Practice Guidelines for Evaluation of Fever in Returning Travelers and Migrants

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Background: Fever upon return from tropical or subtropical regions can be caused by diseases that are rapidly fatal if left untreated. The differential diagnosis is wide. Physicians often lack the necessary knowledge to appropriately take care of such patients.

Objective: To develop practice guidelines for the initial evaluation of patients presenting with fever upon return from a tropical or subtropical country in order to reduce delays and potential fatal outcomes and to improve knowledge of physicians.

Target audience: Medical personnel, usually physicians, who see the returning patients, primarily in an ambulatory setting or in an emergency department of a hospital and specialists in internal medicine, infectious diseases, and travel medicine.

Method: A systematic review of the literature—mainly extracted from the *National Library of Medicine* database—was performed between May 2000 and April 2001, using the keywords fever and/or travel and/or migrant and/or guidelines. Eventually, 250 articles were reviewed. The relevant elements of evidence were used in combination with expert knowledge to construct an algorithm with arborescence flagging the level of specialization required to deal with each situation. The proposed diagnoses and treatment plans are restricted to tropical or subtropical diseases (nonautochthonous diseases). The decision chart is accompanied with a detailed document that provides for each level of the tree the degree of evidence and the grade of recommendation as well as the key points of debate.

Participants and consensus process: Besides the 4 authors (2 specialists in travel/tropical medicine, 1 clinical epidemiologist, and 1 resident physician), a panel of 11 European physicians with different levels of expertise on travel medicine reviewed the guidelines. Thereafter, each point of the proposed recommendations was discussed with 15 experts in travel/tropical medicine from various continents. A final version was produced and submitted for evaluation to all participants.

Conclusion: Although the quality of evidence was limited by the paucity of clinical studies, these guidelines established with the support of a large and highly experienced panel should help physicians to deal with patients coming back from the Tropics with fever.

Background

Today, more and more people are crossing borders, either temporarily as tourists or permanently as migrants. Travelers who move into different climatic zones are often exposed to pathogens not encountered in their own country, and they are usually fully susceptible to them. Tourists may fall ill after their return with diseases rarely encountered by the health services of their home country. Similarly, migrants may become ill after arrival as a result of infections acquired before they left their own countries or during their trip. Fever is one important and frequent symptom in travelers upon return from tropical or subtropical regions.[1,2] Apart from specialists in travel or tropical medicine, physicians often feel uneasy when dealing with imported fever, because they do not have extensive knowledge about tropical diseases, and they are confused by the wide differential diagnosis and the numerous diagnostic tests potentially available. Moreover, they know that some tropical diseases can be rapidly fatal when not recognized and treated immediately, such as malaria, typhoid fever, or meningitis. Little evidence-based information exists to guide clinicians on which specific diagnostic tests to propose in a particular situation[3] and when to consider presumptive treatment.[4] Thus, there is considerable variation in the management of such cases.[5] A computer program has been developed to assist physicians in the differential diagnosis of fever (*GIDEON*, Global Infectious Disease and Epidemiology Network, San Francisco, CA).[6] It is an excellent tool for teaching

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and practical case solving, since it gives an exhaustive list of all possible diagnoses; however, it does not provide indication on the management of such cases (specific diagnostic procedures and treatment), and is not freely available for health professionals.

We therefore decided to develop practice guidelines for the evaluation of fever in travelers and migrants in order to support decision making and improve the knowledge of physicians, using an evidence-based approach completed by a process of gathering explicit international expert opinion. To be useful for all,these guidelines are available free of charge on the website <www.fevertravel.ch>.

Objectives

Physician's Perspective

The guidelines will help the physician in charge of a patient presenting with fever upon return from a tropical or subtropical region in the evaluation and decision making, by providing evidence-based suggestions about: (1) asking relevant questions on the travel experiences and the health problems;(2) looking for specific signs; (3) deciding on which specific diagnostic test(s) to perform; (4) deciding whether it is appropriate to propose presumptive treatment or not;(5) deciding on the need for hospitalization.

The guidelines are also aimed at improving knowledge about tropical diseases among physicians and other health care professionals.

Patient's Perspective

The use of the guidelines by physicians should help patients by reducing (1) morbidity (duration and severity of symptoms) and potentially mortality; (2) exposure tounnecessary invasive procedures or drugs with potential adverse events;(3) unnecessary transfer to a specialized center or hospitalization. Finally, the use of a more rational approach should reduce costs.

Target Audience

Given the large variation in knowledge and practice of medical professionals about care for returning travelers presenting with fever, we have defined a target audience that includes primary care practitioners, specialists in internal medicine, emergency care, and infectious diseases as well as beginners in travel medicine. The decision chart is not designed for experts working in reference or specialized tropical medicine centers.

Target Population

The guidelines should be useful for health professionals caring for travelers and migrants coming from a tropical or subtropical region (i.e.,where the epidemiology of communicable diseases is clearly different from the one of temperate climates) and complaining of fever. This is defined as a history of raised temperature or feelings of alternating hot and cold or chills, sweating,or headache or an axillary temperature of more than 37.5°C. This broad definition allows patients to be included who complain solely of symptoms that often accompany fever. This was the case, for example, for 3% of malaria patients (mean value from several studies, reviewed in Genton and D'Acremont[7]).Although migrants constitute a distinct population from returning travelers, we decided to include them as a target group for our guidelines since they have been exposed to the same agents and can present,therefore, similar diseases. We acknowledge that the probability of some diagnoses is either higher (e.g.,tuberculosis) or much less (i.e.,Katayama fever, Löffler syndrome),but is never equal to zero. Indeed, with globalization and considerable population movements, the physician in charge is not always aware that migrants may have transited or lived temporarily in areas where diseases other than those present in their country of origin can be present. Moreover, although the prognosis of some diseases is different in migrants than returning travelers, the clinical presentation at the onset of symptoms is the same,[8-10] and the decision chart is therefore appropriate. Also, in the latter, we do not take into account the incidence of the diseases mentioned, which means that there is no reason to make a distinction between returning travelers and migrants. So the results of the studies, and hence the evidence, are based on studies made of mixed populations. The guidelines are not designed for pregnant women, children less than 8 years old, immunocompromised patients, or patients with severe underlying chronic disease. When the patient has already taken antimalarials or antibiotics, the algorithm should be used with caution.

Methods

Documentation Available

In a systematic review of the literature performed up to April 2001, we extracted publications from the *National Library of Medicine* database by a *MEDLINE* search using the keywords "fever + guidelines (or synonyms)" or "travel (or derivates) + guidelines (or synonyms)"or "fever + travel (or derivates)"or "fever + migrant (or derivates)". For several diseases (the majority of those mentioned in the decision chart), we searched using "travel + name of the disease". We also explored the *Cochrane Database of Systematic Reviews* using "fever"as a search term,the *HealthSTAR* database using "fever or travel", and the *Current Contents Clinical Medicine* database using "fever + travel".Additional articles were selected from the reference list of some key papers. Two

institutional guidelines were obtained directly from the authors (Guidelines for doctors, Hospital for Tropical Diseases, London, unpublished data, 2000) and Ebnöther.[11] From the 1,709 titles retrieved, we selected 250 articles based on the title or, in case of doubt, the abstract. Only one of the latter was presented as a guideline for fever in the international traveler.[12] Four articles consisted of randomized controlled trials, and 15 were prospective or case-controlled studies. The remaining documents included descriptive case series. These series were usually small and the discussion of the results was most often mixed with additional personal experience and opinions.

Drafting and Evaluation of the Guidelines

Based on the documents listed above and on our own experience,[4] we constructed a draft decision chart. For each step of the decision chart, we also documented the background, corresponding level of evidence, main points of debate, final proposals and grade of recommendation. We compared our differential diagnosis with the one obtained after entering similar conditions, such as history, symptom(s), sign(s), laboratory value(s), in the *GIDEON* software.[6] The guidelines and attached document were then reviewed by a first group of European experts (development panel), including 6 specialists in tropical and travel medicine from reference centers or university outpatient clinics, 2 specialists in tropical medicine, working as private practitioners, 1 specialist in infectious diseases from a university center, and 2 specialists in general internal medicine, working as private practitioners. They all gave their views individually on the target population, the potential users, and the basic assumptions, and they made an appraisal of the format and content of the algorithm. Written comments and proposals for changes were sent by mail by the experts of the development panel, and we prepared a second draft.

This draft was discussed in detail with a second group of 15 international experts in travel and/or tropical medicine (assessment panel with members of all continents but Oceania), attending the 7th Conference of the International Society of Travel Medicine (CISTM) in Innsbruck, Austria, in June 2001. Members of this panel were invited, and provided with the draft documents in advance. After the meeting, they gave written suggestions. We then elaborated a third draft. In a final step, the experts of both the development and assessment panel were asked to evaluate the revised version quantitatively, using a scale graded from 1 (extremely inappropriate) to 9 (extremely appropriate) for each step of the decision chart. Since several changes have been made in the next and final version due to convergent suggestions or important comments of the experts, the grading of appropriateness (grade of recommendation) and its variability (level of consensus) are not mentioned in the present paper. Indeed, they would not reflect the experts' opinion on this last version. But they had already been solicited several times, and the process tended to be indefinite.

