around 1,184 million international tourist arrivals in 2015, some 50 million more than in 2014 (an increase of 4.4%). International tourist arrivals for the year 2016 were forecast to increase by 4%, both worldwide and regionally. Regional growth was expected to be highest in Asia and the Pacific (between 4% and 5%) and the Americas (between 4% and 5%), followed by Europe (between 3.5% and 4.5%), and Africa and the Middle East (between 2% and 5%)¹. *Familitur* data showed that international tourist movements made by Spaniards were 11.8 million in 2014, 1,140,000 of which were to the African continent, 764,000 to America (Central Caribbean and South) and 520,000 to Asia².

The most frequently visited tourist destinations include tropical and sub-tropical countries where there is a higher risk of contracting an infectious disease³. Travel to economically less developed countries frequently involves exposure to biological agents that cause infections or to infectious diseases transmitted by different routes (digestive, respiratory, mucocutaneous, vector, and so on). One point that should be highlighted from the outset is the possibility that an infection in the international traveler could also be caused by cosmopolitan agents found within our own country, an example of which would be sexually transmitted diseases (STDs), a set of infectious conditions that has been insufficiently studied among travelers. The differential diagnosis therefore should always include diseases that have a restricted geographic distribution as well as those with a global presence. Furthermore, the severity of the clinical pictures presented here varies a good deal, so that a special section has been included on managing the seriously ill patient. Finally, there are certain situations that are physiological (such as pregnancy) or pathological in nature (for example, the immunocompromised patient, whether or not associated with HIV infection) that have special characteristics that warrant further discussion.

From a medical point of view, these guidelines will be useful to primary care physicians as well as specialists in internal medicine, infectious diseases and tropical medicine who treat travelers returning from tropical and sub-tropical areas with infections. The target population in this document is *adults* with infections imported after returning from international travel. The *prevention* of imported diseases and infections imported by *immigrants* are explicitly excluded here, since these have been

considered in recent EIMC reviews. Also left out here in a general sense are other non-infectious illnesses among travelers, although certain aspects will be indicated in specific sections.

Objectives of the document

Various types of professionals (clinicians, microbiologists and parasitologists) have helped produce this consensus document by evaluating the evidence-based information available and making recommendations on the following aspects:

- Definitions
- General evaluation of the returned traveler with a potential infection
 - The need to evaluate the asymptomatic traveler
 - The main syndromes associated with imported infectious diseases
 - Evaluation of the traveler with severe infectious disease
 - Evaluation of the traveler with a potentially transmissible disease and isolation precautions
- Main infectious syndromes in the returned traveler
 - Acute or persistent diarrhea
 - Fever of unknown origin
 - Localized cutaneous lesions
 - Respiratory infections
 - Eosinophilia
 - Neurological infections
 - Urinary tract infections
- Special characteristics of the pregnant traveler
- Special characteristics of the immunocompromised traveler

General methodology of the document

A systematic review of the bibliography was performed to evaluate all data concerning the causes, diagnostic methods and therapeutic options for infections imported by travelers. A search of the PubMed database was performed using the following selection criteria: articles published between 1968 and March 2016, in English or Spanish, and limited to humans only. The search terms used were "travel*" associated with each of the items explored (e.g. "fever", "diarrhea", and so on). This search was complemented with a review of the *Cochrane Database of Systematic Reviews*, using "travel*" as the key term, and also of the international guidelines dealing with each of the separate aspects evaluated. The

search was conducted using PRISMA criteria⁴, and was reviewed by the contributors in the first instance, then by those coordinating the text version. A total of 436 publications were selected, eliminating those that were duplicated or not relevant. The specific set of references selected for each section may be requested from the contributors.

The recommendations were based on the international standards used in the consensus guidelines of the Infectious Disease Society of America (IDSA) and the Appraisal of Guidelines Research & Evaluation (AGREE) instrument⁵. The coordinators and authors of the document issued a consensus version, which was published on the SEIMC website between 13 November 2016 and 14 December 2016 for external review. The final submitted article was returned with approval for publication. The management board of the SEIMC will designate coordinators to review this document in the next 5 years.

Definitions

This section indicates the main definitions used in this document and are based on those used internationally by the World Tourism Organization. The bibliographical reference includes extended versions of these definitions⁶.

Tourism trip, or travel, is defined as the movement of a person to countries or places outside his usual environment involving at least one overnight stay but less than 12 months. Movement that does not involve an overnight stay is referred to as an **excursion**.

With respect to the destination, there are two types of tourism trip: **domestic tourism** (occurs within the country of reference) and **outbound tourism** (involving travel to a different country). Although there are many classifications of the geographic regions and sub-regions of the world, one of the most commonly used is the United Nations classification⁷.

With respect to the duration of the trip, three types can be distinguished: **short-term** (< 3 weeks), **medium-term** (3 weeks to 3 months) and **long-term** (>3 months). Finally, there are two main purposes of tourism trips: for **personal reasons** and **professional reasons**. Trips for personal reasons can be further subdivided into: *i*) leisure, recreation and holidays; *ii*) visiting friends and relatives (VFR); *iii*) shopping trips; *iv*) trips for purposes of education/training; *v*) health tourism; *vi*) for religious reasons/pilgrimages, and *vii*) trips to do with cooperation and humanitarian aid. Trips for professional reasons include *business trips/conferences* and *military purposes*.

General evaluation of the returned traveler with a possible infection

Need to evaluate the asymptomatic traveler

KEY DATA

KF1. Systematic evaluation is not indicated for all international travelers in the absence of clinical signs and symptoms (A-II).

KF2. Immigrant travelers visiting friends and relatives may benefit from evaluation, even if they are asymptomatic (C-II).

KF3. Long-term travelers (>3 months), those to high-risk areas and/or including high-risk activities may benefit from a directed evaluation (B-II).

KF4. Travelers who have been in contact with freshwater sources in endemic areas or who have walked barefoot on contaminated soil may benefit from screening for schistosomiasis and strongyloidiasis respectively (A-II).

KF5. Any traveler who has engaged in risky sexual practice without protection may benefit from serological testing for the detection of STIs, HIV, hepatitis B and C and syphilis (A-II).

KF6. Health aid workers exposed to patients with active tuberculosis may benefit from the tuberculin skin test or interferon-gamma release assays (IGRAs) (B-II).

RATIONALE

Most trips made by international travellers are short-term and to areas that present little health risk. In these situations, the chances of acquiring any kind of disease are very remote. Indeed, only 8% of travellers to developing areas require medical attention during or after a trip, which means that the remaining 92% are asymptomatic^{8,9}. In this patient group, the cost-benefit relationship is not enough to justify systematic screening for all possible infectious diseases that may have been acquired while abroad, so that systematic screening is indicated only if it is very likely that the patient became ill during the trip, if the diagnostic procedure used to detect it is sensitive and with very high positive predictive value, and if the disease will benefit from an effective treatment. In consequence, evaluation of the asymptomatic traveler should be limited to a series of special situations, which are set out below.

There is a positive correlation between the duration of the trip and the risk of acquiring an infection. In general, trips that last more than three months are considered to present the highest risk¹⁰. In this group, therefore, patients who engaged in activities with a higher risk of acquiring infection (swimming, eating food that is contaminated or has not been thoroughly cooked or handled properly, sexual relations, entering caves, etc.) or visited areas with specific endemic infection (such as malaria, dengue or the Zika virus) may benefit from a directed evaluation.

On the other hand, there are some specific activities that have a higher risk of acquiring certain infections, regardless of the length of the trip. So, it is necessary to rule out infection with

schistosomiasis after swimming in freshwater in endemic areas, since this infection can remain asymptomatic for months or years in up to 30% of exposed travelers. Consequently, an examination of stools and urine for the eggs of *Schistosoma* spp., or serological testing to detect antibodies in the early stages of the infection are tests that should be performed on such asymptomatic travellers^{11,12}.

Likewise, travelers who report that they walked barefoot on soil potentially contaminated with human feces may have been infected by *Strongyloides stercoralis*, which is able to penetrate unbroken skin. While infection with *S. stercoralis* is often asymptomatic, the parasite load can become very high over time. It may therefore be beneficial to use direct techniques or serology to screen asymptomatic subjects with this risk profile for strongyloidiasis, particularly if peripheral blood eosinophilia is detected or they are about to undergo any type of immunosuppressive treatment (see **section 26 IV.5**).

Immigrants residing in Western countries who travel to their countries of birth during holiday periods to visit family members constitute a special subgroup of travelers, because they often do not seek advice before they set off or receive adequate chemoprophylaxis or immunoprophylaxis. In addition, they visit rural areas that are a long way from the usual tourist circuits, which places them at greater risk of acquiring infectious diseases. Indeed, the rates of parasitic infection (malaria, intestinal parasites, etc.), febrile syndromes and need for hospital admission are all higher in the VFR group compared to other travelers^{13,14}. In these cases, screening of asymptomatic subjects may be indicated, especially those who visited areas with malaria, bearing in mind that some may also have asymptomatic malaria as a result of having acquired partial immunity, or asymptomatic filariasis (more so if there is peripheral blood eosinophilia), schistosomiasis and other parasitic diseases¹⁵.

It is common knowledge that some travelers frequently engage in unprotected sexual relations, often with strangers, occasionally with professional sex workers. In all these situations, screening for the main sexually transmitted diseases (HIV, hepatitis B and C virus, *Chlamydia trachomatis*, herpes viruses or human papillomavirus) is recommended, since many of these infections have an asymptomatic phase¹⁶.

Finally, tuberculosis infection is highly prevalent in some developing countries. Hence, volunteers and other humanitarian aid workers (in hospital centers, refugee camps and crowded human settlements) may have been exposed to *Mycobacterium tuberculosis*. In this situation, if recent infection has been documented in the form of a Mantoux tuberculin skin test conversion or Interferon-Gamma Release Assay (IGRA), asymptomatic travellers may benefit from prophylactic anti-TB therapy¹⁷.

Major syndromes of imported disease in travelers

KEY FACTS

KF7. In overall terms, the most common syndromes affecting travelers who return home feeling ill are gastrointestinal (acute or persistent diarrhea), fever of unknown origin, localized skin lesions and respiratory infections (A-II).

KF8. The relative frequency of these syndromes varies depending on the geographic area or region visited (B-II).

KF9. The severity of these syndromes is variable. Fever of unknown origin or associated with other symptoms (such as diarrhea or respiratory problems) accounts for the majority of hospital admissions (B-II).

RATIONALE

The most reliable information we have about the main patterns of illness in diseases imported by travelers comes from cohorts treated in particular clinics in the USA, Canada and Western Europe that are linked to the *GeoSentinel Surveillance Network*, which has operated under the auspices of the *International Society of Travel Medicine* (ISTM) since 1995. This surveillance network tracks patterns of disease among international travelers who cross international borders. It may be inferred from the studies carried out by this group^{18,19}, as well as information found in other publications from Australia²⁰ or Europe²¹, that the main reasons for visiting a doctor after returning from travel involve, in descending order, gastrointestinal complaints (mainly acute or persistent diarrhea), fever, skin lesions, and respiratory infections.

Acute diarrheas are some of the most frequent complications in travelers, although most cases resolve during the trip or shortly afterwards. They are found in 5-10% of cases, and represent 22–30% of the reasons why a traveler seeks medical advice after returning home¹⁹⁻²¹. *Persistent diarrheas* are present in 1–3% of travelers and represent 8-11% of the reasons for consultation after returning¹⁹⁻²¹. Long-term expatriates in developing countries, including those who live in large cities, are at greater risk of diarrhea, particularly if they visit restaurants frequently²².

Febrile syndromes occur in 3% of travelers and represent 14–18% of the reasons for visiting a doctor post-travel¹⁹⁻²¹. Unlike the other patterns of illness, fever is associated with a very high rate of hospital admissions, both when the origin is unknown (the most common) and also when it accompanies diarrhea or respiratory symptoms^{14,20,24,25}. The frequency and cause of febrile syndromes in travelers are associated with the travel destination, and are more common after travel to sub-Saharan Africa, the islands of the Indian Ocean and Oceania than to other destinations⁹.

Cutaneous syndromes appear in 8% of travelers and represent 17% of the reasons for consulting a doctor after returning home¹⁹⁻²¹. In overall terms, skin disorders are the third most frequent

cause of illness among travelers, but the chief reason why travelers consult medical practitioners for some destinations, such as the Caribbean, or Central and South America⁹. In travelers, skin complaints are not a common reason for admission to hospital, but are frequently the reason for seeking advice as outpatients²⁶.

Respiratory problems occur in 26% of travelers and represent 8% of the reasons for seeking medical advice when they return home¹⁹⁻²¹. One in ten European travelers falls ill during or after a trip due to a respiratory infection, and they are the most frequently reported syndrome in those returning from Eastern Europe and Asia¹⁸. In some series, upper respiratory tract infections were the second most frequent cause of illness, after acute diarrhea¹⁰.

Evaluation of the traveler with serious infectious disease

KF10. The initial evaluation of the international traveler with severity criteria should be carried out at three levels: assessment of vital functions, syndromic evaluation and diagnostic strategy (B-III).

KF11. The immediate evaluation of hemodynamic stability should necessarily include blood pressure, respiratory rate, oxygen saturation, diuresis, heart rate and level of consciousness. Other variables to be taken into account are body temperature, the presence of edema, capillary refill and the presence of ileus (A-III).

KF12. The syndromic picture should be clearly established, since this will make it possible to select the most appropriate diagnostic tests and prognostic scales (B-III).

KF13. The analytical determinations that should be ordered for the seriously ill patient include blood count, biochemical tests including serum transaminase, bilirubin and blood coagulation, renal function, glycemia, arterial blood gas, and an analysis of urine. When possible, C-reactive protein and procalcitonin levels should also be requested (A-III).

KF14. The diagnostic strategy requires tests that are able to rule out malaria and dengue fever, and at least two sets of blood cultures, plus serological tests to detect rickettsial diseases, Q fever, HIV, HBV or HCV infection. (A-III).

KF15. It is recommended that a specialist in tropical medicine or infectious diseases assess the patient as quickly as possible. (C-III).

RATIONALE

The initial evaluation of patients returning from international travel with severity criteria is similar and does not depend on the underlying process, since the clinical manifestations reflect failure of the respiratory, cardiovascular and neurological systems. Care of the seriously ill patient should begin with

an assessment of the need for and the application of **resuscitation procedures**²⁷.

Secondly, the patient should be evaluated for the presence of **sepsis and septic shock** using established criteria^{28,29} and assigned a score using a **severity of disease classification system**. In this respect, the SAPS-II and WHO scoring systems are good predictors of mortality in malaria patients³⁰, while the APACHE IV scale is used worldwide for risk-adjusted mortality rates and ICU length of stay and performance associated with travel-related illnesses (pilgrims attending Hajj)³¹.

There are few specific studies about the **serious causes of imported diseases** in travelers^{32,33}. Most of the cases in these studies involved febrile syndromes and, to a lesser extent, respiratory problems. The most common febrile diagnosis was *P. falciparum* malaria, followed by typhoid fever and leptospirosis. Rickettsial infections and dengue were also diagnosed, but less often. Not infrequently, patients with malaria also have other infections (“complicated malaria”), such as pneumonia, cholecystitis or bacteremia³⁴. The main serious respiratory conditions are associated with respiratory distress in malaria, pneumonia or infection with coronaviruses. It is not common for traveler’s diarrhea to give rise to a serious condition, although the symptom may manifest clinically in the context of other illnesses. Potentially severe skin diseases manifest as petechial lesions or purpura (generally accompanied by fever, as in viral hemorrhagic fevers or meningitis), or blistering diseases (Stevens-Johnson syndrome)³⁵.

The imported pathology depends on the region or country visited, the date of travel, whether appropriate anti-malaria chemoprophylaxis and vaccination was given prior to departure, the type of travel and behavior during it (aquatic activities, consumption of contaminated food, etc.), as has been mentioned previously. Complementary tests requested should be useful both for diagnosing cause of infection (see following sections) and also for evaluating the severity of the disease. Table 2 shows the major measures used to assess severity, and hence the prognosis for infections imported by travelers^{28,29,34,36-41}.

Evaluation and isolation precautions for travelers with potentially transmissible infectious diseases

KF16. In the returned traveler, the clinician should initially evaluate not only the individual disease, but also the possibility that it may involve a current public health alert (A-III).

KF17. The recommended methods (in Spain) are by phoning the *Departamento de Alertas de Salud Publica* (Department of Public Health Alerts) of the appropriate Autonomous Community, or by consulting the web page of the *Ministerio de Sanidad, Servicios Sociales e Igualdad* (Ministry of Health) (A-III).

KF18. Different isolation precautions will be applied depending on the clinical syndrome and the traveler’s

travel itinerary (B-III).

KF19. High-level isolation units (HLIU) for patient management are indicated for confirmed and suspected cases of specific viral hemorrhagic fevers, highly pathogenic emerging respiratory diseases, multidrug-resistant tuberculosis (MDR-TB) and outbreaks of potentially serious transmissible diseases (PSTD) caused by unknown agents (A-III).

KF20. A basic pillar of control of PSTDs involves the selection, education and training of staff. This should be regarded as one more isolation precaution (B-III).

KF21. Restricting the use of invasive tests is also an isolation precaution. The selection of tests and the staff involved should be agreed by protocols adapted to the center where the patient is being treated (B-III).

KF22. All travelers transferred from foreign hospitals should be regarded as potential carriers of multidrug-resistant organisms and should be proactively screened (by rectal smear) (A-III).

RATIONALE

Infections acquired during international travel constitute a personal risk, which is the view taken in the remaining sections of this document. These infections however can also pose a risk to the healthcare personnel looking after them and/or spread to the general population. Thus, with respect to the **risk to healthcare personnel**, the percentage of *healthcare workers* who fell ill with potentially transmissible serious diseases ranged from 1-27% in the case of the MERS-CoV, 2.5-12% for Ebola, and 11-57% in the case of SARS⁴². In the case of Ebola, 81% of 27 patients treated in Europe were healthcare workers, and 100% of the three infected outside the endemic area⁴³. In overall terms, the main group affected was the nursing staff, both in endemic areas and in other countries. Furthermore, healthcare professionals may also constitute a **risk for the introduction or reintroduction** of these diseases into the general population^{44,45}.