Decision Chart Design

We made a list, based on the existing literature, of each key feature of the patient's history, the physical examination, and the basic laboratory tests that are relevant for the establishment of a single diagnosis, a narrow differential diagnosis and/or a treatment plan. These features were selected using two main criteria: (1) conditions that represent an immediate or deferred vital risk for patients themselves or their close contacts; (2) conditions sufficiently specific to suggest at least one specific nonautochthonous diagnosis. Symptoms, signs, or laboratory abnormalities that are found in most of the tropical diseases (e.g., headache, myalgia, arthralgia, adenopathies, mild liver impairment) have not been retained as an entry criterion. We then considered all tropical diseases that can present with at least one of these features. At each step, we retained the diseases for which the feature(s) had a reasonably high specificity, based on common knowledge and on the case series available. A procedure to lead to the diagnosis and/or management of the patient was developed. Finally, we formatted all the data into a decision chart.

General structure of the decision chart. In the Initial Evaluation section of the algorithm (see Appendix), following a general warning on the necessity of malaria tests and on the restrictions of the algorithm to tropical or subtropical diseases (not autochthonous ones), a set of 18 main steps is listed. All steps should be dealt with one after the other. When the response to a step is yes or positive, the examining physician should look at the corresponding tree development, which is either on the initial evaluation pages for the first 4 steps ("any danger sign"; "any bleeding sign, including petechiae"; "contact with body fluids…," and "malaria-endemic area") or on separate pages for the next 14 steps (Figures 1 to 14 in Appendix). When the response to a step is No or Negative, the next step should be considered.

The steps are structured as follows: the first 4 steps are the assessment of parameters of the history or physical examination that should lead to the decision of immediate hospitalization and management of the patient. The next 5 steps are a set of specific questions related to travel history. Then there are 8 steps asking about selected symptoms or signs, and a last step corresponding to 1 abnormal laboratory result. When all steps have been reviewed and none of the responses are Yes or Positive, the algorithm leads to a final box, which describes the appropriate case management.

Structure of the figures themselves. A branching structure starts with either a clinical or paraclinical question (for which two or three answers are possible) or a list of one or more possible diagnosis(es) to consider. Diagnoses that should be considered but have already been mentioned in a preceding step of the decision chart, where a necessary condition is the entry criterion, are indicated at the bottom of the figure as a reminder; for example, in Figures 5, 8, and 13, "malaria has already been considered in the Initial Evaluation section" (after "malaria-endemic area"). Some of the items (question or diagnosis) are associated with one or two condition(s), introduced by "if...", related to the travel history (generally the destination and/or the time from return [usually the last day of exposure] up to the first symptoms [Time RS] and/or the time from first exposure to the first symptoms [Time ES]) or, rarely, the presence of another symptom or sign. The list of questions or diagnoses leads finally to one of four decisions: (1) to perform specific investigations (sometimes after contact with a specialist in travel/tropical medicine); (2) to give specific treatment (either presumptively or after documentation of the diagnosis); (3) to hospitalize the patient; (4) simply to consider the next step on the decision chart.

Some boxes in the figures have been shaded to indicate that, at this point, a physician with limited skills in the field (light) or any physician (dark) should consult a specialist in travel/tropical medicine. The choice of the threshold for such consultation was extensively discussed with private practitioners and other experts. It will depend on the expertise of the user, and can only be an indication.

Notes on the Use of the Decision Chart

For an appropriate reading and use of the algorithm, the following points should be kept in mind:

1. Only crucial clinical and laboratory parameters to consider for the management of a presumed or documented disease are mentioned. Apart from the malaria test and full blood count, investigations to be done in a patient presenting with fever are left at the discretion of the physician.
2. Except for malaria and schistosomiasis, no information on the follow-up after the first assessment of the patient is given.
3. To be useful, the laboratory results should be obtained within 24 to 48 hours after the initial visit (except for the malaria tests which should be obtained within 3 hours).
4. When a diagnosis is confirmed by a specific test, no further investigation is necessary, except in the presence of an atypical symptom or sign.
5. When a presumptive treatment is proposed, the laboratory tests for a retrospective diagnosis are not mentioned in the figures.
6. When "ad hosp" is given to indicate hospitalization at the end of a figure, the patient should not be followed as an outpatient. For all other proposed attitudes, the decision to hospitalize the patient is left at the discretion of the physician in charge.
7. The list of the diagnoses proposed under the heading Consider is not exhaustive. It includes the most frequent diseases and the ones that can potentially be rapidly fatal.
8. Diseases with a very localized epidemiology are usually not mentioned; if none of the diagnoses mentioned is plausible, a specialist in tropical/travel medicine should be contacted.
9. No estimation of the relative probability of each diagnosis in a given situation has been mentioned since no good incidence data exist.
10. Although very rare, some diseases have still been included (i.e., Marburg disease or melioidosis), since they bear a high case fatality rate.
11. When there is a contraindication to the specific drug proposed for treatment, alternatives should be discussed with a specialist.
12. When the reading of the entire algorithm leads to two or more different diagnoses, decisions and/or presumptive treatments, all should be considered in parallel. When the situation is too complex (many symptoms or signs are present), a specialist in tropical/travel medicine should be contacted.

Use of the Chart in Different Countries

Some important points should be considered:

1. For the sake of clarity, most autochthonous diseases that would be considered in a nontraveler are deliberately not mentioned but should always be considered in parallel to the tropical diseases. The guidelines may, however, need some refinements according to the country where they are to be used, since autochthonous diseases are by definition specific to the country. In addition, for some diseases, changes may be needed to bring the chart into line with the standard policy in a given country; for example whether patients with falciparum malaria should be hospitalized.[13]
2. Autochthonous diseases are included when the incidence rate differs between travelers/migrants and the general population in the country where the chart is used (e.g., human immunodeficiency virus [HIV], hepatitis A or B).

Computerized Version of the Decision Chart

In order to simplify and to widen the use of the decision chart, a computerized version is now available on the website <www.fevertravel.ch>.

Procedure for Updating the Recommendations

The senior authors of this publication (BG, BB) will be responsible for bringing the guidelines up to date in response to the emergence of new evidence or new diseases in the field of travel/tropical medicine. The literature review will be regularly updated,and changes to the guidelines will be made accordingly. A formal reassessment and revision of the guidelines will be made with a maximal delay of 3 years.

Recommendations

For each of the 18 steps, a short discussion is presented in the paper, summarizing the evidence-based information extracted from the literature, the level of evidence for the whole figure, the key points of debate about the content, the final proposals made for those points,and the grade of recommendation for the figure. The levels of evidence and grades of recommendation have been determined according to the Oxford Center for Evidence-Based Medicine scale (version, May 2001).[14] When studies on the main subjects of the figure had different levels, the best level was chosen.

Initial Evaluation of Fever (see Appendix)

Any danger sign. Whatever the medical problem of the patient, specific signs known to be associated with an increased risk of death should lead to immediate hospitalization.Some signs have been shown to carry a bad prognosis for diseases rapidly lethal in a febrile patient upon return. These are, any degree of neurologic impairment with meningitis or malaria and respiratory distress with malaria.[15]

- Level of evidence: 2b
- Grade of recommendation: B

Any bleeding sign, including petechiae. Imported cases of hemorrhagic fever are very rare:from 1984 to 1998, only 3 cases of the contagious species were notified in the United Kingdom[16]; from January to August 2000, 5 cases of Lassa fever were reported in Europe.[17]

Because some of the hemorrhagic fevers are highly contagious and have a high mortality rate, it is of prime importance to rapidly rule out the diagnosis of hemorrhagic fever in a patient upon return. The viruses causing Crimean-Congo, Ebola, Marburg, and Lassa fever are those for which a nosocomial amplification (person-to-person transmission) has been proven. The decision to isolate the patient, obviously after discussion with an expert, must be the first action. There is a consensus that these diseases should only be considered when the time from the end of exposure (usually return) up to the first symptoms (Time RS) does not exceed 3 weeks. The major debate is about the minimal conditions, which make it reasonable to consider these diagnoses. One criterion is the country, or even better the area,visited. Considering a diagnosis of hemorrhagic fever in travelers coming from regions with a recent epidemic is certainly not enough.Considering all places known to be endemic is feasible for Crimean-Congo (parts of Asia, Eastern Europe, East-, West- and South Africa),Ebola, and Lassa fever (a few sub-Saharan African countries [18]), but not for Marburg virus, which is present in too many countries.

Each temperate country has its own policy, but these are often considered impractical by the physicians concerned,because where the criteria are wide, a huge number of patients would meet them and thus be unnecessarily isolated. Furthermore, since the procedures for isolating patients and their body fluids are time consuming,the patient might be left with no treatment of any kind for a long period of time and die of a rapidly lethal disease other than a hemorrhagic fever, such as malaria. The international expert panel found it reasonable to restrict the measures of isolation to specific patients,i.e., those with fever and hemorrhagic signs who had come in the last 21 days from an area where cases of viral hemorrhagic fever have been reported in the last 5 years. For those patients, immediate contact with experts should be made. A presumptive treatment for falciparum malaria should also be strongly considered.