In view of this, clinical workers require up-to-date **information** about PSTDs. This need becomes especially obvious during an international health alert. A study conducted in Spain during the Ebola alert in 2014 showed that 58% of enquiries made to the Department of Public Health Alerts in the Community of Madrid were made by healthcare workers⁴⁶. Another similar study carried out in the United States indicated that 78% of enquiries made to the Centers for Disease Control and Prevention (CDC) were made by healthcare staff⁴⁷. To find out whether there is a possible public health alert, enquiries may be made directly to staff in Public Health Departments, or indirectly, by consulting web pages that are kept up-to-date with the most reliable information, such as the Ministry of Health, Social Service and Equality (accessible at <http://www.msssi.gob.es/profesionales/saludPublica/ccayes/alertasActual/alertActu.htm>), the health

alert network of the CDC in the USA (Health Alert Network—HAN; accessible at <http://emergency.cdc.gov/han/>) or the weekly epidemiological record (WER) of the World Health Organization (accessible at <http://www.who.int/wer/en/>). Other real-time information systems such as Promed (<http://www.promedmail.org/>) are useful, but less reliable in terms of their information.

There are several aspects that are fundamental to managing patients with potentially transmissible imported infections. Firstly, **standard precautions** should apply to all patients; secondly, **isolation precautions** should be implemented in accordance with the clinical syndrome presented by the infected individual⁴⁸ (Table 3).

An aspect of particular interest is the use of **high-level isolation units (HLIU)**. A selection of *diseases* that should be treated in such units is shown in Table 4⁴⁹. *Selection of the healthcare staff* who will care for the patients is an important aspect of HLIU use. In Europe, in fact, some studies have shown that less than 50% of healthcare workers potentially involved in providing care for PSTDs perceive that they have been properly trained for the task; for personnel in specific units, this situation is the reverse⁵⁰. The selection of healthcare staff should be based on the following principles⁵¹⁻⁵³: *i*) Limit the number of staff involved, in order to reduce the number of contacts with the patient, although there must be enough to cover needs and avoid excessive caseloads; *ii*) Evaluation of physical capacity. Given the complexity of setting up and dismantling certain items of personal protective equipment (PPE), staff should be physically capable of carrying out these operations on their own, even when the established protocol indicates that it should be carried out with help. The durability of the PPE for the length of time established by protocol should also be assessed, and *iii*) Evaluation of psychological capacity. It should be borne in mind that caring for patients with PSTDs is stressful and that media attention given to these patients is similarly intense. Both factors may be compromised in staff unsuited to isolation measures, whether individuals or groups. On the other hand, invasive measures (such as dialysis, fibrobronchoscopy and surgery) are contemplated for some PSTDs, such as Ebola and MERS-CoV⁵⁴⁻⁵⁶. For all these scenarios, it is recommended that the team responsible for these tasks be voluntary, well trained and experienced, given the risk of contagion. Another important point is **the introduction of infections** whose aggressive nature or resistance profile make therapeutic management difficult⁵⁷⁻⁶¹. The recommendations of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) indicate that cultures and/or molecular methods be used in order to proactively rule out the presence of infection or colonization with multidrug-resistant organisms (MDROs)⁶².

Main infectious syndromes in the returned traveler

Diarrhea (acute or persistent)

KEY FACTS

Causative agents

KF23. Most cases of acute traveler's diarrhea are caused by bacterial pathogens. Enterotoxigenic *Escherichia coli* (ETEC) is the most frequently identified causative agent worldwide (A-III).

KF24. In a significant percentage (30-50%) of cases of acute traveler's diarrhea, an etiological diagnosis cannot be made (A-III).

KF25. There are notable geographical variations with respect to the etiology of acute traveler's diarrhea, independent of the length of the trip (A-III).

KF26. In acute traveler's diarrhea, microbiological studies should be restricted to patients who present with fever, dysentery, choleric form diarrhea, or who are dehydrated, immunosuppressed or have significant comorbidities (A-III).

Diagnostic methods

KF27. The diagnostic method of choice for acute traveler's diarrhea is the classic stool culture or cultures on selective media (depending on clinical suspicion) together with serial blood cultures if there is fever, although the diagnostic yield is low (A-III).

KF28. In any traveler with fever and acute diarrhea arriving from an endemic area, malaria should be ruled out with the appropriate methods (B-III).

KF29. Before traveling, the patient should be given information about the main self-treatment measures to be taken in case of diarrhea, and told to seek medical care in the presence of high fever, severe abdominal pain, bloody diarrhea, uncontrolled vomiting, or if self-treatment is ineffective (A-III).

KF30. For previously healthy adults, rehydration with conventional liquids, especially associated with loperamide, should be enough in cases of mild diarrhea (A-I).

KF31. Rehydration and restoration of electrolyte balance with antidiarrheal drugs and non-absorbable antibiotics (rifaximin) is indicated for moderate diarrhea, and for the old or immunocompromised with no previous history of invasive disease (A-III).

Therapeutic measures

KF32. In the presence of severe diarrhea with obvious signs of dehydration, it is recommended to restore fluids and electrolytes intravenously (A-III).

KF33. The use of antidiarrheal agents is contraindicated in the presence of invasive disease (A-III).

KF34. The most useful drugs for the treatment of invasive diarrhea are fluoroquinolones or azithromycin, chiefly in single doses (A-I).

KF35. The pathogenesis of persistent traveler's diarrhea can fall into one of three major groups: persistent infection or co-infection; post-infectious syndromes (transient lactose intolerance, post-infectious irritable bowel syndrome, small intestinal bacterial overgrowth (SIBO) and tropical sprue); or an underlying gastrointestinal disease unmasked during or after the trip (A-III).

KF36. The most common infections in persistent traveler's diarrhea are due to protozoan pathogens, for which the diagnostic method of choice is the standard Comprehensive Parasitology profile, using specific stains based on clinical suspicion, and antigen detection methods and PCR, as available, for increased sensitivity (A-III).

KF37. Diagnosis of post-infectious irritable bowel syndrome is exclusively clinical (Rome criteria III-IV) and it is especially important to determine the state of digestive health before travel and to consider at an early stage whether there are clinical and analytical signs of alarm/organicity (A-III).

KF38. The incidence of tropical sprue may be underestimated. Its main differential diagnosis is with celiac disease. Upper endoscopy (EGD) to examine the jejunum and biopsy are often required to differentiate them (A-III).

KF39. Some authors recommend empirical therapy with nitroimidazoles if *Giardia intestinalis* is highly suspected, even if specific studies are negative (C-III).

RATIONALE

Traveler's diarrhea occurs in the context of travel. It is characterized as three or more bowel movements that are looser than usual within a 24-hour period, or any number of bowel movements if accompanied by at least one of the following: nausea, vomiting, abdominal pain or fever. Conventionally, it is called *acute diarrhea* when it lasts for less than 15 days, and *persistent diarrhea*, if it lasts for longer. Clinical data are used to assess the severity of diarrhea. Hence, *mild diarrhea* is defined as fewer than three bowel movements per day with no fever or blood in the feces; *moderate diarrhea* is defined as three or more bowel movements and the absence of fever or blood in the feces; *severe diarrhea* is defined as the presence of significant dehydration and signs suggestive of tissue invasion (such as fever or blood in the stools).

Acute traveler's diarrhea

Causative agents

Acute traveler's diarrhea is triggered by the ingestion of food or water contaminated by pathogenic microorganisms. It is a common occurrence among travelers and there is an estimated 10-60% risk of experiencing a diarrhea episode during a two-week stay, depending on the destination and the characteristics of the traveler^{63,64}. Although most diarrhea episodes are acute and self-limited, a

proportion of affected sufferers may develop persistent gastrointestinal symptoms. According to a recent review, the most frequently identified etiological agents are, in decreasing order: ETEC (enterotoxigenic *E. coli*), EAEC (enteroaggregative *E. coli*), enteroadherent *E. coli*, norovirus, rotavirus, *Salmonella* spp., *Campylobacter jejuni*, *Shigella* spp., *Aeromonas* spp., *Plesiomonas shigelloides*, enterotoxigenic *Bacteroides fragilis*, and *Vibrio* spp⁶⁴.

In various series, the causative agent was not identified with standard methods in 38% to 50% of cases⁶³⁻⁶⁵. The general effectiveness of empiric antibiotic therapy in shortening the duration of this illness in these patients seems to suggest that the predominant etiology of diarrhea is bacterial in cases where stool cultures are negative⁶⁴. In clinical practice, the high proportion of diarrhea with negative stool cultures is due to enterobacteria that cannot be identified by conventional methods⁶⁶, and less commonly, to viruses⁶⁷, *Clostridium difficile*, and/or parasites, although the latter are more frequently implicated in persistent traveler's diarrhea^{68,69}.

There is geographic variation with respect to the causative agents^{22,65,70}. In a systematic review of the literature (1973–2008), the main enteropathogens identified in travelers with diarrhea after a stay of less than 40 days in Latin America and Africa were: ETEC (33%), norovirus (15%), EAEC (13%), *Shigella* spp. (8%), *Campylobacter* spp. (4%), *Salmonella* spp. (4%) and parasites (*Giardia* spp., *Cryptosporidium* spp., *E. histolytica*, 4%). In travelers to southern Asia, the main pathogens identified were *Campylobacter* spp. (20%), ETEC (19%), EAEC (16%), *Vibrio* spp. (10%), parasites (*Giardia* spp., *Cryptosporidium* spp., *E. histolytica* 10%), *Salmonella* spp. (8%), *Shigella* spp. (5%), *Plesiomonas* spp. (5%), norovirus (4%) and *Aeromonas* spp. (3%).

A systematic review of long-stay travelers (such as expatriates and military service personnel) in 2006 also found regional differences in the etiology of diarrhea. Thus, in Southeast Asia, the prevalence of ETEC was relatively low, but higher for *Campylobacter* spp. and *Salmonella* spp. compared to other regions. On the other hand, the pathogen most frequently identified in Latin America, the Caribbean, the Middle East and sub-Saharan Africa was ETEC.

It is important to remember that some systemic infections in travelers, such as malaria, dengue and other arboviruses, as well as enteric fever (typhoid and paratyphoid fevers) may initially present with diarrhea, so that these should be adequately ruled out in anyone presenting with acute traveler's diarrhea and fever (see **section IV.2**).

Diagnostic methods

Diagnostic tests for traveler's diarrhea are normally reserved for patients who present with fever (temperature of 38 °C or more), blood in the feces (dysentery), choleric diarrhea, or accompanied by some degree of dehydration⁶⁴, as well as those that occur in immunosuppressed patients or those with

major comorbidities⁷¹.

The microbiological diagnostic method of choice is the stool culture^{72,73}, which yields the most favorable results when the stools are liquid or unformed, complemented with a blood culture if there is fever. The conventional stool culture offers a good yield for *Salmonella* spp. and *Shigella* spp., while other pathogens require selective media (*Campylobacter* spp., *Yersinia* spp., *Vibrio* spp.). It is therefore essential to notify the microbiologist if there is clinical suspicion. Identification of the various pathotypes of *E.coli* involved in acute traveler's diarrhea (enterotoxigenic *E. coli* (ECET), enteroaggregative *E. coli* (EAEC))^{66,74-76}, and of viruses (especially norovirus) and food-borne diseases (*Bacillus cereus*, *Staphylococcus aureus*) is not routinely available and should be diagnosed in a reference laboratory^{67,77}.

The usefulness of new molecular techniques for the simultaneous detection and analysis of multiple pathogens (*PCR-based multiplex assay* with capability for identifying between 7 and 23 microorganisms in a single assay)^{78,79} has not been well evaluated for acute diarrhea⁸⁰. These methods are an attractive option in terms of increasing the sensitivity of conventional methods, but present some disadvantages in their interpretation^{64,67,81}.

Finally, in selected cases, other analytical tests may be useful, such as fecal markers for detecting intestinal inflammation (methylene blue dye for fecal leukocytes, lactoferrin released from leukocytes, fecal occult blood test (FOBT) and/or fecal calprotectin) or systemic inflammation (differential white blood cell counts, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)) for invasive ventricular assist devices (VAD), as well as basic biochemistry to monitor dehydration, renal function and fluid-electrolyte imbalance⁸².

Therapeutic measures

Acute traveler's diarrhea is a health problem that impairs the quality of life not only of the traveler but of those accompanying them, and causes disruption to travel plans and activities. Its management is peculiar in the sense that it appears principally in the context of countries whose medical or sanitary resources (drugs or sterilization measures) are minimal or difficult to find^{83,84}. Complying with standard water and food hygiene rules and advice, as well as chemoprophylaxis in specific cases, may help prevent acute traveler's diarrhea^{83,84}. Before the traveler sets off, it is also necessary to indicate the main means of self-treatment for diarrhea during the trip. The traveler should also be advised that if there is high fever, intense abdominal pain, blood in the diarrhea, uncontrolled vomiting, or if self-medication does not prove effective, he/she should seek medical assistance. If it persists once he has reached his destination, the therapeutic measures will be based on the tests previously indicated.

Self-treatment for acute traveler's diarrhea has three basic components: rehydration, symptomatic treatment, and antibiotics. The use of each of these measures depends on the severity of

the diarrhea and the patient's characteristics.

Rehydration is the basic component of therapy in acute traveler's diarrhea. In mild cases and less vulnerable patients (healthy adults), liquids containing salt and sugar will help maintain hydration. More specifically, if loperamide is added, there is no difference between oral rehydration solutions and conventional liquids⁸⁵. For moderate cases and people at greater risk (children, old people, people with chronic illnesses), oral rehydration therapy (ORT) using a commercial or "homemade" preparation is indicated.

Of the commercially sold preparations, the hypotonic formula (with less sodium and glucose content) causes less vomiting, fewer bowel movements and is more effective than the standard formulation. Another option consists of preparing a litre of water and adding lemon juice, salt (half a coffee spoon), bicarbonate (half a coffee spoon) and sugar (6 coffee spoons). Isotonic drinks aimed at sportsmen are not recommended because they do not contain sufficient concentrations of electrolytes. In severe cases, intravenous rehydration should be used to replace fluids and electrolytes. With respect to the diet, after oral hydration has started, it is not advisable to go more than four hours without food; mucosal recovery is enhanced by small but frequent intakes of foods that are rich in energy and micronutrients throughout the day (rice, pasta, meat, fruit and vegetables)⁸⁶.

Use of **anti-diarrheal medication** should be restricted to non-invasive diarrhea (that is, without fever or blood in stool). The two most commonly used agents are loperamide and racecadotril. *Loperamide* inhibits motility and intestinal secretions. It should be administered for mild diarrhea, and in combination with a non-absorbable antibiotic when the diarrhea is more severe⁸⁷. It should be taken only until the symptoms improve if there is no improvement within 48 h, or for a maximum of 5 days.

Loperamide alone does not increase the risk of acquiring extended-spectrum beta-lactamase bacteria⁸⁸. *Racecadotril* inhibits intestinal enkephalinase and reduces intestinal secretions without altering motility. Its efficacy in traveler's diarrhea has not been systematically evaluated.

The use of **antimicrobials** in therapy should be considered very carefully, weighing up the advantages and disadvantages. Among the advantages: they shorten the duration of diarrhea (from several to 1-2 days) and prevent complications (such as reactive arthritis, Guillain-Barré syndrome and post-infectious irritable bowel syndrome). The main disadvantages: their cost, side-effects (alterations in the QT interval by macrolides, musculoskeletal complications with quinolones) and the risk of colonization with multidrug-resistant enterobacteria^{88,89}. The drugs used fall into two groups: non-absorbable (rifaximin) and absorbable (quinolones and macrolides). *Rifaximin* is a non-absorbable antibiotic with activity against non-enteroinvasive strains of *E. coli*, has a good safety profile and can be given to children over 12 years old. The symptoms improve more rapidly when combined with loperamide, than when

the two drugs are administered separately⁹⁰. Clinical trials have demonstrated the utility of a new formulation of rifamycin with colon-targeted delivery⁹¹, although to date there are no data on its efficacy. The generally recommended antibiotic treatment is *fluoroquinolones*, for two or three days, although a single dose of ciprofloxacin may be enough⁹². Fluoroquinolones are active against the principal enteropathogenic bacteria, although in Southeast Asia, increased resistance has been reported, basically in *Shigella* spp.⁹³, *Campylobacter* spp.⁹⁴ and ETEC⁹⁵. Fluoroquinolones are contraindicated for pregnant women and children; they also predispose to *Clostridium difficile* overgrowth, causing persistent diarrhea⁹⁶. A single 1,000 mg dose of *azithromycin* is more effective than the three-day regimen, and also more effective than a three-day regimen of levofloxacin. The only drawback is that there may be nausea in the first 30 minutes⁹⁷.

Other measures potentially useful for self-medication are *antiemetics* (metoclopramide, domperidone and ondansetron). Interactions between metoclopramide and atovaquone/proguanil for malaria chemoprophylaxis should be noted here. The use of probiotics (such as *Lactobacillus acidophilus* or *Saccharomyces boulardii*) has been associated with the reduced frequency and duration of diarrhea, although the studies are heterogeneous, which is why they cannot be recommended⁹⁸.

Persistent diarrhea in the traveler

Causative agents

Although persistent traveler's diarrhea is less common, it poses a greater challenge for diagnosis. It may appear during or after a trip, be continuous or recurring, and it may or may not be accompanied by other digestive symptoms (abdominal pain, bloating, weight loss, malabsorption) or systemic ones (asthenia, low-grade fever). From a practical point of view, there are three possible causes: infectious causes, the so-called "post-infectious syndrome", and the existence of a previous or concomitant chronic gastrointestinal disease not diagnosed before travel or that starts during it^{64,99}. It is estimated that infectious causes of persistent diarrhea involve less than 40% of final diagnoses in such cases¹⁰⁰.