- Level of evidence: 5
- Grade of recommendation: D

Contact with body fluids of a person or animal potentially infected with Crimean-Congo, Ebola, Marburg, or Lassa fever virus. Since hemorrhagic signs are not always present, viral hemorrhagic fever should also (and perhaps primarily) be suspected in the case of a history of contact with body fluids of a person or an animal potentially infected with one of these viruses; for example, a biology student returning from Côte d'Ivoire with Ebola after having assisted in the dissection of a monkey.[19]

- Level of evidence: 5
- Grade of recommendation: D

Malaria-endemic area. Any febrile traveler (as defined previously) coming back from an endemic area (if the Time ES is at least 6 days) should undergo all available tests for malaria (at least a thin smear; an additional thick smear is very useful to increase sensitivity, and a rapid antigen test to speed up availability of the result).After long discussion, the experts in travel medicine agreed that the results should be obtained within 3 hours.As soon as one of the tests is positive and whatever the species of

Plasmodium is (since mortality has been documented for all species), the physician should carefully assess the patient and decide whether hospitalization is required, following the national or local policy. In countries were hospitalization for falciparum malaria is not mandatory, outpatient management is possible after exclusion of symptoms and signs associated with a bad prognosis.[20] A list of clinical and laboratory criteria for hospitalization has been validated in a prospective study in an outpatient clinic in Switzerland and can be used for guidance.[13] The mostappropriate treatment (depending on the degree of severity, the species and density of parasites, the origin of infection, the potential contraindications, and the standard national policy) should be given, and a close clinical and parasitologic follow-up insured. Malaria tests should be repeated every 12 to 24 hours, at least twice[21] when they are initially negative and no clear alternative diagnosis can be made.[3] A frequent problem is that malaria test results are only available after a long delay, mainly because of the lack of experience of microscopists in western laboratories. The expert panel considered that, when the delay exceeds 3 hours and no other diagnosis is documented, oral treatment should be given on presumptive grounds, provided the probability of malaria is high, that is, in the presence of an enlarged spleen, or a platelet count $<150\times10^9$/L or an hemoglobin level <12g/dL (likelihood ratios for a positive diagnosis of malaria of 13.6, 11.0, and 4.6 respectively).[4]

- Level of evidence: 2b
- Grade of recommendation: A (because of the high incidence of malaria among febrile travelers, of the high mortality when left untreated and the high level of consensus of the panel participants)

Skin Contact with Fresh or Brackish Water in Schistosomiasis-endemic Area and Time RS less than 12 Weeks and Time ES more than 2 Weeks (Fig. 1)

Conditions suggestive of schistosomiasis. A history of skin contact with fresh (or brackish) water suggests schistosomiasis. In a retrospective study of 595 asymptomatic long-term travelers to schistosomiasis-endemic areas, 19% of those who reported frequent contact with fresh water, 13% of those who occasionally had contact and 5% of those who reported no contact at all were found positive by enzyme-linked immunosorbent assay (ELISA).[22] In an outbreak among 29 travelers, only one who had not been swimming remained seronegative.[23] In 16 cases of Katayama fever, all had swum in water known to contain schistosomes.[24] In a cross-sectional study of expatriates and tourists near Lake Malawi (a place of very high endemicity), the 1-day absolute risk of acquiring schistosomiasis was between 52 and 74%.[25] A history of swimming itch just after bathing was found only in 36% of 25 travelers in a case series recollected during 15 years.[26] The endemic areas for schistosomiasis are well defined.[27] Many travelers have been infected after swimming or diving in Lake Malawi [25;28]. The incubation period for Katayama fever ranges from a minimum of 2 weeks (Time ES) to a maximum of 12 weeks (Time RS).[29] In the studies mentioned, the ranges were 14–63 days[23] and 15–60 days.[30]

Diagnosis of schistosomiasis. Since the majority of confirmed cases of Katayama fever have no physical signs apart from fever (9 of 16 patients in Doherty and colleagues[24]), the diagnosis is generally made on the basis of a combination of conditions, i.e., history of recent exposure + negative malaria slide + eosinophilia. Eosinophilia is more sensitive than serology early in the course of Katayama fever (14 of 16 versus 4 of 16, respectively, at the time of admission[24]). Combining both tests increased the probability of confirming the diagnosis at an early stage. When both tests are initially negative, but schistosomes are indeed present, an additional eosinophil count performed 6 days later will certainly be elevated. Searching for ova in stools or urine is not useful in Katayama fever; in the cases described by Visser and colleagues,[23] the first egg appeared 45 days after exposure.

Treatment of confirmed schistosomiasis. Since acute schistosomiasis is a self-limited condition with nonspecific symptoms and signs, it is often misdiagnosed as a viral illness and left untreated. Some patients may eventually receive treatment because of a symptomatic chronic phase but others (probably the majority) will never be treated. Nevertheless, complications of schistosomiasis in travelers have seldom been reported, probably because the parasite load is usually light in travelers. One case of late complication in a traveler was reported namely a dorsal myelitis that developed 1 year after exposure and resolved completely with treatment.[31] Some physicians, therefore, suggest that patients should be treated with praziquantel at an early stage to prevent neurologic sequelae.[32] However, early treatment often leads to transient exacerbation of the symptoms of Katayama fever or even to severe allergic reaction.[33] The majority of experts in tropical medicine, therefore, advise administration of corticoids during the acute phase[34] and to wait until recovery (and generally until confirmation of the diagnosis by positive serology) to give praziquantel (or repeat the dose of praziquantel if it has been given already). New data on the efficacy of artemether against the early stages of infection may lead to a change in the therapy of Katayama fever.[35]

- Level of evidence: 4
- Grade of recommendation: C

Professional Contact with Farm Animals or Swimming or Rafting in Freshwater and Time RS less than 4 Weeks (Fig. 2)

Conditions suggestive of leptospirosis. Infected individuals usually have a history of swimming, rafting, or wading in fresh surface water.[36,37] In a study of 32 confirmed cases in travelers, all but one had had contact with water (21 had participated in a rafting tour[38]). Risk factors for contracting the disease during rafting were ingestion of water or immersion underwater.[36] Other possible sources of contamination are contact with dogs, farming, or gardening in contaminated soil.[39] In a study in The Netherlands, autochthonous cases occurred in people working in the fields, whereas travelers had caught it through leisure activities involving water.[40] Since leptospirosis is a common cosmopolitan zoonosis found in virtually every country (see *GIDEON* software[6]), no definite endemic area can be defined.

In a study of an outbreak among travelers,[36] the median time from the first day of exposure to the first symptoms was 12 days. In a recent outbreak, involving participants in the Ecochallenge 2000, the maximum time from the first day of exposure and first symptom was 23 days.[41]

Diagnosis of leptospirosis. Beside the history of exposure, the key features leading to a suspicion of leptospirosis are the presence of jaundice (see Fig. 5), conjunctival suffusion, or mild liver/renal impairment. Each of these conditions is present in only about half of the patients, but conjunctival effusion is the most specific.[42] The earlier the patient presents in the course of the disease, the less likely is the presence of specific symptoms.

Blood cell count is unspecific and the diagnosis at this stage relies almost exclusively on specific diagnostic tests.[29] The microscopic agglutination test (MAT) comparing acute and convalescent sera is the gold standard, but its use is restricted to experienced laboratories, and the result gives only a retrospective diagnosis.[37] A blood culture taken rapidly after onset of symptoms may become positive, but the spirochete will take 1 or more week(s) to grow. In the course of the disease, the sensitivity of the different alternative tests will vary considerably according to the time between onset of symptoms and collection of sample; MAT with a titer ≥1:100 (threshold that may have poor specificity for recent infection) is overall the best. A case-control study in Les Seychelles (case definition: leptospirosis confirmed by a fourfold increase in acute/convalescent level of antibodies by MAT, or by a positive polymerase chain reaction [PCR] at any stage) showed that during the first 4 days of symptoms, 4% of indirect hemagglutination assays, 12% of dipstick assays detecting immunoglobulin M (IgM), 16% of ELISA, 36% of MAT (with a titer ≥1:100) and 38% of PCR were positive.[43] When the serum was taken between the seventh and the tenth day of symptoms, the rates changed to 29%, 79%, 71%, 88%, and 46%, respectively. In another study in confirmed autochthonous cases in the United States, 71% of the acute samples taken on the day of admission (mean time from onset of symptoms to the collection of the sample: 6.1 days, range 1–17) were positive using a commercial dipstick assay.[42] In the various studies, the specificities of these different tests were similar (over 90%) and thus high enough for febrile travelers in whom leptospirosis is a rare disease.

Treatment of presumptive or confirmed leptospirosis. Icteric cases should be hospitalized immediately (see Fig.5).[42] Anicteric cases, provided they do not meet a criterion mentioned in the Initial Evaluation section ("Any danger sign"), can generally be managed as outpatients. Treatment should be initiated early in the course of the disease with doxycycline, amoxicillin, or penicillin because of the potentially fatal outcome of leptospirosis and because it has been demonstrated that antibiotics are efficient, especially when given during the first 2 days of symptoms.[36,37] In the study by van Crevel and colleagues, only 44% received adequate antimicrobial therapy, but all recovered completely.[38]

We recommend that, in a suspected case (fever + compatible exposure and incubation + conjunctival suffusion) that presents early (before the seventh day of symptoms), it is wiser to give a presumptive treatment straight away (and confirm retrospectively the diagnosis by MAT or by any other kind of serology) than to wait a few days for the serology result. When the patient presents after the seventh day of symptoms (and even in the absence of conjunctival suffusion), it is worth doing serology as its sensitivity will then be high enough to treat only when positive, particularly because the treatment becomes less urgent (the clinical manifestations being then mainly immunologically mediated).

- Level of evidence: 3a
- Grade of recommendation: B

Sexual Contacts with a New Partner or Injections Received (Fig. 3)

Conditions suggestive of primary HIV illness. The classical presentation of primary HIV illness is easily mistaken for tropical diseases (fever, adenopathy, rash, features of aseptic meningitis, leucopenia, and/or thrombopenia). Pendle and Sacks[44] found that a history of recent travel initially confused the diagnosis. Among the 11 patients investigated, 55% had a transient, macular or morbilliform rash, similar to that of rickettsiosis or arbovirosis. The most consistent and specific sign was the presence of a palatal enanthema.

The key feature to suggest acute seroconversion illness is a history of possible exposure to HIV, but patients are sensitive about giving such information, and it is often

omitted. Pendle and Sacks reported that the incubation period ranged from 6 to 56 days.[44] However, very often a traveler who takes risks of getting HIV while abroad also takes risks in his own country.[45] No Time RS is therefore indicated.

Diagnosis of primary HIV illness. Since serology is often negative at this stage, the diagnostic criterion is antigen positivity (p24), in the absence of clinical features of acquired immunodeficiency syndrome (AIDS). Reverse transcription (RT)-PCR is a complementary option when p24 is negative, but cannot be systematically recommended because of its cost. This test is left at the discretion of the attending physician, depending on the financial resources of the patient. In the series of 11 patients investigated by Pendle and Sacks, 6 had serologic tests positive for a recent infection with another agent (3 rickettsia, 1 Coxsackie virus, 1 mumps, and 1 mycoplasma).[44] Whether these results represented anamnestic responses to an acute HIV infection (polyclonal response to B cell stimulation) is unclear, but they may serve further to confound the diagnosis.[44]

Management of primary HIV illness. Since patients are highly contagious during the acute illness, it is essential to brief them in order to avoid further transmission and investigate the sexual partner(s). Although not formally proven, some evidence exists to support rapid initiation of tritherapy.[46]

- Level of evidence: 3b
- Grade of recommendation: B

Consumption of Raw Dairy Products and Symptoms for more than 7 days (Fig. 4)

At present most of the reported cases of brucellosis are imported and associated with the consumption of dairy products.[47,48] The clinical presentation is rather unspecific (except in case of bone or joint involvement) and generally subacute. The diagnosis is often made after several days or weeks of fever (undulant fever), once all other causes have been excluded[47]; documentation is done by serology or prolonged blood culture during 7 to 10 days.[49]

Since brucellosis is a rare cause of fever in travelers, and because the treatment includes a combination of antibiotics for at least a month, a laboratory confirmation should be obtained before starting therapy. However, the earlier the diagnosis is suspected and the specific investigations are initiated, the lower is the risk of serious acute or chronic complications.

Another possible disease associated with consumption of raw dairy products, seen more often in migrants than in short-term travelers, is *Mycobacterium bovis* infection (accounting for 1–3% of all tuberculous disease).[50] This infection is expressed more often in extrapulmonary sites (cervical and mesenteric nodes, the peritoneum, and the genitourinary tract) than are other infections due to *Mycobacterium tuberculosis* complex. In San Diego, over a 12-year period, up to 50% of the patients presented with extrapulmonary disease.[50] The proportion of transmission by ingestion of unpasteurized milk versus aerogenous transmission is not known.

- Level of evidence: 4
- Grade of recommendation: C

Jaundice (Fig. 5)

Acute viral hepatitis (mainly due to hepatitis A virus [HAV] or hepatitis B virus [HBV], less frequently to hepatitis E virus, [HEV] and rarely to hepatitis C virus [HCV]) is probably the most frequent cause of febrile jaundice in travelers,[51] although the incidence is declining due to extensive vaccination.

In the absence of other specific or danger signs, the result of serologies for viral hepatitis should be awaited before considering another diagnosis. When the results for all hepatitis viruses are negative, the patient should be hospitalized to be carefully investigated for tropical and nontropical causes. The second most common cause is malaria. When a patient with malaria presents with jaundice, the parasitemia will usually be high enough to be detected by microscopy.

Fever and jaundice (often in the context of mild liver impairment) are signs found in various tropical infections,[52] but are generally associated with other major symptoms or signs mentioned in the other figures of the algorithm. This is the case for amebiasis and fascioliasis, which are characterized by abdominal pain and/or liver enlargement/tenderness; rickettsiosis, in which jaundice is a sign of severe advanced disease; trypanosomiasis, in which a chancre is found; Lassa fever; Rift Valley fever; and dengue hemorrhagic fever, in which jaundice is accompanied by severe liver impairment.[51]

Other diseases are associated with fever and jaundice only.

1. Typhoid fever: in one study, 30% of children presented with jaundice.[53]
2. Yellow fever: one imported case presented with jaundice as the first specific symptom (on the fourth day after symptoms onset).[54] Another imported case had sudden onset of fever associated with one episode of hematemesis as the only specific sign. This patient was suspected of having viral hemorrhagic fever, and all appropriate measures were taken. The jaundice appeared on the third day.[55]
3. Leptospirosis: other dangerous signs generally accompany jaundice when the bacteria are of the icterohemorrhagic serovar. Other serovars leading to milder forms of the disease can still produce jaundice.

In a series of 159 cases of confirmed leptospirosis (37% of which were of the icterohemorrhagic serovar),52% had jaundice.[40] In another, including 32 cases (only 4 of which were of the icterohemorrhagic serovar), 25% had jaundice.[38] A case of icteric leptospirosis should be hospitalized immediately, generally in the intensive care unit for close management of the associated renal insufficiency.[42]

4. Relapsing fever: louseborne relapsing fever often leads to impairment of liver function and jaundice; 23% in an Ethiopian study of an outbreak (there is no information in travelers).[56] It may occur in tickborne relapsing fever but not as commonly; it was present in 10% of confirmed cases reported in the United States and Canada.[57]

- Level of evidence: 4
- Grade of recommendation: C

Maculopapular Rash (Fig. 6)

Rashes can be roughly divided into petechial or maculopapular. When the rash is petechial, the patient should be considered as having a bleeding sign and be hospitalized as mentioned in the Initial Evaluation section ("Any bleeding sign including petechiae").

Rash is a sign found in various tropical infections,[51,52] among which only those that can manifest themselves with fever and rash are listed in Figure 6. In the other infections, rash is associated with major symptoms or signs mentioned in other figures of the algorithm:leptospirosis will be suspected from the history (see Fig. 2); plague, anthrax, or trypanosomiasis are associated with an eschar or a chancre (see Fig.7);bartonellosis can be associated with a maculopapular rash, but the only type that is not autochthonous (the South American one) is a septicemia without any rash;HBV has other major clinical criteria (Figs.5,12), as does histoplasmosis (Fig. 8). The possibility of a drug reaction should not be omitted in travelers who are prone to take self-administered drugs during their trip.

Several important diagnoses should be considered:

- dengue
- rickettsiosis
- typhoid
- relapsing fever
- primary HIV illness

Conditions suggestive of dengue fever. Dengue fever is endemic or potentially endemic in more than 100 countries, i.e., in the greater part of the tropical and subtropical areas. It is now recognized as a frequent disease in travelers,probably underdiagnosed because of the poor specificity of its clinical presentation.In a study among Israeli travelers to Southeast Asia, the attack rate of symptomatic disease (defined as febrile illness with positive antidengue IgM) was estimated at 3.4 of 1000 (the median length of travel, which is crucial, is unknown).[58] Reports of the disease in travelers frequently mention it being acquired in Thailand[59] (especially between March and July[58,60]), India, or the Caribbean islands,[61] depending mainly on the usual destination visited by the tourists from the reporting country. The maximum Time RS reported in travelers was 14 days.[62]

The percentage of confirmed cases among suspected cases depends highly on the inclusion criteria. In the study by Jelinek and colleagues,a suspected case was defined as a patient returning from an endemic area and having either fever + arthralgia/myalgia + headache or rash; among the latter, only 7% had a serologically confirmed recent infection.[63] It was not specified whether a negative blood slide for malaria was an inclusion criterion. In the study by Shirtcliffe and colleagues, 25% of all the diagnostic tests performed for suspected cases of dengue fever (included retrospectively and without defined criteria) were positive.[62] Magill and colleaguesreviewed the Centers for Disease Control and Prevention (CDC) reports from 1986 to 1995 and showed that among 1,377 samples of suspected cases, dengue was confirmed in 21% of them.[39] None of these studies was designed to determine the predictive factors for dengue. Only Shirtcliffe and colleagues compared the clinical presentation of the serologically positive patients with the negatives ones, and they found no difference.[62]

The rash is classically described as macular or maculopapular and localized on the trunk, the limbs, palms,and soles.[64] However, in practice, the rash is often atypical. In travelers,a rash was present on admission in 33%[62] to 59% of the cases.[61,65] The fact that the rash is inconstant, delayed,and unspecific in dengue fever means that this sign is of limited value for the diagnosis.[64]

A more specific symptom is retroorbital pain,[39] but in the studies, this symptom is not distinguished from general headache, and its likelihood ratio cannot therefore be estimated.