The most common **infectious causes** of persistent traveler's diarrhea are parasites (specifically protozoans)¹⁰¹, and diarrhea associated with *Clostridium difficile*^{64,96}. They are occasionally caused by enterobacteria (when there was no empiric therapy or initial stool culture) or by bacteria with more prolonged incubation periods or potentially resistant to the antimicrobials commonly used for acute diarrhea. Three of the most commonly recognized protozoan parasites are: *Giardia intestinalis*, *Entamoeba histolytica* and *Cryptosporidium hominis*, followed by three less common ones: *Dientamoeba fragilis*, *Cyclospora cayatanensis* (the risk of *Cyclospora* is greatest in countries such as Nepal, Peru, Haiti, and Guatemala), *Cystoisospora (Isospora) belli*, *Sarcocystis* spp., *Balantidium coli* (a cause of dysentery) and different species of microsporidia (*Enterocytozoon bieneusi* and *Encephalitozoon*

intestinalis). *C. belli* and microsporidia play a major role in chronic diarrhea in HIV-infected patients. The so-called “**post-infectious syndromes**” comprise a heterogeneous group of functional alterations to intestinal motility or persistent or fluctuating intestinal secretions triggered by a previous intestinal infection while traveling. They include four main entities: transient lactose intolerance, post-infectious irritable bowel syndrome, small intestinal bacterial overgrowth (SIBO) and tropical sprue. Often, there are several possible diagnoses for this group of conditions, in addition to other chronic intestinal diseases, such as celiac disease in young patients¹⁰², and microscopic colitis in older adults¹⁰³.

The most common is *transient lactose intolerance*, especially in children. There is not typically a good clinical correlation between the intensity of the symptoms (abdominal pain, watery diarrhea, nausea, abdominal bloating and/or flatulence) and the underlying degree of malabsorption¹⁰⁴. The key symptom (and *sine qua non* for diagnosis) of *post-infectious irritable bowel syndrome* (PI-IBS) is pain or persistent or recurrent abdominal discomfort, together with changes in bowel habits (predominantly diarrhea). This syndrome is not specific to any one microorganism in particular, but has been described following bacterial infections (due to *Shigella* spp., *Campylobacter* spp., *Salmonella* spp., and recently, following infection with ETEC producing heat-labile toxins), as well as viral and protozoan infections (such as *Entamoeba histolytica*, *Giardia* spp., *Cryptosporidium* spp., *Dientamoeba fragilis*). Little is known of its pathogenesis, which is probably multifactorial^{105,106}. No one is really certain of the true incidence of PI-IBS among travelers. In a cohort of 2,476 Swiss travelers, 3% of those who suffered an episode of traveler’s diarrhea developed PI-IBS in the following 6 months¹⁰⁷. Given that diagnosis of PI-IBS is fundamentally clinical and symptom-based, and that an episode of traveler’s diarrhea can exacerbate further a pre-existing irritable bowel syndrome in the traveler, it is critical to obtain details of the gastrointestinal status of the patient before travel^{108,109}.

Small intestine bacterial overgrowth causes fat malabsorption. This complication occurs as a result of the deconjugation of bile salts by intraluminal bacteria leading to impaired fat digestion, and can look like *Giardia intestinalis* infection. It is frequently associated with anatomical or functional alterations of the small intestine (such as celiac disease, Crohn’s disease, jejunal diverticulosis or post-operative blind loop syndrome).

Tropical sprue is an entity without a definite etiology that occurs in certain tropical and sub-tropical geographic areas. Its guiding symptom is nutrient malabsorption. Its clinical spectrum may simulate anything from PI-IBS to celiac disease and little is known of its pathogenesis¹¹⁰. This entity was essentially described between the 1950s and 1970s¹¹¹, and its incidence may be underestimated, in view of the growing number of sporadic cases reported in recent years^{112,113}. It largely affects long-term residents and expatriates in tropical areas within 30 degrees north and south of the equator, and is particularly prevalent in southern India, Indonesia, Philippines and Papua New Guinea, although it has

also been described in the northern part of South America, the Caribbean and West Africa¹¹⁴.

Diagnostic methods

The diagnostic method of choice for *intestinal parasites* is an examination of the stools, with at least three samples being recommended¹¹⁵, preferably on alternate days¹¹⁶ or collected over a period of 7-10 days given the intermittent fecal excretion of diagnostic forms⁷⁷. Ideally this examination should include, at the very least, a direct smear examination of fresh stool samples or stained with Lugol's iodine solution; an examination of concentrated feces and a preparation of the sediment with trichrome staining or another permanent stain¹¹⁶. Some protozoa require special techniques or stains (modified acid-fast stains, such as Safranin or Kinyoun; fluorescent microscopy for *Cryptosporidium* spp. and *Cyclospora* spp.; fluorescent modified trichrome stain for microsporidial spores)¹¹⁷, which means that the laboratory should be notified if they are suspected. Techniques for the detection of antigens in stool specimens (by enzyme immunoassay (EIA) or direct fluorescent-antibody (DFA) for *Giardia intestinalis*, *Cryptosporidium* spp. and *Entamoeba histolytica*) or for the detection and identification of virus genome in stools by PCR (*Entamoeba* spp. and *Dientamoeba fragilis*) give increased sensitivity compared to conventional methods and enable *Entamoeba histolytica* to be differentiated from *E. dispar*, for example, which are otherwise pathogenically and morphologically indistinguishable. *Blastocystis hominis* cysts are frequently identified in chronic diarrhea and remain a controversial topic^{118,119}; they should be interpreted as non-pathogenic commensals without therapeutic indications, although they serve as markers to confirm oral-fecal contamination or the presence of other unidentified underlying parasites. Nonetheless, given the presence of symptoms and having reasonably ruled out other causative agents, a therapeutic trial may be attempted. The diagnostic methods for helminthiasis associated with persistent diarrhea are indicated in **section IV.5**. Diarrhea associated with *Clostridium difficile* should be suspected in travelers who have received recent antimicrobial treatment (mainly fluoroquinolones)⁹⁶. Even so, the true incidence in those travelers in whom community-acquired *C. difficile* infection is more likely (with no prior history of antimicrobials or contact with the healthcare system), and who may therefore help spread hypervirulent strains, is unknown¹²⁰. The use of ELISA for detection of toxins in fecal specimens has low sensitivity 65-85% despite its speed and high specificity (95-100%), so that detection of antigens in stool specimens (glutamate dehydrogenase, just as quick but higher sensitivity) tends to be used as a screening test, with subsequent confirmation by culture or PCR. Since, detection of *C. difficile* in a clinical sample does not always equate with disease, diagnosis continues to be challenging for the clinician and in the laboratory¹²¹. Finally, some recent studies have suggested that *Tropheryma whipplei* (the causative organism of Whipple's disease) is involved in traveler's diarrhea^{122,123}, although larger, more appropriately designed studies are required.

The usual diagnostic method for *transient lactose intolerance* is to evaluate the clinical response to a strict lactose-free diet for a minimum of 3-5 days or 2 weeks^{124,125}. When the results are unclear or primary intolerance (hypolactasia) is suspected, functional tests should be used. The standard lactose tolerance test tends to be replaced by the hydrogen (H₂) breath test (HBT) with lactose (specificity>80% and sensitivity>70%) or the galactose test (sensitivity and specificity>90%, but less available)^{104,125}. A determination of lactase enzyme activity in small intestinal biopsy material is more efficient but invasive, complicated and rarely used in practice¹⁰⁴. A genetic diagnosis (detection of the C>T (13910) variant of the CC genotype and the G>A-22018 variant of the GG genotype in the lactase (LCT) promoter region) correlates well with primary hypolactasia and could provide a non-invasive diagnostic alternative for this entity¹²⁶.

A diagnosis of PI-IBS requires various data (Table 5): *i*) the patients should fulfill the clinical criteria based on symptoms and chronology (according to the recently modified Rome IV criteria, specificity was 90-100% for PI-IBS and sensitivity less than 70%)¹²⁷; *ii*) other organic or functional processes are excluded¹²⁸, and *iii*) it appears *de novo* in a previously asymptomatic patient after an episode of acute infectious diarrhea (diarrhea with fever or with a positive stool culture). The evaluation of PI-IBS is complex and generates uncertainty in the doctor as well as the patient. Some basic aspects are: *i*) Given the data shown in Table 5, the pre-test probability of an organic disease is less than 1% without requiring complementary explorations (such as ultrasound, gastrointestinal barium studies, colonoscopy and/or oral endoscopy with biopsy tissue sample)^{106,129}; *ii*) by carefully following these criteria, both doctor and patient can feel sure that it is not “organic disease” and avoid “factitious illness or Munchhausen syndrome or delusional intestinal parasitosis”^{124,130}; *iii*) patients should be informed of the favourable life prognosis, as well as the tendency for the symptoms to improve slowly but steadily^{106,131}, and *iv*) it is necessary to use the most objective techniques for a positive diagnosis of this syndrome. In this respect, there is a commercially available serological test (*IBScheck*, Commonwealth Laboratories) based on the detection of antibodies against CdtB (*cytolethal distending toxin B*), which is produced by gram-negative bacteria and has more than 90% specificity and sensitivity of close to 40% for the diagnosis of irritable bowel syndrome, although it has not been validated^{132,134}.

Small intestinal bacterial overgrowth can be diagnosed using a lactulose and D-glucose hydrogen breath test and carbon-14 D-xylose breath test¹⁰⁴. An alternative is therapeutic testing with antibiotics (for example, tetracyclines for 1-3 weeks) and in the last resort, a quantitative bacterial count in a culture of proximal jejunal aspirate (>10⁵ UFC/ μ L). A characteristic finding of bacterial overgrowth is low serum B12 levels and elevated levels of folic acid (due to consumption and production respectively by the bacterial overgrowth). The Schilling test (used to determine rate of vitamin B12 absorption) will show whether the body is absorbing vitamin B12 normally after a course of antibiotic therapy.

A diagnosis of *tropical sprue* requires the criteria indicated in Table 6¹³⁴⁻¹³⁶, and a differential diagnosis with celiac disease (histology and tests for antibodies and HLA) is essential.

Finally, a thorough clinical history of pre-travel digestive symptoms may guide towards *gastrointestinal disease, previously undiagnosed and unmasked during travel*, mainly inflammatory bowel disease, celiac disease, primary hypolactasia, or microscopic colitis (collagenous and lymphocytic)¹³⁷⁻¹³⁹.

Therapeutic measures

In this context, treatment should be etiological (for infections) or pathogenic (for post-infectious syndromes). If there is high suspicion of a parasitic infection at any time regardless of a negative test result, some authors recommend a course of empiric treatment with nitroimidazoles (metronidazole or tinidazole) as *Giardia* spp. is the most frequent protozoan parasite causing persistent diarrhea in the traveler¹¹⁶.

Fever of unknown origin

Causative agents

KF40. The most common causes of fever of unknown origin in the returned traveler are, in order of frequency: malaria, arbovirus (e.g. dengue, Chikungunya, Zika) and bacterial infections (typhoid fever, rickettsial infections, Q fever and leptospirosis) (A-II).

KF41. Even though they are rare, serious diseases that are highly contagious, such as viral hemorrhagic fevers (e.g. Ebola, Lassa, Marburg, Rift Valley fever, Crimean-Congo hemorrhagic fever) should always be considered (C-III).

KF42. The origin of the traveler, period of incubation and specific risk exposures should provide guidance as to the etiology of the febrile process (A-II).

Diagnostic methods

KF43. Travelers who present with fever of unknown origin after visiting a tropical or sub-tropical area should seek immediate medical attention (A-II).

KF44. If there is any possibility of viral hemorrhagic fever (VHF), this should be investigated using the appropriate biosafety measures and techniques that require the least handling possible (rapid tests or PCR) (A-II).

KF45. A significant proportion of fever episodes post-travel either do not lead to a specific diagnosis (A-II) or are due to cosmopolitan infections (A-II).

KF46. If there is no risk of VHF, malaria should be ruled out in the first instance using microscopy techniques

and rapid diagnostic tests (A-II).

KF47. If the acute phase of an arbovirus is suspected (<10–15 days of clinical evolution), the patient should be tested for the presence of (NS1) antigens or viral RNA in the blood and urine (A-II).

KF48. If arbovirus in later stages is suspected (>15 days of clinical evolution), the serological response (principally IgM) should be studied and cases confirmed by neutralization tests (A-II).

KF49. The diagnosis of bacterial infection responsible for fever of unknown origin is based, in the acute phase, on isolating the bacterial organism or using molecular biology techniques, and in later phases, on serological studies of paired serum samples (A-II).

Therapeutic measures

KF50. Treatment (etiological or symptomatic) should be based on identifying the causative agent (A-II).

KF51. If there is a high probability of malaria and a diagnosis cannot be made, or will be delayed for more than 3 hours with no alternative diagnosis, administration of empiric anti-malarial therapy is recommended (A-II).

KF52. Patients with a likely diagnosis of severe acute schistosomiasis or neuroschistosomiasis are treated with corticosteroids in combination with praziquantel (B-II).

KF53. In complicated or severe cases of malaria, use of ceftriaxone plus doxycycline is recommended while waiting for confirmation of diagnosis (C-III).

RATIONALE

Fever of unknown origin refers to a high body temperature (>38 °C) with no suggestive details in the patient's medical and travel history or signs of localized involvement in the physical exploration. Lymphadenopathy, visceromegaly and widespread cutaneous lesions are not considered localizing data. In all situations related to imported syndromes, the cause may also be a cosmopolitan infection or not be an infectious problem at all.

Causative agents

In various case series involving travelers to tropical and sub-tropical countries, the incidence of fever of unknown origin was between 3% and 35%^{8,140-146}. Most febrile processes are non-specific and self-limiting. It is also reckoned that a specific diagnosis is not reached in more than a third of patients who present with fever after traveling¹⁴⁰.

The main causes in order of frequency are: *i*) malaria, if the traveler has visited malarial areas^{9,20,24,25,140,147}; *ii*) infections due to certain exotic viruses (particularly dengue, Chikungunya and Zika)^{140,148-150}, and *iii*) bacterial infections (such as typhoid fever, some rickettsial infections, Q fever

and leptospirosis^{19,25,151-153}. Other less common diagnoses are brucellosis^{19,154,155}, acute schistosomiasis (Katayama fever)²⁴, African trypanosomiasis¹⁵⁶, visceral leishmaniasis¹⁹, recurrent fever due to *Borrelia* spp.^{157,158} and primary HIV infection⁸. Finally, although they are rare, serious, highly contagious diseases, such as viral hemorrhagic fevers (for example, Ebola, Lassa, Marburg, Rift Valley fever, Crimean-Congo hemorrhagic fever) should always be considered.

A detailed medical and travel history should be taken of anyone seeking medical advice who presents with fever of unknown origin following travel, and an exhaustive physical exploration be carried out. For **initial orientation**, it is very important to know the geographic areas visited, the incubation periods of different diseases, and the specific risks associated with the traveler^{142,159,160}. With respect to *geographic area*, the fundamental cause of fever in travel to Africa, especially the sub-Saharan region, is malaria, specifically malaria caused by *P. falciparum*^{8,24,25}. In travelers from Asia and Latin America, however, dengue and malaria caused by infection with other species involve a significant number of cases^{9,25}. The *incubation periods* of different infectious diseases is also useful for diagnosis^{140,142-145,159-161}. The incubation period for malaria is at least 7 days, and the maximum period, depending on the species responsible, can be months or years. Tropical viruses (dengue, Chikungunya, Zika and agents responsible for VHF) have a maximum incubation period of 21 days (the “21-day rule”), except those produced by hantaviruses. Figure 1 shows the typical incubation periods for other infections associated with imported fever of unknown origin. It is also very important to discover *specific risks* associated with the individual traveler. Hence, mosquito bites are associated with malaria, the main imported viruses and, exceptionally, visceral leishmaniasis; other insect bites (bedbugs, fleas, ticks) are vectors for spreading diseases such as endemic African trypanosomiasis, rickettsial infections and borreliosis. Drinking unpasteurized milk may be the means of transmission of brucellosis and Q fever. Freshwater contact in endemic areas could be an epidemiological factor involved in leptospirosis or schistosomiasis. Finally, risky sexual contact should lead to considering the possibility of HIV infection.

Malaria as the cause of imported fever of unknown origin has several important characteristics. It is the major cause of this type of fever in travelers from sub-Saharan Africa (between 32% and 65%)¹⁴⁰. After Africa, the highest malarial burden falls on Southeast Asia (19%)¹⁹, and the Americas (15%)^{140,142,143}. The main causative agent in all series was *Plasmodium falciparum*, followed by *P. vivax*, *P. malariae* and *P. ovale*^{20,23,24,162,163}. Finally, all series have noted that travelers whose reason for traveling was *to visit friends and relatives* (VFR) were at most risk of acquiring malaria because their stays were longer, prophylaxis was inadequate and they took fewer precautionary measures to protect themselves^{23,162,163}.

In global terms, three **exotic viral diseases** caused by the dengue, Chikungunya and Zika viruses and spread primarily by *Aedes* mosquitoes are emerging causes of fever of unknown origin.

In recent decades, there has been a significant growth in **dengue** (flavivirus) as a cause of fever of unknown origin in travelers^{140,164-166}, and it is currently more common than malaria in travelers from Southeast Asia and the Americas^{23,165,166}. Nevertheless, the prevalence of serious forms is less than 1%¹⁶⁷. Even though **Chikungunya** virus infection (togavirus) has been known since the 1950s¹⁴⁹, it was not until 2004 that there were epidemic outbreaks. The East/Central/South African (ECSA) and Asian genotypes have given rise to outbreaks that initially centred on countries bordering the Indian Ocean (Kenya, Comoros Islands and Reunion Island), but subsequently spread southwards and to Southeast Asia, and from these regions to Europe, the Caribbean and South America^{148,149,165}. In Spain, most cases of Chikungunya virus infection have been imported from the Caribbean (Dominican Republic, Haiti, Venezuela and Colombia)¹⁶⁸⁻¹⁷⁰.

The **Zika** virus (flavivirus) has also been known since the 1950s¹⁵⁰, but it was only in 2007 that a major outbreak was reported in Yap State (one of the Federated States of Micronesia) and then, from 2013 to the present, in French Polynesia and other countries in Southeast Asia. Between March 2015 and the present day, this disease has spread massively from Brazil to practically the whole of Latin America, and from there, cases have been exported to Europe. Practically all the cases in Spain have been imported from the Caribbean and northern parts of South America¹⁷¹.

Typhoid fever is a bacterial infection caused by various *Salmonella enterica* serovar Typhi (serovars *Typhi*, *Paratyphi A*, *Paratyphi B* and *Paratyphi C*) and transmitted by eating and drinking contaminated food and water. The risk fluctuates from 1:30,000 travelers in endemic areas to 1:3,000 in highly endemic areas, such as the Indian subcontinent, where the risk is greatest³³. Most cases occur in travelers who have not been vaccinated²⁵.

It is increasingly common to diagnose various species of *Rickettsia* spp. and *Coxiella burnetti* is the cause of fever of unknown origin¹⁵¹. These diseases are linked to outdoor activities, contact with animals and arthropod bites. The main agents involved in travelers' infections are: *Rickettsia africae* (Africa)⁹, *R. conorii* (Mediterranean), *Orientia tsutsugamushi* (Asia)⁸, and *Rickettsia typhi*¹⁷².

Another cause of bacterial infection for fever of unknown origin in travelers is **leptospirosis**, caused by *L. interrogans*. It tends to appear in travelers who have been involved in water activities, such as rafting, or swimming, and has been notified most frequently in males from Southeast Asia, Africa and the Caribbean^{19,33}.

Diagnostic methods

In suspected cases of **viral hemorrhagic fever**, the appropriate biosecurity measures should be implemented. As a result of the recent Ebola virus epidemic (EBOV) in West Africa, diagnostic criteria and clear algorithms for diagnosing EBOV infections were established that can be extended to other VHF¹⁷³.

Diagnosis is basically by detection of the viral genome in blood or serum [detection of RNA by means of PCR preceded by one-step reverse transcription (RT-PCR)]. Samples should be manipulated and inactivated in class III biological safety cabinets, and diagnostic work carried out in biosafety level IV laboratories (although level III is also permitted). Some easy-to-implement immunochromatographic techniques providing rapid diagnosis have been reported, but confirmation would be required. Commercial kits have been developed for the Marburg and Congo-Crimean viruses and Rift Valley fever¹⁷⁴. Detection and identification of Lassa poses a problem because the virus presents a high degree of genetic variability and there is no simple method available for interpreting the results^{175,176}.

Malaria should be the first possible cause of fever with no obvious source in travelers returning from an endemic area. It is useful to remember the classic aphorism, “any patient returning from an endemic area must be assumed to have malaria until proven otherwise”. The techniques for diagnosing malaria have recently been revised and published in EIMC^{177,178}. In summary, the main techniques are *i*) thick blood smear (very sensitive) and thin blood smear (which makes it easier to identify the causative species of malaria) stained with a stain such as Giemsa. This technique requires skilled microscopists; *ii*) malaria rapid diagnostic tests (RDT) to detect specific antigens produced by malaria parasites, which provide a simple and rapid diagnosis. Nevertheless, they can give false-negative results and do not determine all *Plasmodium* species, quantify parasitemia or evaluate response to treatment; *iii*) PCR has very high sensitivity and can detect mixed infections, also when there is low-level parasitemia, and *iv*) serological techniques are not useful for diagnosing acute malaria.

In general, **arboviral diseases** can be detected using *i*) direct methods (RT-PCR or antigen detection (NS1 in the case of dengue fever), which are very virus specific, but only positive in the first days after onset of fever, or by means of *ii*) serological tests that are very sensitive but less specific (with serological cross-reactivity) and have the drawback that they turn positive some days after the onset of symptoms, so that they may be negative at the time of consultation. It is recommended therefore to take whole blood and/or serum samples during the first 7-10 days for the *direct techniques*^{179,180}. It is also worthwhile taking urine samples (for the Zika virus and some other flaviviruses, such as West Nile), since the virus is detectable for longer (a mean of 15 days after onset of symptoms)^{181,182}. Specific antibody detection, especially IgMs (by ELISA or IFA) has high specificity¹⁸³. Positive cases should be confirmed later by neutralizing antibody tests¹⁷⁹. Detection of the Zika virus is more problematic, because there are few commercially available tests and validation of them is incomplete¹⁸⁴.

Typhoid fever is diagnosed mainly by identifying the causative agents in blood culture, or possibly bone marrow or stool cultures¹⁸⁵. After isolation, subculture, biochemical testing and agglutination with specific antisera are typically necessary to identify serovars, or the MALDI-TOF method can be used. Serology (Widal test) is another useful test that measures agglutinating antibodies

in the serum against flagellar (H) and lipopolysaccharide (O) antigens of *Salmonella* Typhi, although it has low specificity. Apart from these two classic approaches, ELISA techniques, rapid tests and PCR are being developed, although none of them have higher specificity or sensitivity than the two described.

In the case of **rickettsial infection** and **Q fever**, serological methods based on IFA (or ELISA) are the most widely used and recommended, although it should be borne in mind that it may not be possible to detect antibody response in the acute phase, which is why it is better to collect two samples 2-4 weeks apart and confirm diagnosis with a fourfold or greater increase in antibody titer between the two¹⁸⁶. Combination with PCR techniques in the acute phase can help provide a more accurate diagnosis¹⁸⁷.

Useful laboratory tests for diagnosing **leptospirosis** vary depending on the phase of the illness¹⁸⁸⁻¹⁹⁰. In the acute phase, direct tests are useful (for detecting leptospire or leptospiral antigen and/or nucleic acids in the blood and/or urine). Leptospire are visible by darkfield and phase-contrast microscopy, although these techniques are not useful for diagnosis because they have low sensitivity and specificity. Serological tests and PCR in that order offer higher sensitivity. A negative serological result in the acute phase does not rule out the disease, so that paired serum samples are required, the first taken during the first 7 days of infection and the second 10-15 days later. With respect to serological testing, the *Microscopic Agglutination Test* (MAT) is the most common way to diagnose leptospirosis. It requires the maintenance of a range of serotype cultures and continues to be used for confirmatory testing. There are also commercial ELISA kits that can differentiate between IgG and IgM and pose no healthcare risk to operatives since they do not require handling of live microorganisms. Rapid immunochromatographic tests are increasingly being used that allow rapid diagnosis with good sensitivity and specificity.

For **other entities**, the diagnostic methods are the same as those used in autochthonous cases.

Therapeutic measures

Fever is a non-specific symptom and one of the earliest manifestations of a minor illness, as well as a potentially fatal one, so that any returned traveler with fever should never be disregarded or dismissed out of hand, even if there are few symptoms. When a patient presents with fever of unknown origin, the main objective is to recognize or rule out diseases with high morbimortality rates (for example, malaria, typhoid fever) or those that represent a threat to public health (viral hemorrhagic fever, tuberculosis, etc.) and to apply therapeutic measures or isolation precautions that are appropriate to each case rather than reach diagnostic certainty in every case^{19,23}.

The application of specific isolation precautions and management of severely ill patients

has been indicated previously (see section III.3).

The treatment of **malaria** was recently revised and published in *EIMC*¹⁷⁷. It is important to remember that the treatment of choice for severe malaria (except in the first trimester of pregnancy) is a dose of 2.4 mg/kg intravenous artesunate (3 mg/kg in children <20 kg) at 0, 12, 24, 48, and 72 hours. Any schedule of intravenous artesunate (minimum schedule 3 doses) must be followed by 3 days of oral artemisinin-based combination therapy (dihydroartemisinin-piperaquine or artemether-lumefantrine). In cases where the patient is severely ill and there is a high probability of malaria (i.e. splenomegaly or platelet count <150,000/mL or hemoglobin <12 g/dL) and a diagnosis cannot be made or would be delayed for more than 3 hours, it is recommended, in the absence of any other diagnosis, to give the patient empiric treatment for malaria. In general terms, the principles of malaria treatment are as follows^{177,192-194}: *i)* severe malaria should be distinguished from malaria without severity criteria; *ii)* it is important to identify the causative parasite and when this is not possible, it should be considered as *P. falciparum*; *iii)* it is essential to discover in which geographic area the infection was acquired, since this is key to determining possible resistance to particular antimalarial drugs; *iv)* quantification of parasitemia is essential; *v)* except in the first trimester of pregnancy, the use of artemisinin derivatives (by both oral and intravenous routes) is preferred because they are more fast acting than quinine, and *vi)* in cases of *P. vivax* and *P. ovale*, a final course of primaquine should be given at the end to complete the cure and eradicate hypnozoites. In this case, glucose-6-phosphate-dehydrogenase (G6PD) deficiency in the patient should first be ruled out.

The treatment for the main **arboviruses** (dengue, Chikungunya and Zika) is symptomatic and the use of acetylsalicylic acid should be avoided.

The drug of choice for **typhoid fever** and **leptospirosis** is ceftriaxone (10-14 days and 7 days, respectively). Azithromycin is an alternative option for patients allergic to beta-lactams. Doxycycline is the drug of choice for treating **rickettsial infections** and **Q fever**. The recommended duration of treatment varies according to the species.

Acute schistosomiasis, or Katayama syndrome, is a disease that requires special consideration. Treatment at an early stage is recommended to avoid clinical manifestations, prevent complications associated with chronic infection and prevent neuroschistosomiasis¹⁹⁵⁻¹⁹⁸. The drug of choice is praziquantel at doses of 40-60 mg/kg, depending on the species, and combined with corticosteroids, administered either simultaneously or shortly after the corticosteroids. Treatment with praziquantel should be repeated after 2-3 months, since this drug is not effective against young migrating schistosomula.

In **hemorrhagic fevers**, supportive care is sometimes the only option, although in the case of hemorrhagic fever caused by *Arenaviridae* or *Bunyaviridae*, such as Lassa fever and Congo-Crimean

hemorrhagic virus, if ribavirin is initiated within the first 6 days of the illness, the mortality rate can be reduced¹⁹⁹⁻²⁰⁴. Treatment consists of a loading dose of 30 mg/kg ribavirin, administered intravenously (maximum, 2 g), followed by 16 mg/kg intravenously (maximum, 1 g/dose) every 6 hours for 4 days, then 8 mg/kg intravenously (maximum, 500 mg/dose) every 8 hours for 6 days. Anti-Lassa fever plasma may be used as adjunctive therapy in very ill patients.

Finally, for seriously ill patients, while waiting for cultures or serological results, **empiric use** of ceftriaxone and doxycycline is recommended to treat the main bacterial causes of fever of unknown origin.

Localized cutaneous lesions

Causative agents

KF54. Various cosmopolitan infections, such as superficial mycoses (e.g. pityriasis versicolor, cutaneous candidiasis or dermatophytosis) and some ectoparasitic infections (such as scabies) are more frequent in travelers (A-II).

KF55. Classic bacterial infections constitute the leading cause of consultation for skin lesions and specifically, for those due to certain strains of methicillin-resistant *S. aureus* (MRSA) that produce Panton-Valentine leukocidin (PVL) (A-II).

Diagnostic methods

KF56. The primary morphology of the lesion (e.g. papules, pustules, nodules, ulcers, blisters), configuration (e.g. linear) and distribution (exposed versus covered areas, specific parts of the body) are helpful for diagnosis (A-II).

KF57. In most cases, diagnosis is clinical, and dermoscopy is useful for some entities (scabies, cutaneous larvae *migrans*, furuncular myiasis and tungiasis) (B-III).

KF58. A helminth infection should be suspected if eosinophilia is associated with skin lesions (A-II).

KF59. In an imported dermatosis that develops slowly, cutaneous leishmaniasis, mycobacterial infection or a subcutaneous mycosis should be suspected. Histological examination and identification of the causative agent by means of molecular biology techniques or mass spectrometry is essential (A-II).

Therapeutic measures

KF60. For many imported dermatoses, treatment is symptomatic with oral antihistamines (diphenhydramine, hydroxyzine, or loratadine), topical antipruritics (calamine lotion) and topical corticosteroids (low potency for the genitals, medium potency for the trunk or extremities) (A-II).

KF61. The treatment of choice for the main imported dermatoses that are linear in pattern (cutaneous larva *migrans* (CTM), cutaneous larva *currens* and *gnathostomiasis*) is ivermectin, with albendazole an alternative option (A-I).

KF62. Surgical removal (associated with antibacterial anti-tetanus chemoprophylaxis where appropriate) is the treatment of choice for furuncular myiasis, tungiasis, and *D. repens* infections (A-II).

RATIONALE

Localized skin lesions are one of the main reasons why returned travelers seek medical advice²⁰⁵⁻²¹³. There is considerable variation in the time of appearance, since they can manifest while traveling, shortly after returning or much later, depending on the causative agent. Several cosmopolitan skin lesions (such as pityriasis (tinea) versicolor, cutaneous candidiasis, dermatophytosis, and scabies) are very common among travelers²¹⁴. The *classic bacterial infections* constitute the most common cause of skin lesions in travelers, most of which are due to *Staphylococcus aureus* and *Streptococcus pyogenes*. Infection with strains of methicillin-resistant *S. aureus* is very frequent, especially when returning from South America, and occasionally associated with more serious conditions such as the necrotic lesions caused by Pantone-Valentine leukocidin (PVL)^{215,216}.

Diagnosis of the majority of localized imported dermatoses is based on clinical and epidemiological criteria: the morphology of the lesion (macules, papules, wheals, nodules, ulcers), their localization and distribution, and exposure factors (Table 7). Dermoscopy may be useful for diagnosing scabies, cutaneous larva *migrans*, furunculoid myiasis and tungiasis. The first diagnostic possibility if there is eosinophilia should be a helminth infection (see **section IV.5**). In some circumstances, a biopsy of lesion tissue with histological examination, molecular biology techniques and/or mass spectrometry are all essential for an etiological diagnosis (leishmaniasis and nontuberculous mycobacteria).

In many imported dermatoses, **treatment** is symptomatic with oral antihistamines (diphenhydramine, hydroxyzine, or loratadine), topical antipruritic therapy (calamine lotion) or topical corticosteroids (low potency for the genitals, medium potency for the trunk and extremities). In serious cases, oral corticosteroids may be used (prednisone, prednisolone). In other cases, treatment based on etiology should be used (filariasis, gnathostomiasis, leishmaniasis, atypical mycobacteria, etc.). Surgical removal is the treatment of choice for furuncular myiasis, tungiasis, and *D. repens* infections. After *mammal bites*, it is essential to assess the need for tetanus prophylaxis, rabies immunoprophylaxis in rabies-endemic areas²¹⁷, and the use of prophylactic antibiotics (usually amoxicillin/clavulanate or moxifloxacin). Acyclovir is indicated to prevent herpes B infection from monkey bites, especially Old World macaques²¹⁸.

Cercarial dermatitis

- 1 ***Cercarial dermatitis*** (also known as swimmer's itch) has a worldwide distribution, although it is concentrated in the countries of Africa. It is an immune reaction caused by the cercariae, or larvae, of various *Schistosoma* species²¹⁹⁻²²², including bird schistosomes (*Trichobilharzia* spp.). It is transmitted when unbroken skin comes into contact with freshwater contaminated with the larvae. Approximately half an hour later, an urticarial rash appears on exposed areas (especially the legs and feet), which becomes pruritic after 12 hours. Generally speaking, within a day, the lesions develop into erythematous papules or vesicles, or painful, intensely itchy pustules. The diagnosis is clinical. Eosinophilia and/or the detection of antibodies against *Schistosoma* spp. are exceptional. Treatment is symptomatic, with oral antihistamines to control the itching, topical corticosteroids and emollients.

This condition should not be confused with another cutaneous manifestation of schistosomiasis: *ectopic schistosomiasis*^{223,224}. In this case, post-exposure clinical manifestations appear later, the lesions are discrete, erythematous, pruritic growths and the localization is different (in the genital and perineal area, to a lesser extent on the back, shoulders and lower abdomen), with granulomas observable upon histological examination. Praziquantel should be used for treatment.

Seabather's eruption

Seabather's eruption is an exanthema that breaks out hours after swimming in saltwater, especially in the Caribbean, the Atlantic off the USA and Brazil, the Pacific coast of Oceania and Southeast Asia^{225,226}. It is associated, etiologically-speaking, with toxins injected into the skin by the stinging cells (nematocysts) of sea anemones (*Edwardsiella lineata*) or thimble jellyfish (*Linuche unguiculata*). The lesions are similar to those produced by cercarial dermatitis, although they can be differentiated by the fact that seabather's eruption occurs on areas of the skin that are covered by the swimsuit (above all, those subject to most pressure).

Diagnosis is based on clinical suspicion and epidemiology. Histopathology from skin biopsy shows non-specific perivascular and interstitial inflammatory infiltrate. The rash generally resolves in 1-2 weeks. Treatment is symptomatic, using the therapies mentioned previously.

Cutaneous filariasis

Infection with the different species of filarial nematodes is a very infrequent cause of skin lesions among travelers. With very few exceptions, it tends to appear in long-term travelers who stay in areas where filariasis is endemic; the clinical manifestations appear later and are often not immediately associated with travel²²⁷⁻²³¹. All filariasis is spread by being bitten by diptera (flies or mosquitoes), although the species involved are different. The species of filarial worms that most frequently give rise

to skin lesions are *Onchocerca volvulus*, *Loa loa*, *Wuchereria bancrofti* and *Dirofilaria repens*²³². Infection with the different species of *Brugia* (*B. malayi* or *B. timori*) or *Mansonella* (*M. perstans*, *M. ozzardi*, *M. streptocerca*) is rare among travelers. Clinical symptoms vary depending on the species involved: nodules (*O. volvulus*, *D. repens*), diffuse disfiguring alterations of the skin, such as papules, sowda, lichenification, atrophy or depigmentation (*O. volvulus*), Calabar swellings (*L. loa*) and lymphedema (*W. bancrofti*). A suspected diagnosis of filariasis is based on clinical manifestations, history of travel to endemic areas and the presence of eosinophilia. Definitive diagnosis is based on the detection of microfilariae in the blood or skin, as well as the results of biopsy of the nodules. In most cases, treatment is etiological and includes three anthelmintics (ivermectin, diethylcarbamazine, albendazole), depending on the species identified. Surgical removal of the lesion is only necessary in cases of *D. repens* infection.