Thrombopenia or liver function abnormalities are frequently reported (47% had thrombopenia and 27% abnormal liver tests in the study by Shirtcliffe and colleagues,[62] 100% had thrombopenia in the study by Schwartz and colleagues[60]) but are nonspecific.

Diagnosis of dengue fever. The diagnosis is usually made retrospectively by serology, comparing IgG levels in acute and convalescent sera (isolation of the virus itself by culture is very rare and the result is only obtained after 5 days). Serology is thus of little use in the acute phase and can even be falsely positive in travelers previously vaccinated against Japanese encephalitis (JE) or yellow fever (YF).[66]

New rapid tests that detect both IgG and IgM (e.g., PanBio, Brisbane, Australia) have been developed.[67] In a

study among travelers in Israel, those with clinical dengue fever who could be followed daily from the onset of symptoms had detectable IgM between the fourth and the eighth day.[66] The control group (who had not traveled) were all IgM negative, whether vaccinated or not. For IgG, 17% and 44% of the group vaccinated for JE or YF, respectively, had a positive reaction, but usually close to the cut-off point (no IgG was detected in the unvaccinated control group). To help with positive diagnosis during the febrile episode, we recommend the use of these rapid tests instead of classical serology, provided the symptoms duration is greater than 5 days (and bearing in mind that a negative test result does not allow one to definitely rule out the diagnosis).

Management of dengue fever. As long as there are no bleeding signs, treatment is not necessary. A documented diagnosis in the acute phase is mainly helpful to avoid further investigations and prevent unnecessary treatment against other diseases.[66] Patients should, however, be closely monitored to detect early signs of dengue hemorrhagic fever, that is the appearance of cutaneous or mucosal petechiae, hemoconcentration, or hypoproteinemia.[68] In the presence of these abnormalities, they should be hospitalized immediately to receive supportive treatment. For the 289 confirmed cases declared to the CDC between 1986 and 1995,hospitalization was required in 1 to 2% of the cases.[39] A posteriori, the benefit to patients from knowing that their febrile illness was in fact dengue, is only to be aware of the higher risk of developing hemorrhagic features if they get infected again.

Conditions suggestive of rickettsiosis. Mediterranean tick typhus due to *Rickettsia conorii* accounts for the majority of imported rickettsiosis acquired in Africa,[69] whereas typhus due to *Rickettsia tsutsugamushi* is usually caught in Asia/Oceania.[70] African tick bite fever, due to the recently discovered species *Rickettsia africae*, is now often being recognized in travelers coming back mainly from South Africa and Zimbabwe.[71] Probably, virtually all cases originating from these regions that were described in the older studies, were actually caused by *R. africae*, which was previously serologically indistinguishable from *R.conorii*.

The incubation period is not clearly reported in the studies of Marschang and colleagues;the range seems to be from 5 to 28 days.[70]

The clinical presentation is nonspecific when the cutaneous manifestations are lacking.The rash was only present in 41% and the eschar in 50% of the cases in a series of 22 travelers with different types of rickettsiosis (mainly *R.conorii*).[70] In 119 travelers with African tick bite fever (*R.africae*), a rash was found in 46% and an eschar in 95% of the cases.[71] In 645 Sicilian children with "fièvre boutonneuse" (*R. conorii*), 96% had a rash and 72% an eschar.[72] The rash was mainly maculopapular, rarely petechial (1.4%) or vesicular (0.5%) and could often not be distinguished from rash of other origins.

Although not specific, headache was a frequent symptom (72% in Smoak and colleagues[73] or 68% in Cascio and colleagues[72]) and was considered by the international experts of the panel as the second most important condition for suspecting rickettsiosis. More specific features, but often lacking, are the history of a tick bite (61% in the study by Marschang and colleagues[70] and 9% in the study by Cascio and colleagues[72]) and regional lymphadenopathy (59% and 49%, respectively). In an outbreak among soldiers posted to Botswana, the authors attempted to calculate the odds ratios (OR) for various symptoms.[73] Lymphadenitis was the best predictor (OR=20, 95% CI 8–47), followed by fatigue, chills, myalgia, and headache. The laboratory parameters did not help much;leukocytosis was often not marked or even absent.

Diagnosis of rickettsiosis. The serology at the start of the symptoms can be useful, provided IgM are quantified, which is not the case in most laboratories. In the studies of Marschang and colleagues and Cascio and colleagues 73% and 65%, respectively, had a first sample positive for IgM.[70,72] The others developed IgM and/or IgG after a period of 1 to 4 weeks.Detection of IgG on the acute phase sera is of little help at the time of symptom onset because of the delay in occurrence. Among clinical cases in soldiers exposed to *R. conorii* in Botswana, IgG (comparing acute and convalescent sera) was only useful for retrospective diagnosis.Even in this context, it was of limited sensitivity (24 of 39 and 32 of 36 seroconverted as assessed by indirect immunofluorescent antibody test [IFAT] and Western blot, respectively).[73]

Treatment of suspected or confirmed rickettsiosis. Since confirmation of diagnosis is difficult in the acute phase and specific antibiotics are essential for good recovery, presumptive treatment with doxycycline is strongly recommended.In travelers,the outcome of rickettsiosis was clearly good,probably because the clinical features were usually mild, and antibiotics were given. Among 22 travelers, 5 (23%) had to be hospitalized.[70] Among the latter, 4 had been misdiagnosed and mismanaged before referral to the specialized center.

Conditions suggestive of typhoid fever. For travelers,the risk of acquiring typhoid depends on the country visited, their vaccination status, and/or prior immunity. The incidence is 10 times higher in India (1:30,000) and North Africa than in other tourist destinations.[74,75] In the United States,28% of the cases reported to CDC from 1985 to 1994 came back from Mexico and 25% from India.[76]

Not much is known about the time from return from travel to onset of symptoms. Since studies are retrospective and based on all reported cases,they include a mixture of domestically acquired and imported cases (defined as

having a history of travel to an endemic area in the preceding month). In one textbook, the incubation period ranges from 3 to 56 days for *Salmonella typhi* and 1 to 10 days for *Salmonella paratyphi*.[29]

The classical clinical presentation of typhoid is well known, with several key features that allow for orientating the diagnosis (abdominal pain, constipation, typical rash, relative bradycardia, slight cough, leucopenia, low eosinophilia). Unfortunately, these features are often absent; for example, only 17% of 479 patients (adults and children)[77] or 5% of 55 children[53] with proven typhoid fever had abdominal pain. Diarrhea was much more frequent than constipation in the former study (56% versus 3%) and even more so in children (77% in the latter study). The rash was present in 3% of the cases. We do not know anything about the routine laboratory findings in these studies.

Diagnosis of typhoid fever. Since the diagnosis is often difficult to establish clinically, and the disease is potentially rapidly fatal, the results of blood cultures and stool cultures (useful even in the absence of diarrhea) are essential and should be obtained rapidly. In the retrospective studies, the diagnostic was made by blood culture for the vast majority of the patients (between 66% and 93% positive) or stool culture (between 35% and 54% positive).[53,76,77] Those with a positive serology alone were not considered as confirmed cases, because the specificity of this test is not sufficient. Serology is thus not recommended in febrile travelers.

Treatment of typhoid fever. Clinical improvement follows the rapid administration of antibiotics (quinolones, third-generation cephalosporins or azithromycin for adults,[78,79] and third-generation cephalosporins or azithromycin for children[80,81]). In the studies mentioned above, the overall case fatality rate ranged between 0.4 and 1.5%, the young children and the elderly being at greater risk. When there is a high index of suspicion on clinical grounds, and in the absence of another documented diagnosis, presumptive treatment should be seriously considered while waiting for the stool and blood culture results.[53]

Measles. Few data exist on the incidence of measles acquired abroad. During 1998 in the United States, 100 cases were reported, of which 26% were imported.[82] In a study of 195 adults with fever,[83] as in a study of 31 children,[84] none was diagnosed with measles. In our study of 584 travelers with fever or malaise, measles was never diagnosed.[4]

Conditions suggestive of relapsing fever. Very little evidence-based information is available for relapsing fever in travelers, probably because of the low incidence (clearly lower than that of rickettsiosis) or at least because of underreporting.