Cutaneous gnathostomiasis

Gnathostomiasis is a systemic parasitic infection caused principally by *Gnathostoma spinigerum*, a nematode acquired after ingesting raw or undercooked fish or other foods (snake or frogs)²³³⁻²³⁶. Most cases appear in travelers from Southeast Asia, Central or South America. Cutaneous forms are the most common, although a visceral form (affecting the digestive or central nervous system) is often reported. The characteristic skin symptom is a linear distribution of migratory plaques or nodules, principally on the thorax and upper extremities. It can be differentiated from other linear lesions by the presence of subcutaneous hemorrhages²³⁷. Eosinophilia is also a characteristic feature, although its absence does not rule out the diagnosis.

The definitive diagnosis is difficult and requires the extraction of the worm from the infected tissue. Skin biopsy shows dense dermal and sub-epidermal interstitial and perivascular eosinophilic infiltrates in the form of "flame figures"²³⁷. Immunoblots and immunochromatographic tests are highly sensitive and specific although difficult to obtain^{238,239}. The treatment of choice is oral ivermectin (200 µg/kg/day for 2 consecutive days) or oral albendazole (400 mg/12 hours for 21 days) with no significant differences between them^{240,241}. Patients should be monitored for signs of symptom recurrence.

Cutaneous larva currens

Cutaneous larva *currens* is the name given to one of the most characteristic cutaneous manifestations of infections caused by *Strongyloides stercoralis*^{242,243}. Infection with this nematode occurs when the bare skin comes into contact with ground contaminated with the larvae of this parasite. It is considered to present infrequently in travelers.

Differential diagnosis is made by comparison with other highly pruritic linear lesions,

such as cutaneous larva *migrans*, gnathostomiasis and sparganosis, and is based on speed of progression (more rapid), localization (abdomen, back and shoulders) and the absence of subcutaneous hemorrhages. Skin biopsy is of little use for diagnosis, which is based on the usual techniques for these parasites (see **section IV.5**). The treatment of choice is ivermectin (200 µg/kg/day for 2 consecutive days or given 2 weeks apart), with albendazole (400 mg/12 hours for 3-7 days) as an alternative option²⁴⁴⁻²⁴⁶.

Cutaneous larva migrans

Cutaneous larva *migrans* is caused by uncinaria, nematode parasites commonly found in cats and dogs (*Ancylostoma braziliense* and *A. caninum*)²⁴⁷⁻²⁵⁰. These helminths can also cause folliculitis that does not respond to conventional treatments. It is typically described in travelers returning from the Caribbean, Brazil, South Africa, and Southeast Asia who report visiting beaches and sandy areas and walking barefoot, sitting or lying down on (dry) sand without protection. Humans are accidental hosts; the worm penetrates the unbroken skin and is trapped in the dermis, through which it migrates and eventually dies. After a short incubation period (from hours to days), intensely pruritic, erythematous, edematous, linear eruptions appear, sometimes with vesicles and blisters, distributed in serpiginous tracks as the worm migrates through the skin. The lesions develop in days and, except for eosinophilia (20%), systemic manifestations are rare. Cutaneous larva *migrans* is a self-limiting disease and the lesions resolve spontaneously within 2-8 weeks, although impetigo due to scratching is frequent.

Diagnosis is clinical. Biopsy is not indicated, since the cutaneous lesions correspond to the response to the tracks left by the migrating worm (with eosinophilic infiltrates) without demonstrating the presence of larvae. Epiluminescence microscopy (dermoscopy) has been used to view the larva, although its sensitivity is unknown.

Treatment with anthelmintic drugs is useful to relieve symptoms and reduce the probability of bacterial superinfection²⁵¹⁻²⁵⁷. Oral ivermectin (200 µg/kg/day) for 1-2 days is the treatment of choice, with oral albendazole (400 mg/day) for 3-7 days as an alternative, mainly for extensive forms. Topical treatment with thiabendazole (15%) or albendazole (10%) for 10 days is an alternative, although it is difficult to obtain. Neither cryotherapy nor surgery is effective.

Cutaneous and mucocutaneous leishmaniasis

Cutaneous leishmaniasis encompasses various clinical syndromes caused by protozoa of the genus *Leishmania* that are transmitted to humans and reservoir hosts bitten by infected female phlebotomine sand flies of the genus *Lutzomyia* in America, and *Phlebotomus* on the other continents²⁵⁸⁻²⁶⁰. These infections typically appear in young people who have been traveling for more than a month. *Cutaneous*

and mucocutaneous leishmaniasis are endemic in more than 70 countries in the world, although most cases (>90%) have been reported in seven Old World countries (Afghanistan, Saudi Arabia, Algeria, Iran, Iraq, Pakistan and Syria) and two in the New World (Brazil and Peru). The number of cases in the countries mentioned has risen in recent years, and other countries have joined the New World group, such as Bolivia and Colombia.

Natural disasters, armed conflict (specifically, the war in Afghanistan) and tourism are among the causes of this increase in incidence. Four species cause **Old World cutaneous leishmaniasis**: *L. major*, *L. tropica*, *L. aetiopica* and *L. infantum*, while **New World cutaneous leishmaniasis** is more frequently caused by *L. mexicana*, *L. panamensis*, *L. guyanensis*, *L. braziliensis* and *L. peruviana*, with the two latter species producing more serious and complicated mucocutaneous forms. Lesions appear on exposed areas and can be quite different depending on the causative pathogen (e.g. single or multiple nodules, painless ulcers, with or without scab formation, plaques).

A simple and rapid technique for diagnosis, although not highly sensitive, is direct microscopic examination of a sample of skin tissue from the active border of the lesion. The most common diagnostic method is **histological examination and culture of infected biopsy material in an axenic medium** (with improved sensitivity if various samples are obtained and complementary techniques are performed)²⁶¹. Samples should be Giemsa-stained and viewed under the oil immersion objective to detect amastigotes. The two most commonly used axenic culture media are NNN (Novy-McNeal-Nicolle) and Schneider's, with the proper culture temperature between 26 and 28 °C. **PCR of *Leishmania spp.*** with skin biopsy allows a species-specific diagnosis with very high sensitivity and specificity²⁶¹. Standard serological tests and the intradermal Montenegro test are not useful for diagnosing cutaneous and mucocutaneous leishmaniasis.

In travelers, treatment is complex and not optimized and the patient should be treated on an individual basis with reference to species, geography, host, the aspect of the lesion, local experience, drug availability, cost and adverse effects^{262,263}. Many cases of cutaneous leishmaniasis resolve spontaneously and almost two thirds of patients can be treated with local therapy, such as heat therapy, topical paromomycin, intralesional injections of antimoniate and cryotherapy²⁶⁴⁻²⁶⁶. In complicated cutaneous cases, systemic treatment with oral azoles (fluconazole, ketoconazole or itraconazole) or miltefosine can be used^{267,268}. Treatment for mucocutaneous leishmaniasis should be administered parenterally, with the first choice being pentavalent antimonials, and amphotericin B and miltefosine as alternative options²⁶⁹.

Lesions in the marine environment: coral, fish, jellyfish and bacterial infections

In general, cutaneous lesions associated with the marine environment (which includes seabather's

eruption referred to above) are infrequent. The most important are those due to coral, fish (stonefish or stingray), jellyfish and bacterial infections²⁷⁰⁻²⁷⁴. The term “*coral*” is not used with a taxonomic meaning, but to refer to marine invertebrates in class *Anthozoa* that typically live in colonies of polyps. Coral lesions are caused by the production of multiple toxins and generally involve pain, pruritus and erythema. **Coral wounds** should be cleaned, possibly with debridement, and diluted vinegar can be applied to reduce the pain. A characteristic of lesions caused by coral is that they heal slowly due to the persistence of inorganic matter (calcium carbonate), organic matter (nematocysts) and bacterial superinfection.

The two main types of **fish** that cause skin lesions in travelers are stonefish and stingrays (elasmobranchii). The lesions are extremely painful with erythema and perilesional edema. Treatment is symptomatic, possibly involving surgery to remove foreign matter. Primary closure should be evaluated in the case of extensive lesions or in important aesthetic areas. Patients with deep wounds and/or foreign bodies in them should receive prophylactic antibiotic therapy.

Jellyfish stings are relatively frequent and normally take the form of linear or serpiginous lesions on the skin, with edema, petechiae and urticariform reactions. The initial pain feels like a cigarette burn and fades slowly. Treatment of pain caused by *Carybdea alata* and *Physalia* spp. stings consists of removing the tentacles as quickly as possible by hand or with seawater, followed by immersion of the affected part in warm water (43-45 °C) for 20 minutes. Immersion in cold water, vigorous rubbing and topical application of vinegar or ethanol are not recommended. The pain can be managed with the usual analgesics.

Any **cutaneous lesion due to saltwater contact that could be infectious** should be treated with antimicrobials effective for enterobacteria and halophilic microorganisms (e.g. *Vibrio* spp.), such as quinolones and/or tetracyclines.

Furuncular myiasis

Myiasis is infestation of the dermis by the developing larvae of various fly species within the arthropod order Diptera. The two most frequent forms in travelers are furuncular myiasis caused by the larvae of *Dermatobia hominis* and *Cordylobia anthropophaga*²⁷⁵⁻²⁷⁸.

Furuncular myiasis by *D. hominis* (botfly) is endemic in Central and South America. The flies live in humid areas and lay their eggs on the abdomens of mosquitoes and other blood-sucking arthropods. When the insects bite the host (including humans), the eggs hatch and the larvae penetrate the skin tissue. In a period of 4-14 weeks, a furuncular lesion develops with a sensation of movement within, and a central opening through which the larva breathes and also eliminates a serosanguineous discharge (“frass”). In cases that have not developed, treatment is conservative and involves blocking up the breathing hole with petroleum jelly in order to kill the larva within, and then extracting it by

applying manual pressure round the lesion. In furuncles that have grown to a certain size, topical use of ivermectin kills the larva, enabling it to be released. In more advanced cases, the larva must be extracted with surgical methods.

Furuncular myiasis due to *Cordylobia anthropophaga* (tumbu fly, tutsi fly, or mango fly) is the commonest form in Africa. The pregnant flies lay their eggs on wet clothing outside dwellings. The eggs hatch when the garment is worn and the larva burrows into the skin. Apart from geography, lesions caused by *Cordylobia* spp. can be distinguished in several ways from those associated with *Dermatobia* spp.: *i*) they are frequently multiple; *ii*) the incubation period is shorter (7-10 days); *iii*) the larvae are smaller in size; and *iv*) the lesions frequently affect parts of the body that are covered by the garment. Because the larvae are smaller and the lesions not as deep, it is usually possible to use conservative methods to extract the larvae. In both cases, a clinical diagnosis can be made and dermoscopy may be helpful²⁷⁹.

Atypical (nontuberculous) mycobacteria

The main atypical mycobacteria responsible for cutaneous lesions in travelers are *M. marinum* (nodular or ulcerated lesions with sporotrichoid distribution following exposure to contaminated aquaria or tropical saltwater fish) and *M. abscessus* and *M. chelonae* (associated with liposuction)²⁸⁰⁻²⁸⁴.

The clinical diagnosis is quite distinctive in infections by some species. Skin tissue biopsy shows granulomas, sometimes known as “fishtank granulomas”. An etiological diagnosis is made by stain and culture. Molecular biology techniques or mass spectrometry (MALDI-TOF) is used for species identification. Most atypical mycobacteria are ubiquitous in the environment, so that isolation should be evaluated on the basis of clinical presentation and histopathology.

Standardized treatment regimens are not well established for atypical mycobacteria and are derived from guides used for respiratory complaints²⁸⁵. An attempt should be made to evaluate sensitivity to different pharmaceutical drugs. It is reasonable to use dual therapy at least (to minimize possible selection for resistance) and to treat for 4-8 weeks after the lesions themselves have healed. For some infections, surgical debridement, as well as antimicrobial treatment, may be useful. Other effective techniques for treating atypical mycobacterial infections affecting the skin are cryotherapy, photodynamic therapy, electrodesiccation and local hyperthermia, although their use is not widespread.

Buruli ulcer is caused by *M. ulcerans* and is rarely found in travelers. It causes large cutaneous ulcerations, with subcutaneous nodules that progress along tunnels in the dermis and are difficult to treat.

Superficial and subcutaneous mycoses

Two common forms of **superficial cutaneous mycoses** in travelers are the two types of piedra (black piedra and white piedra) and tinea nigra; they affect the outer layers of the skin or hair and do not involve significant inflammation⁸². The two types of piedra can be characterized as hard nodules on the hair shaft. The two main varieties are distinguished on the basis of the causative agent, geographic location, and the part of the body affected. Diagnosis is based on the morphological characteristics of the infected hair treated with a 10-15% KOH solution, and fungal culture of the hair. They are normally harmless infections, although they may present social problems (such as an unpleasant underarm odour). Treatment is based on shaving the affected area and using a topical treatment with ketoconazole shampoo. Other oral therapeutic options are available for recurring cases.

Tinea nigra is caused by *Hortaea werneckii*, a halophilic fungus formerly known as *Exophiala werneckii*. The infection has been reported in Central and South America, Africa and Asia. It mainly affects young, healthy individuals whose clinical history includes spending time on beaches. The lesions are single, unilateral, dark (grey or dark brown) macules. Pruritus is rarely reported. The lesions tend to occur on the palms of the hands and soles of the feet. It is a benign infection that tends not to recur. Diagnosis is based on a microscopic examination of skin scrapings treated with KOH. Treatment consists of keratolytic agents and possibly topical use of antifungal agents (terbinafine, ketoconazole).

Subcutaneous fungal infection is more rare among travelers, although cases of sporotrichosis, chromoblastomycosis, lobomycosis and mycetomas have been described^{287,288}.

Arthropod bites / dermatitis linearis

The most frequent skin lesions among travelers are due to bites and comprise almost 20% of consultations due to dermatosis. Although distributed worldwide, insect bites are especially common in travel to tropical areas. The most common are those associated with arthropods (for example, mosquitos, fleas, ticks, bedbugs and spiders)²⁸⁹. The clinical manifestations are highly varied. *Mosquito bites*, for example, can manifest as wheals, papules or bullae. This diagnosis is suggested by the presence of a central punctum in the lesion. *Flea bites* generally give rise to papules, often in groups of three. A characteristic feature of being bitten by a tick is the presence of a black necrotic lesion (black eschar or "tache noire"), very common in travelers to South Africa²⁹⁰. A *bite from a bed bug* is very painful, causing a chancre that discharges serosanguineous fluid. There is a special form called *dermatitis linearis*²⁹¹ associated with travel to tropical regions after the rainy season. It is caused by beetles in the *Paederus* subtribe ("fire bug") and commonly manifests as stinging, intense pain and pruritus, with later development of erythematous plaques and blisters in a linear array, which appear 6-24 hours following contact.

In the majority of cases, diagnosis is clinical, and biopsy is necessary for doubtful cases.

Treatment is symptomatic. Oral antihistamines may be given if there is a good deal of pruritus, or topical corticosteroids or calamine lotion. The possibility of vector-borne disease transmission should always be considered.

Tungiasis

Tungiasis is an inflammatory skin infection caused by the female flea, *Tunga penetrans*, an ectoparasite that penetrates the epidermis^{291,292}. This parasitic infestation of the skin is prevalent in Latin America, the Caribbean and sub-Saharan Africa. The flea infects poultry, dogs, cats, rats, pigs and occasionally human beings. Its habitat is dry soil or sand, where the eggs are deposited and subsequently hatch. The male flea dies after copulation. In humans, the gravid female penetrates the skin (generally the feet, the spaces between the toes, round and under the nails) and burrows into the epidermis to feed on the blood of its host. In most cases, the lesion is a single white papule in the form of a halo with a dark brownish-black spot in the center. For seven to ten days, the female lays 150-200 eggs daily through a small opening in its abdominal cavity, dying shortly afterwards and so completing the cycle.

Diagnosis is based on the clinical history of the patient, including prior travel to endemic areas, risky practices, and on the morphology and localization of the lesions²⁹³.

Dermoscopy may be useful for diagnosis, with a distinguishing feature being the “radial crown” (a pigmented peripheral ring with a black pore in the center)²⁹⁴.

The treatment of choice is surgical removal of the entire flea and curettage of the cavity, as well as tetanus prophylaxis for secondary infection, which is frequent²⁹⁵.

Respiratory infections

KEY FACTS

Causative agents

KF63. The most common causes of respiratory infection in the local environment are also the most common among travelers, and exotic imported infections are much less frequent (A-II).

KF64. In general, viral and bacterial infections are more frequent than those caused by fungi and parasites (B-II).

KF65. Most respiratory infections in travelers are mild, affect the upper respiratory tract and are caused by viruses (A-II).

KF66. The most serious respiratory infection in travelers is pneumonia, and the most common causes of it in the traveler are similar to those in the autochthonous population, although with a greater incidence of infections due to *S. aureus* and *Legionella* spp. (A-II).

KF67. During short trips, the risk of tuberculosis is low and depends on the incidence of the disease in the countries visited (B-III).

KF68. The main causes of respiratory conditions associated with eosinophilia are acute schistosomiasis, Löffler's syndrome and paragonimiasis (B-III).

KF69. Travelers may also have non-infectious problems that have respiratory manifestations such as pulmonary embolism and mefloquine toxicity (B-III).

Diagnostic methods

KF70. Most respiratory infections during and after travel do not require diagnostic confirmation because they are mild, self-limited upper respiratory tract infections (A-II).

KF71. The diagnostic methods for pneumonia are no different from those used with autochthonous patients (B-II).

Therapeutic measures

KF72. In patients with pneumonia, the decision as to whether a patient with pneumonia should be admitted to hospital or the ICU should be based on severity scales used in the autochthonous population (A-II).

KF73. Procalcitonin levels can help guide the clinical judgment of the attending physician in prescribing antibiotics for respiratory infections (B-II).

KF74. If tuberculosis is suspected or any other infection transmitted via respiratory secretions (such as the MERS-CoV coronavirus), respiratory isolation and droplet precautions are recommended (A-I).

KF75. Most respiratory infections during and post-travel do not require specific treatment because they are mild and self-limiting. Treatment may be given for the symptoms (B-III).

KF76. For pneumonia in travelers, antibiotic therapy is initially empiric and should include drugs effective against the most common community-acquired pathogens, including *Legionella* spp. (B-II).

KF77. In travelers with influenza and severity criteria or risk factors, treatment with oseltamivir or zanamivir is recommended (B-II).

KF78. If the traveler with tuberculosis has come from a country with a high incidence of antimicrobial resistance, it would be reasonable to evaluate treatment with at least 4 drugs and rapid DNA-based tests to detect mutations associated with resistance (B-III).

RATIONALE

Causative agents

Some general comments can be made about the etiology of respiratory infections in travelers: *i)* the most frequent causes are similar to those found in the autochthonous population; *ii)* the most common

symptoms of respiratory infections in the traveler affect the upper respiratory tract; *iii*) viral, followed by bacterial pathogens, are the commonest causes of respiratory infections, while fungi and parasites are much rarer²⁹⁶; *iv*) studies with well-designed methodologies have observed that between 26% and 56% of travelers with fever and respiratory symptoms present with viral infections (influenza, rhinovirus, coronavirus, respiratory syncytial virus (RSV), adenovirus or human metapneumovirus (hMPV))^{297,298}; *v*) an influenza virus is the commonest cause of respiratory infection in travelers (and can also be prevented by vaccination), although its incidence depends on the series and seasonal factors (for example, the recent H1N1pdm09 pandemic)²⁹⁹; *vi*) in recent years, the possibility of MERS-CoV (Middle East Respiratory syndrome coronavirus) infection should be considered in travelers returning from areas where it is endemic (Saudi Arabia and the United Arab Emirates)³⁰⁰; *vii*) sporadic cases of infection in travelers caused by hantavirus and the measles virus (also preventable by vaccination) have been described^{301,302}; *viii*) the most frequent causes of pneumonia in travelers are similar to those in the autochthonous population (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*)^{25,303,304}. Other bacterial causes should also be considered, such as *S. aureus*³⁰⁵ and *Legionella pneumoniae* (particularly on cruise ships or where there is spa use)³⁰⁶; *ix*) some systemic febrile illnesses (such as malaria, dengue, leptospirosis and Q fever) occasionally manifest with respiratory symptoms (see **section IV.2**); *x*) melioidosis should be included for travelers to Southeast Asia, where it is a major source of infection³⁰⁷. Melioidosis in travelers is less often associated with risk factors (such as diabetes mellitus), can manifest years after a stay in a tropical or subtropical area and has a lower mortality rate than infections in the autochthonous population; *xi*) active tuberculosis is very rarely diagnosed in recently returned travelers. In general, it is more frequent in the VFR subgroup of travelers, in long-stay travelers, in the immunocompromised, and following travel to Africa. Some authors suggest that the risk of travelers acquiring pulmonary tuberculosis is similar to that in the general population of the country of destination³⁰⁸. Furthermore, if traveling in the company of an infected person, the risk of tuberculosis varies depending on the means of transport, being higher in an aeroplane and lower on a bus or train; *xii*) in travelers, the three main respiratory conditions with eosinophilia are Katayama fever (acute schistosomiasis, see **section IV.2**), Löffler's syndrome (transient pulmonary infiltrates related to the transit through the lung of *Ascaris* spp., *S. stercoralis*, and, exceptionally, *uncinaria*) and paragonimiasis (which characteristically affects the pleural cavity); *xiii*) the main primary deep mycoses that affect the lungs in travelers are histoplasmosis and coccidioidomycosis (valley fever), particularly returning from the Americas, and *xiv*) finally, there are non-infectious causes of travel-related conditions with respiratory system involvement, such as pulmonary thromboembolism³⁰⁹ or pulmonary toxicity due to mefloquine³¹⁰.

Diagnostic methods

The clinical history is fundamental for guiding diagnosis in the returned traveler with respiratory symptoms. In most cases, illness is mild and self-limiting, so that medical advice in a health center is not sought and diagnostic tests are not necessary¹⁶². Pneumonia, however, is a very serious respiratory infection in travelers, especially in those with risk factors (chronic diseases and illnesses, immunosuppression or advanced age)^{25,162,311}. Pneumonia can account for 4% of cases requiring post-travel admission to hospital with fever, 11% of ICU admissions³², and up to 25% of deaths¹⁶², which means that diagnostic effort and treatment should be concentrated on these patients.

The chest x-ray continues to be the gold standard for pneumonia diagnosis. In the case of travelers, it is recommended that this test be used selectively in the subset of patients with fever, cough, leukocytosis, elevated C-reactive protein levels and fever without a clear obvious diagnosis³¹¹. Other imaging techniques, such as a CAT scan of the chest, may be useful for defining the radiographic pattern of the pneumonia or for evaluating complications.

It is not possible to make an etiological diagnosis using only clinical presentation, basic analysis or imaging techniques. Furthermore, even using appropriate techniques, it is possible to make a microbiological diagnosis in only half the cases³¹².

There are no systematic studies of microbiological diagnostic tests for travel-related pneumonia, although it is recommended initially to use the usual techniques for microorganisms of global distribution, which account for most episodes^{25,303,304,313}. If there is clinical suspicion, abnormal analytical signs (such as eosinophilia), a specific geographic destination or risky activities during travel, the study should be extended with other directed tests³¹⁴ (Table 8).

Molecular techniques are very useful for diagnosing common viruses, emerging viruses and endemic fungal infections³¹⁵⁻³¹⁷. In other potentially serious systemic infections, such as enteric fever, dengue, leptospirosis and malaria, specific diagnostic tests are recommended, described in **section IV.2**.

Therapeutic measures

There are no specific studies on the treatment of travel-related respiratory infections. The first decisions to be made about these patients concern the need for hospitalization and implementation of isolation precautions.

Most upper respiratory infections do not require **hospitalization**. In cases of pneumonia, the severity scales used to determine whether autochthonous patients should be admitted to a general ward or the ICU should be applied³¹³. Patients without severity criteria or risk factors can be treated on an outpatient basis. In the emergency service, indications for antibiotic therapy guided by clinical judgment and procalcitonin levels can help reduce antibiotic use without increasing the risk of complications³¹⁸.

In returned patients with respiratory infections, **isolation** with airborne precautions is recommended for patients admitted to hospital with tuberculosis, and droplet precautions for *Mycoplasma pneumoniae*, *Bordetella pertussis*, diphtheria, melioidosis, influenza, adenovirus, syncytial respiratory virus or MERS-CoV³¹⁹.

Symptomatic treatment will be sufficient for most travel-related respiratory infections, using analgesics, antipyretics, anti-inflammatories, decongestants, cough suppressants, antihistamines and bronchodilators. Targeted antibiotic treatment is however indicated for some upper respiratory infections, such as pharyngitis due to *Streptococcus pyogenes*, diphtheria and whooping cough, or antiretrovirals for acute HIV infection.

In the absence of any associated clinical suspicion, **empiric therapy for pneumonia** will be similar to that administered to the autochthonous patient. If there is no clinical, analytical or epidemiological suspicion of a tropical disease, antibiotic treatment for pneumonia in travelers should initially provide coverage for the typical bacteria of global distribution found in community-acquired pneumonia³¹³. However, given the greater incidence of infection due to *Legionella* spp., it is reasonable to use regimens that include levofloxacin or macrolides.

Treatment based on identifying the causative pathogen presents some differential features. So, for patients with influenza who have been admitted to hospital or present factors that involve risk of complications, early treatment with oseltamivir or zanamivir is recommended in the first 48 hours³²⁰. Some tropical infections, such as *melioidosis*, require various combinations of antibiotics administered intravenously, followed by a lengthy period with oral antibiotics³²¹. For travelers who acquire *tuberculosis* in areas with a high incidence of resistance, it is reasonable to consider treatment with at least 4 drugs and to perform a rapid and sensitive test (such as the Xpert MTB/RIF®) in order to adjust therapy to the results^{322,323}. Mild cases of primary deep mycoses require only treatment for symptoms. In serious cases, the drug of choice is amphotericin B, with itraconazole if it becomes chronic³²⁴. *Helminth infections* require targeted therapy, as well as corticosteroids in the case of acute schistosomiasis or Löffler's syndrome.

Eosinophilia

Causative agents

KD79. The causes of imported eosinophilia vary a good deal and depend on the characteristics of the patient, particularly whether the person is a traveler or an immigrant, and on the geographic destination, itinerary and length of exposure (B-II).

KD80. When a patient presents with imported eosinophilia of non-filarial etiology, it is important to rule

out infection due to parasites, principally helminths (A-II).

KD81. In patients with imported eosinophilia, the cause is identified as a parasite in 60-75% of cases (B-II).

KD82. The three most frequently found parasitic infections are strongyloidiasis, schistosomiasis and soil-transmitted helminth infections, as well as filariasis in the case of Equatorial Guinea (B-II).

Diagnostic methods

KD83. All returning travelers with eosinophilia should request a stool examination to search for parasites using a concentration method and *Strongyloides stercoralis* serology (B-II).

KD84. Travelers returning from Africa should request tests for diagnosing schistosomiasis (examination of the urine sediment and feces, and *Schistosoma* spp. serology (B-II).

KD85. In cases where a diagnosis cannot be made with direct techniques, serological methods are a useful diagnostic tool, although their possible drawbacks should not be forgotten (B-III).

Therapeutic measures

KD86. When the cause cannot be identified, the empiric treatment for imported eosinophilia should be a combination of oral ivermectin plus albendazole. Praziquantel should be added for cases with possible epidemiological exposure to schistosomiasis (B-III).

KD87. Before starting empiric ivermectin therapy, the possibility of *Loa loa* infection should first be ruled out (A-II).

KD88. When empiric anthelmintic treatment is administered, the patient should receive clinical follow-up with monitoring of peripheral blood eosinophil counts, since some parasites, like *Trichuris* spp. and *Schistosoma* spp., have developed resistance leading to anthelmintic treatment failure (A-II).

RATIONALE

Causative agents

The diagnostic work-up of imported eosinophilia is one of the most complex challenges in clinical practice to do with imported diseases. The main reasons for this are that some parasitological tests have low sensitivities and some serological tests have low specificities³²⁵.

According to the series analyzed, a parasitic cause was identified in a very high percentage of cases, depending on the center and the characteristics of the patients³²⁶⁻³²⁸, and similar figures were found in children with imported eosinophilia³²⁹. The diagnostic yield of studies involving travelers was noticeably less than those performed with immigrants³²⁷⁻³³¹.

In most of the published series, strongyloidiasis, schistosomiasis and soil-transmitted

helminth infections (ascariasis, trichuriasis and ancylostomiasis) are the most common parasitic causes depending on the patient's status (immigrant or traveler) and provenance³²⁶⁻³³⁰. Filariasis is the major suspected cause in patients from the Gulf of Guinea (Equatorial Guinea or Cameroon)³²⁹.

Diagnostic methods

Eosinophilia caused by helminth infections is generally mild and self-limiting. Nevertheless, it has been estimated that between 10% and 73% of travelers returning from tropical areas with eosinophilia could have potentially serious infections, with consequences not only for their own health, but also for those who have been in contact with them³³⁰⁻³³⁴. Prompt and appropriate effort should be made to determine the etiology in travelers presenting with imported eosinophilia, since some of the helminths involved can cause additional morbidity, and sometimes mortality, as in the case of toxocariasis³³⁵ or strongyloidiasis^{336,337}.

The cause of eosinophilia can be identified in roughly 50-60% of cases of travelers with imported eosinophilia^{325,326,331,338}. Screening should begin with an *exhaustive clinical history*, which will serve as a prompt for additional tests and studies. The main epidemiological aspects to be emphasized are³³⁹⁻³⁴¹: *i*) the itinerary and countries visited (paying attention to routes passing through rural areas); *ii*) the dates when travel started and finished; *iii*) type of accommodation; *iv*) a dietary history during travel that indicates food-borne helminthic infections (e.g. ingestion of uncooked greens [*Fasciola* spp.], raw fish [*Anisakis* spp., *Gnathostoma* spp., *Clonorchis* spp., *Opisthorchis* spp.], meat [*Trichinella* spp., *Taenia* spp.], crabs or shellfish [*Paragonimus* spp.], snails [*Angiostrongylus cantonensis*], frogs or snakes [*Gnathostoma* spp.]³⁴⁰; *v*) risky activities during travel that suggest different parasites (for example, walking barefoot and/or contact with contaminated soil or sand [Cutaneous larva *migrans*, *Strongyloides* spp.], swimming or bathing in contaminated freshwater [with *Schistosoma* spp. for example]); *vi*) insect bites [filarial nematodes] and contact with local animals; *vii*) a history of allergies and atopy, and *viii*) usual medication, to rule out drugs and other compounds such as vitamins and dietary supplements associated with eosinophilia³⁴². In addition, a touchscreen questionnaire that documents the symptoms that can accompany eosinophilia (such as fever, diarrhea, pruritus, respiratory or neurological problems) can be helpful for leading to a definitive diagnosis^{340,343}. A thorough physical examination should then be made to detect lesions on the skin and soft tissues, in the eyes, or enlargement of the abdominal organs and respiratory involvement. This is then complemented with a basic analytical study, including a complete blood count and blood chemistry with determinations of liver and muscle enzymes, and a basic study of renal function. This initial evaluation will be highly useful in leading to an etiological diagnosis^{334,341,344}. If the physical exploration indicates signs and symptoms or abnormalities, imaging tests can be carried out, for example, chest x-rays, ultrasound scans or abdominal CT scans³⁴⁵⁻³⁴⁷ (Table

9).

The clinical information should be complemented with tests for parasites, which should be based on the geographic provenance of the traveler, since the endemic areas of certain parasitic diseases are region-specific, whereas others are cosmopolitan, as can be seen in Table 10^{333,340,341}. The initial examination of the traveler with eosinophilia should comprise: *i*) studies of intestinal parasites in stool samples, with three serial specimens taken on alternate days and using various methods (for example, Ritchie's method and the Kato-Katz technique) to improve identification³⁴⁸⁻³⁵⁰; *ii*) a stool sample on agar-plate or charcoal culture for the detection of *Strongyloides stercoralis*³⁵¹; *iii*) if the traveler has come from a region with endemic schistosomiasis or filariasis, the sediment of a urine sample should be searched to detect *Schistosoma haematobium* eggs^{341,352}, and the blood and/or skin for microfilariae, using concentrated blood techniques (such as Knott's technique) or skin scrapings, respectively³⁵³.

If the results obtained are negative, a second set of serological tests can be applied for the detection of: *i*) *S. stercoralis* antibodies³⁴⁵, and *ii*) *Schistosoma* spp. antibodies (as long as the traveler has come from an endemic area)^{326,352}, or different parasites depending on epidemiology (for diagnoses of filariasis, fascioliasis, toxocariasis and hydatidosis)³²⁶. It is important to bear in mind the limitations of serological testing since: *i*) it cannot distinguish resolved infection from active infection³⁴¹, *ii*) most serology tests are not positive until 4-12 weeks after the infection³⁵⁴, *iii*) there may be cross-reactions between different helminthic infections; cross-reactivity is very common between *Strongyloides* and filarial parasites, between schistosomes and *Fasciola* spp. and between *T. solium* and *E. granulosus*^{340,346}, and *iv*) Many serological methods can only be performed in specialized centers.

If the cause of eosinophilia is highly suspected but cannot be determined using all the diagnostic tests previously outlined, it is important to repeat the direct parasitic tests, since the test can be negative at the onset of infection and when the elimination of eggs is scant or intermittent. Table 10 indicates the prepatent period (length of the migratory phase) of the principal helminths. The prepatent period is the period between infection with a parasite and their appearance in the blood or tissues in the form of eggs or larvae; Accordingly, stool examinations for eggs or larvae will be negative during this period^{340,354}.

Therapeutic measures

Clearly, when the cause of eosinophilia has been identified, targeted treatment should be given with the anthelmintics of choice^{325,354}.

If a traveler presents with eosinophilia and an etiological diagnosis cannot be made after further testing, empiric treatment is indicated³²⁵. This intervention strategy is based on the good safety profile of the anthelmintics available and their enhanced effectiveness and ease-of-use in oral

regimens^{325,354}. Few studies have evaluated the effectiveness of empiric therapy for imported eosinophilia^{326,328}. A positive response of 90% was reported in patients with unexplained eosinophilia treated with empiric albendazole therapy for 5 days³²⁶. In another study carried out among sub-Saharan immigrants, eosinophilia was resolved in 94% of those who received empiric therapy with ivermectin, albendazole and praziquantel³²⁸. Ivermectin is a key drug used in the empiric management of imported eosinophilia, since its objective is to treat strongyloidiasis, a chronic disease that can infect the human host for decades and cause severe disseminated disease that is deadly in more than 60% of cases, especially those involving immunosuppression³³⁶. Furthermore, ivermectin is also effective against other parasites that are more difficult to diagnose (such as *Gnathostoma* spp.).

Empiric therapy for imported eosinophilia does not preclude investigation of other non-imported causes of eosinophilia, some potentially serious, such as hematologic disorders or neoplasia³²⁵.

It is assumed that the disappearance of eosinophils in patients who have received empiric therapy is a sign that the causative agent has been eliminated. It should be borne in mind, however, that eosinophilia does not always follow a consistent course, which can lead to error³²⁵.

It is necessary to monitor eosinophilia and its causes after administering anthelmintic therapy. The major causes of persistent infection are parasite resistance to the drug of choice (as in the case of schistosomiasis)³⁵⁵, and the possibility of presentation with an associated causative agent.

Neurological infections

KEY FACTS

Causative agents

KF89. The most frequent causes of neurological disease in travelers are malaria, viral infections and bacterial meningitis (A-II).