The incubation period ranges between 2 and 18 days (see *GIDEON* software[6]). Exposure to ticks was frequently reported among autochthonous cases acquired in northern United States and south Canada; 76% had either visited or lived in cabin or rural home, and 23% had a history of recent outdoor activity.[57]

Patients with louseborne relapsing fever (due to *Borrelia recurrentis*) often present with a petechial rash, but during the first attack, the rash may be erythematous, resembling that of typhoid.[29] Regarding tickborne relapsing fever, rash was found in 20% of confirmed cases reported in the United States and Canada, but the type of rash was not specified.[57] An eschar was only found in 3% of the cases. Only 23% of the confirmed cases were diagnosed at the first febrile episode; in the remaining ones, a history of relapsing fever was the key feature that led to the diagnosis. All other conditions found in these patients were unspecific.

Diagnosis of relapsing fever. The gold standard is examination of a Giemsa-stained thick-blood film (obtained during a febrile attack) for spirochetes. This technique requires some experience. Culture is primarily a research tool. Serologic tests are not widely available and are of limited value due to their lack of sensitivity and specificity.

Treatment of relapsing fever. Administration of tetracycline is important for full recovery of the acute episode and relapses but carries a high risk of Jarisch-Herxheimer reaction. The incidence of the latter seems to depend highly on the species of *Borrelia* involved and the magnitude of the bacteriemia; 54% of the patients had this reaction in Dworkin and colleagues.[57] Treatment should be given after confirmation of the diagnosis and under close surveillance.

Primary HIV illness. Acute HIV should be suspected in the presence of a rash, even in the absence of a history of sexual or intravenous exposure (see Figure 3), as the history is often unreliable, either because the patient omitted the information or questioning by the doctor was incomplete.

- Level of evidence: 4
- Grade of recommendation: C

Ulcerative Skin Lesion (excluding Genitals) (Fig. 7)

Eschar or chancre. Eschar and chancre are distinctive skin lesions but not always easy to recognize for a nonspecialist (see photographs in Fig. 7).

An eschar is typical of rickettsiosis (possibly borreliosis) transmitted by ticks (for more discussion about rickettsiosis, see above). The only differential diagnosis for a true eschar is bubonic plague, which is still endemic in a few places in the world. It is very unlikely for travelers to catch bubonic plague, except if they have a clear history of close contact with reservoir animals. Following a short prodrome of flulike syndrome, a suppurative lymphadenitis

develops, commonly in the groin. Pustules in the region drained by the affected nodes may ulcerate to form an eschar. One case, an American biologist who acquired the disease during her job in Bolivia, has been reported.[85]

African trypanosomiasis is the only febrile disease that is associated with a true chancre. It is very rare in travelers:in 20 years,15 cases have been declared in the United States.[86] All have been acquired in East Africa, mostly during organized safaris. The only other significant risk factor was exposure to tsetse flies. The chancre was present in 67% of the 15 cases.A rash was found in 47% of them. Two cases, diagnosed with a delay of 10 and 19 days, respectively, had central nervous system (CNS) involvement. Hospitalization was required for all cases. Recently, a cluster of 6 travelers who acquired trypanosomiasis in the Serengeti National Park, Tanzania, was notified to the TropNetEurop (2 of them reviewed in Ripamonti and colleagues[87]).At least 4 of 6 patients developed a chancre shortly before the onset of high fever. In patients with specific information provided,the time between departing from the park and notification of a chancre was less than a week.Maximum incubation time is generally considered as 3 weeks.

The acute phase of American trypanosomiasis often presents with a chancre or ulcer, but is unlikely to be seen in a traveler, since the disease requires prolonged exposure in a poorly constructed house infested with bugs,[88] and in a migrant who is already, if infected,in the latent or chronic phase.

It is sometimes difficult to distinguish a chancre or an eschar from an ulcer, and the etiologies mentioned below should then all be considered in the differential diagnosis.

Ulcer. In a traveler, the most common cause of ulcer is a skin infection due to various agents (mostly *Staphylococcus aureus*),often complicating a wound or an insect bite, more rarely a specific tropical disease like cutaneous leishmaniasis (that otherwise would not provoke fever). Other causes mentioned in Felton and Bryceson are:(1) anthrax, which is seen in the context of professional exposure (outside the very special context of bioterrorism) and for which a specialist in tropical/infectious disease should be consulted; (2) histoplasmosis (the African type), which is not associated with a systemic illness (and therefore fever) outside the context of immunosuppression (condition excluded from the guidelines); and (3) leprosy, in which ulcers are only seen at the late stage of the disease when other major signs are present.[52]

- Level of evidence: 4
- Grade of recommendation: C

Cough or Dyspnea (Fig. 8)

Respiratory infections account for up to 11% of febrile illnesses in travelers.[89] Respiratory signs are mainly due to common organisms also found in nontravelers, but among the bacteria,there is a higher proportion of atypical etiologies, such as legionellosis. For nonimmune travelers (not for migrants), helminthes are important microorganisms,causing fever and acute respiratory manifestations, either during the migration of the larvae through the lungs or through an immunologically mediated process, early in the cycle. An eosinophil count is thus essential to distinguish between bacterial and parasitic etiologies.

Eosinophils greater than 500/mm^3. No study mentions the time from the start or the end of exposure to the first symptoms for the different helminthiases. For ascaridiasis, Loeffler syndrome appears between 4 and 16 days after infection and for ankylostomiasis before the third week.[29] For strongyloidiasis,where autoinfection occurs,parasites can pass through the lungs again at each new cycle and thus lead to respiratory symptoms at any time after infection. *Paragonimus* has a prepatent period of at least 3 weeks,[29] and lymphatic filariasis of at least 4 weeks. Schistosomiasis can sometimes present with respiratory symptoms during the acute phase, 44% of cough in the cases described by Doherty and colleagues,[24] 4 cases with prominent pulmonary involvement described by Cook and colleagues.[33] In a retrospective study of 60 patients, 8 were identified with respiratory problems that appeared a few days after a febrile episode.[90] Thus, these cases presented a syndrome slightly different from Katayama fever, but probably also due to an immunological process. Management should follow the one mentioned in Figure 1 under skin contact with fresh or brackish water.

The presence of eosinophilia should lead to specific serologic investigations (schistosomiasis, ascaridiasis, strongyloidiasis,ancylostomiasis,and,depending on the destination of travel or the patient's country of origin and the time from return,lymphatic filariasis).[91,91,92] Unfortunately, cross-reactions of serologic assays for helminthiasis are frequent. A presumptive treatment is, therefore, often necessary. The choice between diethylcarbamazine (DEC), ivermectin, or albendazole should be discussed for each case, based on the probability of the different parasites.[93] The eggs (or larva for strongyloidiasis) in stools do not appear before 8 weeks after infection with *Ascaris*, 3 weeks with hookworm, and 4 weeks with *Strongyloides*. Stool examination is thus less useful than serology during the acute phase.

Eosinophils less than 500/mm^3. According to Ellis,[94] a dry cough in a traveler should lead to a chest X-ray, even in the absence of physical signs. In the presence of a history and a radiologic infiltrate compatible with community-acquired pneumonia, the antibiotic of choice is a macrolide

rather than an aminopenicillin, as stated in the Infectious Disease Society of American (IDSA) guidelines.[95] This is especially true in travelers because of the higher proportion of atypical pneumonia.[96]

Another etiology to consider is tuberculosis, mainly in migrants or in people having lived abroad or having had professional exposure to affected persons. In a study based on tuberculin skin testing of 656 travelers, beside the duration of the stay abroad, professional medical care was an independent risk factor for seroconversion upon return.[97] Pulmonary histoplasmosis in travelers is clearly associated with exposure to bats in caves [98,99] but can also sometimes be found after other type of contact like sleeping on the ground. Melioidosis can present as an infiltrate of upper lobes or cavities, similarly to tuberculosis. Travelers usually catch it in Southeast Asia, but recently several cases were imported from Bangladesh, India, and Pakistan.[100] The disease is also endemic in Papua New Guinea and northern Australia.

For Hantavirus pulmonary syndrome, once respiratory symptoms appear, the disease has such a rapid course that when patients are seen, they always present with respiratory distress leading to hospitalization in an intensive care unit (see "Any danger sign" in the Initial Evaluation section of the Appendix).

Mild cough can also be associated with typhoid fever (13% had cough in the study by Mathieu and colleagues[77]). In the absence of pulmonary infiltrate, this diagnosis should be considered, even if abdominal pain is lacking. However, since the probability is low in this situation, documentation before treatment is advisable. Malaria can also present with a mild cough (13% in a review of several studies[7]), but has already been considered under "Malaria-endemic area" in the Initial Evaluation section.

Finally, pulmonary embolism is seen in travelers whose lower limbs have been immobilized for hours during a long trip.

- Level of evidence: 3b
- Grade of recommendation: B

Sore Throat (Fig. 9)

Beside viral or bacterial pharyngitis, which is by far the most common cause of sore throat even in travelers, some tropical etiologies should be considered in particular situations.

Diphtheria. Since travelers are generally immunized, and the disease is epidemic in places with poor health systems where tourists seldom go, imported diphtheria is very rare. The presence of the typical pharyngeal membrane is a key sign to define a probable case.[101]

Confirmation is done by culture or histopathology. Two cases imported from the Russian Federation and the Ukraine are described in the *Morbidity and Mortality Weekly Report (MMWR).*[102] Both patients had no known contact with a diphtheria patient. Vaccination status was unknown for the first patient; the second patient was fully vaccinated, which possibly prevented her from developing toxic complications.

Marburg virus disease and Lassa fever. Although patients with other types of viral hemorrhagic fever can present with a sore throat, this sign is specific for Marburg virus disease and Lassa fever. Two of the 3 imported cases of Marburg in South Africa in 1975 had red and congested soft and hard palates.[103] When no clear history of contact exists (see "Contact with body fluids…" in the Initial Evaluation section), the diagnosis is very difficult to make when only fever, myalgia, or headache is present. After some days, hemorrhagic manifestations or severe renal and liver function impairment will appear and lead to the diagnosis.

Primary HIV illness. As mentioned above (see Fig.3), the more consistent and specific sign was the presence of a palatal enanthema (11 of 11 patients in the study by Pendle and Sacks[44]).

- Level of evidence: 5
- Grade of recommendation: D

Abdominal Pain (Fig. 10)

When signs of peritoneal irritation are present, management for acute surgical abdomen must be undertaken by a surgeon, keeping in mind the possibility of ileal perforation due to typhoid fever, colitic perforation due to amebiasis or rupture of an amebic liver abscess. Otherwise, typhoid fever is the first diagnosis to consider in an adult traveler with fever and abdominal pain (present in 17 to 34% of the cases[77,104]). In children, it is probably malaria, which is often characterized by gastrointestinal complaints (75% of 70 cases had either abdominal pain or diarrhea or vomiting[105]). Another potential diagnosis, especially when the abdominal tenderness is located in the right upper quadrant, is amebic liver abscess.[106] To orientate the diagnosis, it is essential to consider the leukocyte count (leukocytes are rarely higher than 10×10^9/L in typhoid fever without perforation and the mean is 16×10^9/L in amebic liver abscess[106]) and usually to do an ultrasound examination.

Felton and Bryceson report that many diseases can lead to abdominal pain.[52] Apart from the three diagnoses already mentioned, a wide range of bacteria or parasites of the intestinal tract can cause fever + abdominal pain, but almost invariably with some degree of diarrhea (see below). The other etiologies have other major features.

Typhoid fever. Typhoid fever should always be suspected in the presence of fever and abdominal discomfort, regardless of the presence of other specific symptoms or

signs or vaccination status. When malaria has been ruled out, enteric fever is the most common cause of fever lasting 10 or more days.[3]

When the leukocyte count is $<10\times10^9$/L, and after blood and stools have been obtained for cultures, quinolones[78,79] (third generation cephalosporins or azithromycin in children[80,81]) should be given as presumptive treatment for typhoid fever, particularly since quinolones would treat bacterial gastroenteritis at the same time (see under diarrhea,Fig.11).When the leukocyte count is $\geq10\times10^9$/L, an abdominal ultrasound examination should be performed to rule out an amebic liver abscess (see below).

Amebic liver abscess. In a hospital in Japan,among 227 patients admitted for amebiasis, 69 (30%) had a liver abscess.[107] In these 69 cases,only a few had a history of previous intestinal amebiasis. On clinical examination, 75% had abdominal tenderness (we do not know whether it was localized or not),67% had hepatomegaly, and 44% had diarrhea (16% with blood). In a review that mentions 4 case studies,including altogether 241 patients,pooled data show that 89% complained of abdominal pain, 73% had right upper quadrant tenderness, and 29% had hepatomegaly.[106] The diagnosis of liver abscess is made in the presence of a typical liver lesion seen by ultrasound or computed tomography (CT) scan examination.The sensitivity of the ultrasound alone is not specified in the studies by Lee and colleagues or Weinke[107,108] but another study showed that it is only slightly lower than that of CT scan.[109] Taking into account the higher cost and the lower availability of the latter, it should be restricted to cases with normal ultrasound results but high suspicion (i.e.,positive serology; very early presentation in which hepatic changes may not yet be visualized by ultrasound).

In practice, when the leukocyte count is $\geq10\times10^9$/L, an abdominal ultrasound scan should be performed to look for a hepatic abscess. If this is positive, serology should be carried out for ameba. Serology is very sensitive in the case of extra intestinal amebiasis (94% in the study by Lee and colleagues[107]) and is essential to determine the etiology of the abscess.Stool microscopy is much less sensitive (ameba was found in 45% of 69 patients, whether or not they had associated diarrhea[107]). Stool antigen detection tests are still less sensitive than serology in this situation.[106] These assays do not provide a definite confirmation of the etiology of the liver abscess but may give a reasonable justification to give a presumptive treatment with imidazoles and avoid an abscess puncture. When all results are negative, the most likely etiology is pyogenic, secondary to biliary tree infection, and appropriate investigations should be performed.At this stage, abscess puncture is essential to determine the exact etiology and decide on the right antibiotic (it should be noted that ameba were found in the pus in only 62% of 63 patients with abscess[107]). In particular cases (depending on size and peripheral location), percutaneous drainage may be necessary both for amebic and pyogenic abscess.[106]

- Level of evidence: 4
- Grade of recommendation: C

Diarrhea (Fig. 11)

There is no study, and a fortiori no guidelines,on diarrhea with fever. The most likely etiology in travelers is bacterial gastroenteritis.However, as diarrhea is the most common problem among travelers, it may be difficult to know whether diarrhea is part of the disease or a dual infection.

Traditionally, typhoid fever in adults is considered to be associated with constipation rather than diarrhea. Some studies show the contrary (3% with constipation versus 56% with diarrhea in the study by Mathieu and colleagues[77]). In children, diarrhea is frequent (77% in the study by Misra and colleagues[53]).Malaria may present with diarrhea but,in a sample of adult travelers coming back with fever, this symptom was rather negatively associated with malaria.[4] When there is a history of previous antibiotic intake (often self-administered in travelers), *Clostridium difficile* should be suspected and the toxin searched for.

Bloody stools suggest the presence of a bacteria (primarily *Shigella*, also consider *Escherichia coli* 0157) or ameba. The symptom is also found in viral hemorrhagic fevers, but other major clinical features are required to suspect a case. It is very rarely found in malaria;among 441 adult travelers with malaria, only 3 had bloody stools (reviewed in Genton and D'Acremont[7]).

Theoretically, bacteria cause diarrhea with a maximum incubation period of 7 days, except for *Campylobacter* (up to 10 days).In practice, symptomatic salmonellosis can occur after much more than 4 weeks.

Parasitic etiologies are rather rare, the most frequent being intestinal amebiasis.[110–112] *Cryptosporidium* is seldom found but can sometimes present with fever.[110;113] Recently, a new cause of diarrhea upon return has been described, mainly from Nepal and South America; *Cyclospora cayetanensis*.[114] However, it is not clear how often fever is associated with this pathogen.[115] This microorganism should be considered at a later stage, that is, in cases of prolonged febrile watery diarrhea.[116] Giardiasis and chronic schistosomiasis are not associated with fever.

Other etiologies of febrile diarrhea (measles, legionellosis, relapsing fever, melioidosis, viral hemorrhagic fever, and anthrax) have other major clinical signs[52] and are not dealt with in this figure.

In the IDSA guidelines for the management of infectious diarrhea,there is no mention of the usefulness of testing white blood cells or lactoferrin in the stools

for the management of community acquired or travelers' diarrhea.[117] There is actually no sufficient evidence for their use and no expert consensus.

If the incubation period is less than 8 weeks, the etiology is very likely to be bacterial.Since both *Shigella* and *Salmonella* (as intestinal salmonellosis or typhoid fever) can lead rapidly to a fatal outcome, it is wise to give presumptive treatment with quinolones.[117] Stools should be collected for culture (and at the same time for parasitologic examination) prior to the first administration of antibiotics, mainly to obtain an antibiogram.However there is no reason to delay the latter if no stool is available. Numerous studies in travelers have shown that antibiotics reduce the duration of diarrhea, even in absence of fever.[118,119] The IDSA guidelines for the management of infectious diarrhea clearly recommend the administration of presumptive treatment with quinolones for travelers diarrhea (strength and quality of evidence A-I) and for febrile diarrhea (B-2).[117] Although resistance to quinolones is growing, especially for strains of *S. typhi* originating from the Indian subcontinent[120] and for *Campylobacter* from Southeast Asia,[121] these antibiotics remained active in vitro against most bacterial enteropathogens causing travelers' diarrhea.[112] Quinolones should still remain the drug of choice for empirical treatment of travelers'bacterial diarrhea in adults. Alternative drugs could be azithromycin, which is also the drug of choice in children,or possibly ceftriaxone, which is highly active against the enteropathogens but has the disadvantage of requiring parenteral administration.[121,122]

In the rare cases where the stool examination reveals the presence of a parasite (mainly amebiasis),a specific antiparasitical treatment should be introduced.

If the incubation period is greater than 8 weeks,the etiology is more likely to be parasitical rather than bacterial. It is thus wise to wait for the results of the stool culture and parasitologic examination before deciding on the most appropriate treatment.