KF90. Generally speaking, the main clinical manifestations affect the brain and/or meninges, and more rarely, the spinal cord and peripheral nervous system (B-III).

KF91. The main manifestation in the peripheral nervous system is Guillain-Barré syndrome, which is associated with infection due to *Campylobacter jejuni*, dengue and, more recently, the Zika virus (B-II).

Diagnostic methods

KF92. Any international traveler who returns with fever, severe headaches, light sensitivity and/or a stiff neck should be evaluated urgently to rule out the presence of meningitis or encephalitis (A-III).

KF93. The cerebrospinal fluid (CSF) analysis can adopt four different patterns: normal, raised neutrophils, raised lymphocytes, raised eosinophils, which is useful for differential diagnosis (A-II).

KF94. Direct ophthalmoscopy is recommended for all patients with a diagnosis or suspicion of cerebral malaria, given its high prognostic and diagnostic value for malarial retinopathy (A-II).

RATIONALE

The **etiologic spectrum** of diseases involving the nervous system that can be contracted by the international traveler is a broad one and includes viral, bacterial, fungal and parasitic infections³⁵⁶⁻³⁵⁹. The most common **bacterial infections** are caused by *Neisseria meningitidis* and *S. pneumoniae*³⁶⁰⁻³⁶². Occasionally, the course of rickettsial infections, Q fever and brucellosis includes neurological manifestations^{153,363}.

Among **viral infections**, apart from the typical autochthonous causes (herpes viruses, enteroviruses), dengue fever, some endemic forms of encephalitis (tick-borne, Japanese and West Nile encephalitis, transmitted by infected mosquitos) and rabies are prominent causes of imported infection³⁶⁴⁻³⁶⁶. These exotic viral infections are rare among Spanish travelers^{367,368}. The main **protozoan disease** with a neurological manifestation in travelers is malaria³⁶⁹, while cases of human African trypanosomiasis are rare³⁷⁰. The most frequent **parasitic infections** imported by travelers are neuroschistosomiasis³⁷¹, cysticercosis³⁷² and the pathogens that cause eosinophilic meningitis (*Gnathostoma spinigerum*, *Angiostrongylus cantonensis*, *Baylisascaris procyonis* and *Paragonimus* spp.)³⁷³. Primary deep **mycoses** cause brain lesions in travelers only exceptionally. Very few series have compared relative frequencies; malaria, viral infections, and bacterial infections are the most frequent, in that order³⁵⁹.

As with all imported infections, **diagnosis** of the returned traveler with neurological manifestations is improved by obtaining a detailed clinical and travel history that includes duration of travel, specific destinations, risky activities undertaken and the specific clinical characteristics³⁵⁶⁻³⁵⁸. With respect to the *duration of travel*, malaria, viral and bacterial infections manifest early, while parasitic infections take longer. Generally speaking, the main *clinical manifestations* tend to involve the brain and/or meninges, and more rarely the spinal cord and the peripheral nervous system. Fever (with the exception of neurocysticercosis), headaches, meningeal signs or convulsions normally accompany the cerebral-meningeal forms. Imaging tests and a cerebrospinal fluid analysis obtained by lumbar puncture are useful for diagnosis. Spinal cord involvement is characteristic of schistosomiasis (especially due to *S. mansoni*) and neurobrucellosis. In the peripheral nervous system, the main manifestation is Guillain-Barré syndrome, associated with *Campylobacter jejuni* infection, dengue, and more recently, the Zika virus infection³⁷⁴. In general, *neuroimaging tests* are not very useful and not specific for the entities mentioned, but they are quite useful for identifying focal lesions (infrequent among travelers on the whole). The results of a CSF analysis can adopt four possible patterns: normal (very frequent in cerebral

malaria), raised neutrophils (characteristic of classic bacterial meningitis), raised lymphocytes (for example in some virus infections, brucellosis or rickettsial infection) and raised eosinophils (in the helminth infections mentioned previously). In most cases, the *etiological diagnosis* is based on blood and/or serum tests, and has been referred to in earlier sections.

Cerebral malaria is one of the most important entities to consider in travelers who return from an appropriate geographic context with encephalitis. Its most frequent manifestations involve changes in the level and content of consciousness, and may or may not be associated with seizures. In these patients, the possibility of quinine-induced hypoglycemia should always be considered in the differential diagnosis of neurological signs. On many occasions, cerebral malaria is preceded or accompanied by retinal lesions, the most characteristic of which are patchy retinal whitening and focal changes of the blood vessel colour, although macular edema, retinal hemorrhages, Roth stains and vascular changes can also appear³⁷⁵. Prospective field studies have described malarial retinopathy as the most specific finding in cerebral malaria with respect to other non-malarial causes of coma, and the greatest risk of mortality is associated with the presence of papilledema³⁷⁶. Imaging tests and CSF analyses are usually negative.

Dengue can be expressed neurologically through several different mechanisms³⁷⁷: *i*) hepatic failure or metabolic disorders (encephalopathy), direct damage to the brain tissue and meninges (meningoencephalitis), alterations of hemostasis (thrombosis or hemorrhages) or as an immune response (Guillain-Barré). In up to 50% of dengue cases with cerebral involvement, the CSF is normal. Tests to detect the dengue virus genome (RT-PCR) or viral protein (NS-1 antigen test) in the cerebrospinal fluid have variable sensitivity and specificity.

Treatment depends on identifying the causative agent and has already been mentioned in earlier sections. In the case of viral infection, only symptomatic and supportive measures can be taken. It is worth pointing out that a number of infections can be prevented by immunoprophylaxis (meningococcal, pneumococcal, rabies, Japanese encephalitis and tick-borne encephalitis) or chemoprophylaxis (malaria)³⁵⁶⁻³⁵⁸.

Urinary tract infections

KEY FACTS

KF95. The possibility of infection with extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae should always be considered in travelers with urinary tract infections, principally cases acquired in South and Southeast Asia (A-III).

KF96. In the presence of non-specific complaints and/or hematuria, urinary schistosomiasis (*S.*

haematobium) should be considered in travelers returning from traditionally endemic areas (and other more recently reported ones, such as Corsica) (A-II).

RATIONALE

Urinary tract infections represent a substantial percentage of imported infections in travelers, and are a frequent cause of fever, especially in women and older men³⁷⁸⁻³⁸⁰. From a clinical and analytical perspective, they are indistinguishable from the autochthonous forms, but not from a microbiological point of view. Travel, especially to South and Southeast Asia, has been identified as a risk factor for the acquisition of extended-spectrum beta-lactamase-producing Enterobacteriaceae (Gram-negative bacteria). Previous use of antimicrobials is an independent risk factor³⁸¹⁻³⁸³. Hence, this possibility should be considered for the empiric treatment, which can then be adjusted after microbiological tests.

Acute kidney failure is a complication that appears relatively frequently in imported infections, such as severe malaria, severe diarrhea, leptospirosis, murine typhus and hemorrhagic fevers, particularly Old World hantaviruses.

Urinary schistosomiasis (*S. haematobium*) should be considered in travelers returning from classic endemic areas (and other, more recently reported ones, such as Corsica) if there are non-specific symptoms and/or hematuria. The diagnosis and treatment of this entity have been considered in previous sections^{384,385}.

The pregnant traveler

KF97. Pregnant women are much more susceptible to certain infectious diseases, such as traveler's diarrhea, listeriosis, typhoid fever and malaria (A-II).

KF98. Various diseases that are transmitted by eating or drinking contaminated food or water (traveler's diarrhea, hepatitis E, listeriosis and typhoid fever) are more severe in pregnant women (A-II).

KF99. Mother-to-child transmission of the dengue and chikungunya viruses can occur if the mother has fever in the days close to and during birth, while the main complications of Zika appear in the first trimester of the pregnancy (A-II).

KF100. Azithromycin is the antibiotic of choice for traveler's diarrhea and typhoid fever in pregnancy (B-II).

RATIONALE

Because of physiological changes and the changes in immunity brought about by pregnancy, pregnant women are more susceptible to infection caused by certain organisms³⁸⁶. Moreover, some travel-related infections are associated with increased severity, affecting both the expectant mother and the

fetus^{150,387,388}. Finally, the use of prophylactic and therapeutic measures in the pregnant woman presents a few special characteristics. Collaboration between obstetricians, infectious diseases specialists and microbiological reference laboratories is required for all these infections.

Frequency of imported infections in pregnant women

The pregnant woman is more susceptible to some infections that are *transmitted through food and water* because of decreased gastric acid output, slower intestinal movement and alterations to the immune response system. As a result, there is a higher incidence of traveler's diarrhea in pregnant women³⁸⁹. Specific infections, such as listeriosis³⁹⁰ and typhoid fever^{391,392} are also more frequently found in this subgroup. Of the *vector-borne infections*, malaria is more common in pregnant women. This has been associated with higher CO₂ emissions and an increased body temperature. However, there are no data to indicate an increase in the frequency of arboviruses (such as dengue, Zika) in pregnant women. Nor are there data on a higher incidence of infections transmitted by other routes (respiratory or via contact with water or the soil) in this population.

Severity of imported infections in pregnant women and in the fetus

With respect to the group of infections that can be spread via the ***gastrointestinal tract***, pregnant women who develop *traveler's diarrhea* or other gastrointestinal infections may be more vulnerable to dehydration and acidemia, which increases the risk of premature birth. In the pregnant woman, *listeriosis* is generally a mild infection, but one that carries a very high risk of complications in the fetus³⁹⁰. *Typhoid fever* during pregnancy has been associated with a higher incidence of diarrhea, liver dysfunction, gastrointestinal bleeding and intestinal perforation in the mother, as well as an increase in miscarriages and fetal loss^{391,392}. All cases of fetal loss occurred in mothers who had shown symptoms for five days or more without receiving treatment; hence early diagnosis and appropriate treatment improves the prognosis of the fetus. In overall terms, infection due to the *hepatitis A virus* is no more severe during pregnancy, although there are isolated cases of fulminant hepatitis in the third trimester, as well as an increased risk of uterine contractions, premature labour and fetal death^{393,394}. Transplacental transmission is rare, although it can be transmitted to the neonate during childbirth. Infection with the *hepatitis E virus* is associated with high morbidity and mortality in both mother and fetus^{395,396}. Morbidity, in the form of acute liver failure, hemorrhagic diathesis, or kidney failure acquired in the third trimester of the pregnancy, is much more frequent than in the general population. Maternal mortality is also much higher (15-30%) than in the general population. 50-70% of babies become infected and transmission can be

perinatal or intrauterine, with 40% infant mortality.

Of **vector-borne infections**, imported *malaria*, particularly due to *P. falciparum*, acquired during pregnancy presents some special characteristics³⁹⁷⁻³⁹⁹: *i*) it is associated with a higher risk of complications in the mother (severe anemia, hypoglycemia and acute respiratory distress syndrome (ARDS)) that can lead to the death of the patient; *ii*) it is associated with miscarriages, premature birth, low birthweight and perinatal death; *iii*) it is more prevalent in VFR travelers than autochthonous travelers; *iv*) diagnosis during pregnancy may be more difficult because parasites sequester in the placenta, so reducing parasitemia in the peripheral blood. Because of this, PCR can be a useful diagnostic tool during pregnancy since it can identify parasitemia below the threshold of microscopy, and *v*) in women without immunity, there is a higher rate of congenital malarial infection (7-10%), with onset of symptoms 2-8 weeks after birth. *Yellow fever* does not seem to be more serious during pregnancy. Some studies suggest that *dengue infection* may predispose to certain complications, chiefly towards the end of the pregnancy, such as higher maternal mortality, preeclampsia, a high rate of Caesarean sections, premature birth and low birthweight⁴⁰⁰⁻⁴⁰². There is a low rate of transplacental infection, and the fetus may be minimally affected since protective antibodies are also able to pass through the placenta. Infection due to the *Chikungunya virus* during pregnancy is not more serious than in non-pregnant woman, although there are no direct comparative studies⁴⁰³⁻⁴⁰⁵. Even though the virus can cross the placenta in the second and third trimester, fetal infection and miscarriage are rare (2.5%). There is a high risk of vertical transmission, on the other hand, if the mother is infected during the 4 days before delivery. There is no evidence that *Zika virus* infection manifests in a more virulent form during pregnancy; the consequences for the fetus, however, depend on the trimester^{150,406,407}. A higher risk of neurological complications is associated with the first and second trimester, with the main consequences being microcephaly, intracranial calcifications and cerebellar abnormalities, dysgenesis of the corpus callosum and eye abnormalities.

Among the **airborne infections** that can be transmitted, influenza presents more respiratory complications in the pregnant woman and a higher rate of mortality, especially in the third trimester. It can also lead to miscarriage or premature birth, although it is not a cause of fetopathy. The SARS and MERS coronaviruses can cause rapid respiratory failure, with a high mortality rate among expectant mothers and a very high number of miscarriages and premature births.

Particular aspects of treatment and prevention of imported infections associated with pregnant women

Pregnant woman should avoid or postpone travel to areas where malaria is endemic, particularly those with *P. falciparum* resistance. If travel cannot be avoided, it is essential to take every precaution and use effective chemoprophylaxis and immunoprophylaxis⁴⁰⁸⁻⁴¹⁰. Most live attenuated vaccines containing

weakened forms of bacteria or viruses are contraindicated, with the possible exception of yellow fever vaccine in cases where the risk is very high, although it is rare in travelers. Immunoglobulin prophylaxis is considered safe and may be given following exposure to certain infections, chiefly rabies^{389,408-410}. For the prevention of malaria, the drugs of choice are chloroquine (in areas where *Plasmodium* spp. are chloroquine-sensitive) or chloroquine-proguanil in areas with resistance. Even though data show that taking mefloquine does not increase the risk of teratogenic effects, the recommendation continues to be not to take it during pregnancy. Chemoprophylaxis with atovaquone-proguanil is not recommended, because the effects on the fetus are unknown. Doxycycline is contraindicated because of teratogenic effects on the fetus⁴⁰⁸⁻⁴¹⁰.

Some specific comments may be made concerning the treatment of imported infections in pregnant women: *i) Traveler's diarrhea* should be treated promptly with appropriate oral hydration. Antiemetics (metoclopramide) or antidiarrheals (loperamide) may be given, if clinically indicated. Azithromycin is the antimicrobial of choice for diarrhea in pregnancy, and quinolone use is contraindicated. *ii) Azithromycin* is the treatment of choice for the pregnant traveler with *typhoid fever*⁴¹¹. *iii) Although treatment for intestinal parasites may be postponed, it has been established that metronidazole can be used after the first trimester of pregnancy and paromomycin throughout the pregnancy*⁴⁰⁸⁻⁴¹⁰. *iv) Treating malaria* in the pregnant traveler has been published previously in this journal¹⁷⁷. *v) Management of dengue* is conservative, with supportive treatment and monitoring of hematological status and of the neonate. *vi) The approach to possible infection with the Zika virus during pregnancy* is ongoing review, principally to avoid consequences for the neonate⁴¹².

The immunocompromised traveler

KEY FACTS

KF101. The course of malaria in immunocompromised patients (especially those infected with HIV and with low CD4+ lymphocyte counts) tends to involve more severity criteria than in non-immunocompromised individuals. Early diagnosis and treatment is essential, therefore, if there is clinical suspicion (A-III).

KF102. Immunocompromised individuals who present with traveler's diarrhea should be given the parasitology stool test, including the modified Kinyoun stain for detecting coccidian species, such as *Cryptosporidium* spp., *Cystoisospora belli* and *Cyclospora cayetanensis* (B-III).

KF103. *S. stercoralis* hyperinfection syndrome and disseminated strongyloidiasis are more frequently found in immunosuppressed patients (corticotherapy, transplants, HTLV-1 coinfection) and have very high mortality rates. Early diagnosis and treatment with ivermectin at a dose of 200 µg/kg/per day for at least

7 days is required (A-III).

RATIONALE

The number of situations that cause immunosuppression has increased in recent decades and include HIV infection, hematological and solid malignancies, transplants, asplenia, and immunosuppressive or immunomodulatory treatments. The immunocompromised traveler requires close attention because of the increased risk of acquiring certain infections or that present in a more severe form⁴¹³⁻⁴¹⁵. There are a number of studies on travelers with different types of immune deficiency that give varying data about both the prevalence of infection (36-95%) and the request for pre-travel advice⁴¹⁶⁻⁴²². With respect to pre-travel advice and preventive measures, there are some particular implications for this set of travelers and the following should be avoided: live attenuated vaccines (yellow fever, MMR (measles, mumps, rubella) and typhoid fever, among others), interactions between drugs (especially between antiretrovirals and antimalarials) and those used to prevent traveler's diarrhea^{413,423}.

In immunocompromised patients, **malaria** can be more severe; this has been noted basically in patients infected with HIV. In a study of patients diagnosed with imported malaria carried out in France, the percentage of episodes considered serious was higher in patients with HIV infection, compared to those not infected (40% vs 21%), and as high as 51% in those whose CD4+ lymphocyte counts were <350 cells/ μ L⁴²⁴. The diagnosis and treatment of malaria in the immunocompromised patient is similar to that in the immunocompetent individual. Another protozoan infection highly associated with immunosuppression is **leishmaniasis**. Although it is endemic in our region (*Leishmania infantum*), it can also be acquired after traveling to other countries. HIV infection is clearly associated with visceral leishmaniasis, increasing the risk of relapse and reducing therapeutic efficacy, although other types of immune deficiency are increasingly being reported associated with this infection, such as transplant patients and those receiving immunosuppressant treatment⁴²⁵. Of particular interest is the growing number of cases of cutaneous leishmaniasis reported in patients treated with tumor necrosis factor-alpha (TNF- α) inhibitors⁴²⁶.

Traveler's diarrhea in immune-compromised patients has a broader differential diagnosis, and there is an increasing proportion of cases caused by intestinal protozoa such as *Cryptosporidium* spp., *Cystoisospora belli* and *Cyclospora cayetanensis*. In these patients, the diarrhea is watery and tends to become chronic, even fulminant diarrhea. For diagnosis, a parasitological stool test using the modified Kinyoun stain for acid-fast bacilli is essential for viewing the coccidian oocysts⁴²⁷.

Of the infections caused by helminths, **strongyloidiasis** deserves special mention. Although in most instances it is generally asymptomatic or has only mild symptoms, it can progress in immunocompromised individuals to severe forms, such as hyperinfestation syndrome or disseminated

strongyloidiasis, and is frequently associated with corticosteroid therapy, transplants, and co-infection with HTLV-1, with mortality of around 60%⁴²⁸. Although these clinical pictures have basically been reported in the immigrant population, they have also been observed in travelers⁴²⁹. The treatment of choice for severe cases is ivermectin at a dose of 200 µg/kg/per day for 7 days, or until the symptoms cease.

Melioidosis is a bacterial infection caused by *Burkholderia pseudomallei*, which causes pneumonia and sepsis, and is mainly found in certain Asian and Australian regions³⁰⁷. Patients typically have some risk factor for melioidiasis, with diabetes mellitus being the one mainly associated, although other immune suppressing conditions can favour its appearance^{307,430,431}.

Histoplasmosis is an endemic mycosis that primarily affects the lungs, although in immunocompromised patients (especially reported in HIV-infected individuals), it may manifest as the disseminated variety. This mycosis is endemic in many areas of the Americas, Africa and Asia, and can be acquired after traveling⁴³². **Other endemic mycoses** with disseminated complications in immunosuppressed travelers are coccidioidomycosis and paracoccidioidomycosis⁴³³⁻⁴³⁵. Disseminated *Talaromyces* (formerly *Penicillium*) *marneffe* (TM) infection has also been reported in travelers to Southeast Asia with HIV infection⁴³⁶.

Web sites of interest

Apart from the key facts indicated in this document, it is useful to be familiar with various electronic websites where up-to-date information can be obtained.

Some examples are: <http://wwwnc.cdc.gov/travel>; <http://www.who.int/csr/en/>; <http://ecdc.europa.eu/en/healthtopics/Pages/AZIndex.aspx> or <http://www.istm.org/geosentinel>

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Table 1. Criteria of evaluation of the International Society of Infectious Diseases*

	Category	Definition
Strength of recommendation	A	Good scientific evidence to support a recommendation for or against
	B	Moderate scientific evidence to support a recommendation for or against
	C	Insufficient scientific evidence
Quality of evidence	I	Scientific evidence obtained from at least one properly designed randomized controlled trial
	II	Scientific evidence obtained from at least one well-designed trial, without randomization, or well-designed cohort or case-control analytic studies (preferably from more than 1 center), or multiple time series, dramatic results in uncontrolled trials
	III	Opinions of respected authorities based on clinical experience, descriptive/clinical studies or reports of expert committees

* The periodic health examination. Canadian Task Force on the Periodic Health Examination. Can Med Assoc J. 1979;121:1193-254.

Table 2. Laboratory evaluation in imported diseases: Prognostic value

Laboratory test	Measure	Prognostic value
Complete Blood Count (CBC)		Sepsis Malaria
Hemostasis		Malaria
Blood chemistry	Renal function	Malaria
	Blood glucose	Malaria
	Aminotransferases	Dengue
	Bilirubin	Malaria
	Lactate	Malaria Sepsis
Arterial blood gas (ABG)		Malaria Sepsis
Inflammatory markers	C-reactive protein	Malaria
	Procalcitonin	Malaria

Table 3. Form of isolation according to clinical syndrome

Clinical syndrome	Form of isolation	Comments
Diarrhea	Contact	If diarrhea is profuse and/or there is incontinence
Respiratory	Airborne Droplets Contact	Travelers arriving from areas with avian flu, MERS-CoV or XDR tuberculosis
Meningeal	Droplets Contact	Add respiratory isolation if symptoms and/or X-rays indicate pneumonia
Rash and fever	Droplets Contact	Add respiratory isolation if there are symptoms, vesicular lesions, or an aerosol-generating procedure is performed
Localized cutaneous	Contact	In the presence of abscesses or wounds

Table 4. Diseases that require high-level isolation and control of infection

Group of Microorganisms	Causative agents	
Viral hemorrhagic fevers (VHF)	Marburg virus Ebola virus Lassa virus Crimean-Congo virus Guanarito virus Machupo virus	Person-to-person transmission documented
	Kyasanur Forest Omsk Junin Sabia	Person-to-person transmission not documented
Orthopoxvirus	Smallpox and other highly virulent viruses	
Coronavirus	MERS-CoV SARS	
Orthomyxovirus	Emerging influenza viruses*	
Mycobacteria	Extensively drug-resistant (XDR) <i>M tuberculosis</i> **	
Bioterrorism agents	Whether or not known to be of high virulence	

* Seasonal influenza is excluded.

** Not considered to require a HLIU, although centers that have one may benefit from its use.

Table 5. Criteria for diagnosis of post-infectious irritable bowel syndrome (PI-IBS)

<p>1. Rome-IV criteria</p>	<p>Recurrent abdominal pain, at least 1 day a week in the previous 3 months, associated with 2 or more of the following:</p> <ul style="list-style-type: none"> - Associated with bowel movements - Changes in the frequency of bowel movements - Changes in stool consistency and the onset of symptoms was at least 6 months before the diagnosis 	
<p>2. Exclusion of other organic or functional processes via evaluation of clinical and laboratory data</p>	<p>Clinical data</p> <ul style="list-style-type: none"> - Fever - Macroscopic blood in stools - Inexplicable loss of weight - Age of onset >50 years - Family history of colorectal cancer, inflammatory bowel disease or celiac disease 	<p>Laboratory data</p> <ul style="list-style-type: none"> - Anemia - Leukocytosis - Elevated ESR and/or CRP - Reduction of ferritin levels in blood - Alteration of thyroid function - Markers of celiac disease - Fecal occult blood - Increased calprotectin in feces - Alterations in bacteriological and/or parasitological stool tests
<p>3. <i>De novo</i> appearance of a previously asymptomatic patient after an episode of acute infectious diarrhea</p>	<p>Episode of acute infectious diarrhea defined by at least two of the following criteria: fever, vomiting, diarrhea or positive stool culture</p>	

From Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel disorders. *Gastroenterology*. 2016;150:1393-407.

Table 6. Diagnosis of tropical sprue

Criteria	Observations
1. Compatible clinical presentation	Profuse diarrhea Loss of weight
2. Demonstrated malabsorption of 2 or more unrelated nutrient groups	Lipids (fecal fat test) D-xylose test Schilling test (late) Data of iron deficiency (infrequent)
3. Histological abnormalities of intestinal mucosa	Some flattening of the villi Most often affects the terminal ileum Eosinophilic Infiltrate
4. Exclusion of other causes of intestinal malabsorption	PI-IBS (see Table 5) Celiac disease (not tropical sprue) Anti-endomysial antibodies Tissue transglutaminase (tTG) IgA class antibodies Deamidated gliadin peptide (DGP) antibodies
5. Sustained response to empiric treatment	Doxycycline 100 mg/12 h and folic acid 5 mg/24 h for 3-6 months

Table 7. Differential characteristics of the major imported cutaneous lesions

	Morphology	Localization/distribution	Form of transmission
Cercarial dermatitis	Wheals/papules	Lower extremities	Freshwater contact
Seabather’s eruption	Wheals/papules	Areas covered by the swimsuit	Bathing/swimming in salt water
Cutaneous filariasis*	Varies according to species (see text)		
Cutaneous gnathostomiasis	Linear	Thorax and upper extremities	Consumption of raw or undercooked fish, frogs or snake
Cutaneous larva <i>currens</i>	Linear	Abdomen	Skin contact with contaminated soil
Cutaneous larva <i>migrans</i>	Linear	Areas used for support	Skin contact with contaminated soil
Cutaneous or mucocutaneous leishmaniasis	Papules/nodules Ulcers, mucosal lesions	Exposed areas	Phlebotomine sand fly bite
Furuncular myiasis	Furuncle	Exposed areas (<i>Dermatobia</i>) Contact with clothing (<i>Cordylobia</i>)	Arthropod bite Contact with clothing
Nontuberculous (atypical) mycobacterial infection	Nodules and ulcers	Sporotrichoid pattern	Contact with contaminated water or fish
Superficial or subcutaneous mycoses	Varies according to species	Hair (piedra) Palm of the hand (tinea nigra) Multiple areas (other tineas) Exposed areas (subcutaneous)	Human to human physical contact or inoculation
Arthropod bites	Wheals Papules Blisters Linear lesions	Exposed areas	Insect bites
Tungiasis	Furuncle	On the sole of the foot, on and between the toes	Skin in contact with contaminated soil/sand

Table 8. Tests useful for diagnosing imported respiratory infections

Utility	Type of test	Sample	Determination
General	Image	-	Chest X-rays (PA and lateral)
	Hematology/biochemistry	Blood/serum	Complete blood count Conventional biochemistry Arterial blood gas (ABG) Markers of inflammation (CPR, ESR, and procalcitonin)
Upper respiratory infection	Microbiological	Throat swab	Rapid test for <i>S. pyogenes</i> Bacterial culture Virus culture PCR for pertussis
		Blood (serum)	EBV/CMV/HIV serology
	Imaging	-	X-rays of the paranasal area
Pneumonia	Microbiology	Blood	Blood culture
		Sputum	Gram, auramine or Ziehl-Neelsen, KOH test, culture in specific media, DIF <i>Pneumocystis jirovecii</i> , multiplex PCR for bacteria and virus
		Nasopharyngeal swab	ICT and PCR for influenza virus
		Urine	Pneumococcal/Legionella urinary antigen tests
		Serum	Serology <i>Legionella pneumophila</i> , <i>Mycoplasma pneumoniae</i> , <i>Chlamydomphila pneumoniae</i> , <i>Coxiella burnetti</i> , <i>Chlamydia psittaci</i> , <i>F tularensis</i> , respiratory viruses, <i>Schistosoma</i> , <i>Paragonimus westernmani</i> , <i>Strongyloides stercoralis</i> , <i>microfilarias</i> , <i>Histoplasma capsulatum</i> <i>Coccidioides immitis</i>
	Invasive tests	Fibro-bronchoscopy Lung biopsy Pleural fluid analysis	

Table 9. Main clinical symptoms associated with eosinophilia in parasitic infections

Symptoms/involvement	Presentation	Parasite
Fever	Common	Katayama syndrome (<i>Schistosoma</i> spp.), Loeffler's syndrome (<i>Uncinaria</i> , <i>Strongyloides stercoralis</i> , <i>Ascaris lumbricoides</i>) Tropical pulmonary eosinophilia (<i>W. bancrofti</i> , <i>Brugia</i> spp.), Fascioliasis (<i>Fasciola hepatica</i>)
	Rare	<i>Opisthorchis</i> spp., <i>Clonorchis</i> spp.
Respiratory	Common	Katayama syndrome (<i>Schistosoma</i> spp.), Loeffler's syndrome (<i>Uncinaria</i> , <i>Strongyloides stercoralis</i> , <i>Ascaris lumbricoides</i>), Tropical pulmonary eosinophilia (<i>W. bancrofti</i> , <i>Brugia</i> spp.), <i>Paragonimus</i> spp., <i>Echinococcus</i> spp., <i>Toxocara</i> spp.
Gastrointestinal	Common	<i>Uncinaria</i> , <i>Ascaris lumbricoides</i> , <i>Strongyloides stercoralis</i> , <i>Trichuris trichiura</i> , <i>Trichinella spiralis</i> , <i>Taenia saginata</i> , <i>Taenia solium</i> , <i>Hymenolepis nana</i> , <i>Schistosoma mansoni</i> , <i>Schistosoma japonicum</i> , <i>Anisakis simplex</i> , <i>Toxocara</i> spp., <i>Paragonimus</i> spp., <i>Angiostrongylus</i> spp.
	Rare	<i>Gnathostoma</i> spp.
Cutaneous	Common	<i>Onchocerca volvulus</i> , <i>Loa loa</i> , <i>Gnathostoma spinigerium</i> , larva <i>currens</i> (<i>Strongyloides stercoralis</i>), neurocysticercosis (<i>Taenia solium</i>), cutaneous larva <i>migrans</i> , cercarial dermatitis (<i>Schistosoma</i> spp.), <i>Wuchereria bancrofti</i> , <i>Brugia</i> spp.
	Rare	<i>Trichinella spiralis</i> <i>Opisthorchis</i> spp., <i>Clonorchis</i> spp., <i>Paragonimus</i> spp.
Right upper quadrant pain/jaundice	Common	<i>Ascaris lumbricoides</i> , <i>Fasciola hepatica</i> , <i>Echinococcus</i> spp., <i>Schistosoma mansoni</i> , <i>Schistosoma japonicum</i> , <i>Toxocara</i> spp. <i>Opisthorchis</i> spp., <i>Clonorchis</i> spp.
Neurological	Common	Neurocysticercosis (<i>Taenia solium</i>), <i>Angiostrongylus cantonensis</i> , <i>Gnathostoma</i> spp.
	Rare	<i>Paragonimus</i> spp., <i>Schistosoma</i> spp., <i>Trichinella spiralis</i> , <i>Toxocara</i> spp.
Genitourinary	Common	<i>Schistosoma haematobium</i>

Table 10. Characteristics and diagnosis of the main parasitic causes of eosinophilia

			Diagnosis	
Parasites	Geographical area	Risk factors	Pre-patent period	Diagnostic tests
Nematodes				
<i>Angiostrongylus cantonensis</i>	Southeast Asia, Africa, Caribbean, Central America	Contaminated food	1-3 weeks	Larvae in cerebrospinal fluid
<i>Anisakis simplex</i>	Cosmopolitan (more frequent in Japan, Europe)	Raw fish (saltwater)	2-5 hours	Clinical Serology
<i>Ascaris lumbricoides</i>	Cosmopolitan	Contaminated food	2-3 months	Detection of eggs in feces Serology
<i>Brugia malayi</i>	Southeast Asia	Mosquito bites	3-8 months	Detection of microfilariae in blood
<i>Capillaria philippinensis</i>	Southeast Asia	Raw fish (freshwater)	>1 month	Detection of eggs in feces Intestinal biopsy
<i>Gnathostoma spinigerum</i>	Southeast Asia	Raw fish (freshwater)	>1 month	Clinical Serology Larvae in biopsy
<i>Loa loa</i>	Central and West Africa	Fly bite	5 months	Detection of microfilariae in blood Serology Presence of worms in the eye
<i>Mansonella perstans</i> <i>Mansonella ozzardi</i>	Sub-Saharan Africa/South America	Insect bite (flies, mosquito)	6-12 months	Detection of microfilariae in blood Serology
<i>Mansonella streptocerca</i>	South America, Caribbean	Insect bite (flies, mosquitoes)	6 months	Skin snip biopsy
<i>Onchocerca volvulus</i>	Sub-Saharan Africa	Fly bite	8-20 months	Skin snip Detection of adult worms in subcutaneous nodules Serology
<i>Strongyloides stercoralis</i>	Cosmopolitan	Contact with contaminated soil or mud	4 weeks	Detection of eggs in feces Agar plate culture Currens larva Serology
<i>Toxocara</i> spp. (visceral larva migrans)	Cosmopolitan		Uncertain	Clinical Serology
<i>Trichinella spiralis</i>	Cosmopolitan	Consumption of contaminated pork	2-6 weeks	Clinical Serology Muscle biopsy
<i>Trichuris trichiura</i>	Cosmopolitan	Contaminated food	2-3 months	Detection of eggs in feces
Uncinaria	Cosmopolitan	Contact with	5-6weeks	Detection of eggs in feces

		contaminated soil, mud or food		
<i>Wuchereria bancrofti</i>	Sub-Saharan Africa, Southeast Asia, India	Mosquito bite	3-8 months	Detection of microfilariae in blood Serology Rapid immunochromatographic tests
Cestodes				
Cysticercosis (larva of <i>Tenia solium</i>)	Cosmopolitan	Contaminated food	–	Imaging tests (MNR, CT) Serology
<i>Echinococcus granulosus</i>	Europe, South America, Australia	Contaminated food	Months/ years	Imaging tests (MNR, CT, US, radiography) Serology
<i>Hymenolepis nana</i>	Cosmopolitan	Contaminated food		Detection of eggs in feces
<i>Taenia saginata</i>	Cosmopolitan	Consumption of contaminated beef	2 months	Detection of eggs in feces Detection of proglottids in feces
<i>Taenia solium</i>	Cosmopolitan	Consumption of contaminated pork	2 months	Detection of eggs in feces Detection of proglottids in feces
Trematodes				
<i>Clonorchis sinensis</i>	Eastern Asia	Raw fish (freshwater)	3-4 weeks	Detection of eggs in feces Serology
<i>Fasciola hepatica</i>	Cosmopolitan	Contaminated plants	2-4months	Detection of eggs in feces Serology
<i>Opistorchis</i> spp.	Southeast Asia, Russia	Raw fish	5 weeks	Detection of eggs in feces
<i>Paragonimus</i> spp.	Southeast Asia, Central/West Africa, South America	Consumption of molluscs and freshwater crustaceans	10-12 weeks	Detection of eggs in feces Detection of eggs in sputum Serology
<i>S. haematobium</i>	Africa	Contact with contaminated freshwater	4-6 weeks	Detection of eggs in urine Bladder biopsy Serology
<i>S. mansoni</i>	Africa, South America, Caribbean	Contact with contaminated freshwater	4-6 weeks	Detection of eggs in feces Rectal biopsy Serology
<i>S. intercalatum</i>	Central/West Africa	Contact with contaminated freshwater	4-6 weeks	Detection of eggs in feces Serology
<i>S. japonicum</i>	Southeast Asia, Indonesia, China	Contact with contaminated freshwater	4-6 weeks	Detection of eggs in feces Serology
Protozoan				
<i>Sarcocystis</i> spp.	Southeast Asia (mainly Malaysia)		–	Clinical Muscle biopsy

* CT: Computerized Tomography; MRN: Magnetic Resonance; US: Ultrasound.