- Level of evidence: 1
- Grade of recommendation: A

Hepatomegaly (Fig. 12)

Almost all febrile diseases in returning travelers can produce some degree of hepatomegaly, especially in children.Depending on the etiology, hepatomegaly can be associated with splenomegaly, for example in malaria, which is a frequent cause of hepatosplenomegaly in febrile travelers. Since the majority of the diseases causing hepatomegaly have other major signs, they are considered in other figures. Here, we consider only the diagnoses where hepatomegaly is the prominent or the only clinical feature.

Since it is frequent in travelers,the first diagnosis to consider is viral hepatitis (see *GIDEON* software[6]).When the results of the liver function tests are compatible with this diagnosis, serology should be carried out rapidly, before performing other expensive investigations. The second diagnosis to consider is amebic liver abscess (see above for more details);67% of 69 patients[107] and 29% of 241 patients[106] had such a sign in two studies.Other than malaria,it is the only disease that should be treated rapidly (by aspiration in specific cases),in order to avoid rupture into the peritoneal or pulmonary cavity. .

Although much less common, two other diseases should be considered.

1. Liver flukes: *Fasciola hepatica* is found worldwide and is thus autochthonous, but *Clonorchis* and *Opisthorchis* are only present from Eastern Europe to Asia.Liver flukes can present with fever in the acute phase[123] or at any time because of superinfection (therefore, no Time RS is indicated).

   Hepatomegaly and eosinophilia are almost always found. A specific image (moving parasites or crescent-shaped contents in the biliary tract) can be found by ultrasound (this was the case for 11 of 76 patients described in Richter and colleagues[124]), but in general only nonspecific biliary tract abnormalities are found (52 of 76 patients in the same study) and very rarely a liver mass.[125,126] The diagnosis of certainty that allows a specific treatment to be initiated is obtained mainly by serology and sometimes by microscopic stool examination, although eggs appear only 3 to 4 months after the infection.[127]
2. Visceral leishmaniasis:although less frequent than splenomegaly, hepatomegaly was present in 58% of 89 cases (the majority being autochthonous) inFrance.[128] We do not know whether some patients had hepatomegaly without associated splenomegaly.

- Level of evidence: 4
- Grade of recommendation: C

Splenomegaly (Fig. 13)

Enlargement of the spleen, often to a very large size, is an almost constant feature in visceral leishmaniasis. This diagnosis is suspected in case of pancytopenia and hypergammaglobulinaemia.[39] The maximum incubation period reported is 4 years,[129] but the average is between 2 and 4 months.[29] Fever was present in 88% of all cases and splenomegaly in 100% of the children under 8 years and 80% of older children and adults.[28]

As mentioned previously, splenomegaly had a high likelihood ratio (13.6) for a positive diagnosis of malaria (see under "malaria-endemic area").[4]

- Level of evidence: 4
- Grade of recommendation: C

Eosinophils greater than 500/mm^3 (Fig. 14)

A large variety of helminths can cause fever and eosinophilia during the phase of invasion. The most frequent in travelers are schistosomes that have already been considered under skin contact with fresh or brackish water (Fig. 1). The other important diagnoses to consider are filarial infections, such as loiasis or lymphatic filariasis. Loa Loa is certainly the most frequent filaria in travelers, and the history of transient Calabar edema after a trip to West Africa rapidly orientates the diagnosis (present in 100% of 26 imported cases[130]).

Onchocerciasis is seen in long-term travelers or in migrants,[131] but is almost never associated with fever and has thus not been included. Unlike strongyloidiasis and ancylostomiasis,ascaridiasis does not induce fever in the absence of cough (in the context of Loeffler syndrome, see Fig. 8) and is thus not mentioned here. Finally, trichinosis should be considered in the presence of myalgia.

When both serologies and stool examination are negative for all of these parasites, the tests should be repeated later.

- Level of evidence: 4
- Grade of recommendation: C

Discussion

To make these guidelines readable, we decided to focus on the diseases that are found only, or at least more often, in tropical and subtropical countries. This leads to an algorithm that is only part of the whole evaluation,and the resulting decision making for patients presenting with fever upon return or migration from these regions is incomplete. An algorithm that included all possible diagnoses would have been far too complicated and even impossible to create since it would have meant a decision chart for fever, an enterprise that nobody dared to do. Indeed all guidelines that deal with fever have focused on one particular aspect (e.g., guidelines for the evaluation of fever and infection in long-term care facilities, guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever). This decision chart should,therefore, be seen as an additional tool to consider and rule out diagnoses that the nonspecialized physicians are often not familiar with.

The reasons to include migrants in the target population have already been discussed in the Methods section. We would just like to emphasize here that, although the two populations are clearly distinct, they have not been separated in previous studies and that the evidence thus pertains to the mixture of the two populations. We acknowledge the urgent need to test both cohorts of travelers and migrants separately, and to investigate whether the potential differences observed in guideline adherence would justify the need to have separate recommendations.

We believe that the choice to focus on tropical diseases and to mix the populations of travelers and migrants is justified for the sake of simplicity and safety. Simple and clear guidelines designed to assist physicians and patients in making appropriate decisions may be more effective than numerous and very detailed ones. It is true that relatively simple guidelines may be criticized as being incomplete and close to so-called cookbook medicine. This is a common criticism and must be weighed against the reality of medical practice and the potential usefulness of easily understandable recommendations.

The discussions with the assessment panel highlighted different opinions regarding the desirable complexity of the tree structure (i.e., the amount of details) that should be provided for primary care physicians dealing with patients with fever coming from tropical countries.The less specialized the physicians were, the more pleased they were to have complete information to achieve a diagnosis and make a decision. The experts were worried that too much detailed information might lead the primary care physician to make inappropriate decisions. To accommodate these experts' dissensions, we agreed to flag the situations that need deeper knowledge for patient management. If we had targeted information only to physicians with little expertise in the field, we would have ended up with a tree with very few branches,almost all of them leading to the recommendation of contacting a travel/tropical medicine specialist. Such an approach would have ignored the great variability in the knowledge of primary care or emergency physicians and would have provided little further insight in the field. One may argue that including a great deal of information has resulted in charts that are too complex to be easily readable. This may be true when one looks at all the figures.But using the chart for a defined patient with a defined problem requires the reading of only 1 to 3 figures. Also the computerized version is much more convenient since the physician only opens the relevant figures.Interestingly, the primary care physicians in the panel of development experts did not perceive the chart as too complex to read and use; it was the specialists who argued for simpler figures. We believe that our concept allows greater flexibility than simpler figures in the use and implementation of the guidelines, but it probably does demand more responsibility on the part of the user. In our view, guidelines should be a support to help physicians to make decisions in situations that may be complex and, in the present case, not frequently encountered in the daily practice of primary care physicians.

The main limitation of our practice guidelines is the low level of the evidence available for most issues addressed and hence the low grade of the recommendations. This is partly due to the small number of cases seen by primary care physicians. This makes it difficult to carry out prospective studies in the outpatient setting. Specialized centers have mainly performed observational case studies that are difficult to use for designing formal recommendations. Nevertheless, the broad and varied spectrum of disease presentations of many of these diseases, the symptoms varying with the stage of the disease, and the varying geographical origin will always be responsible for the inherent low predictive value of clinical symptoms and signs. A combination of symptoms/signs may be very suggestive (high specificity), but will invariably suffer from a profound lack of sensitivity. Even larger studies cannot overcome this problem that is inherent to the field studied.

As far as case management is concerned, the quality of the evidence can still be improved, and there is an urgent need to conduct multicentered prospective studies that address specific issues, such as the safety and benefit of presumptive treatment in defined situations, or the cost-effectiveness of routine laboratory tests in patients returning with fever from tropical or subtropical regions. Consideration of probabilities would have definitely improved the grade of recommendations. However, the lack of good disease-specific incidence data in primary care or emergency department patient populations hinders the inclusion of such assessments. An attempt to do so has been done by the authors of *GIDEON*,[6] but the evidence for such ranking is scarce, at least in outpatient or emergency settings.

Another limitation, which is not specific for our practice guidelines, is the fact that we did not include patients in our development panel. We felt that the patients' opinions were partially reflected by those of the primary care physicians who played the role of patient's advocate in the development process. However, no patient version of any guidelines has been developed so far.

To widen prior evaluation, these guidelines have been circulated to the target users and specialists in infectious diseases in European academic institutions and private practices. They have also been pretested on many patients at the Medical Outpatient Clinic, University of Lausanne, by the primary care resident physicians and registrars.

The obvious next task is to validate these guidelines in practice. The first objective would be to evaluate their safety. However, this might well be an impossible task since the primary outcome, that is, mortality, is too rare to be assessable in a manageable study. The assessment of the impact of the guidelines on rates of hospitalization and use of presumptive treatments might be somewhat easier to achieve. We believe, however, that a more realistic approach will be the evaluation of processes like (1) acceptance, implementation, and adherence to the guidelines by physicians and (2) their acceptability to patients in several different clinic settings and regions of the world. Such an evaluation has just been initiated.

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Appendix

Initial evaluation of fever in a returning traveler.
(Pages S46–S47)

Figur e 1 Skin contact with fresh or brackish water in schistosomiasis-endemic area and Time RS less than 12 weeks and Time ES more than 2 weeks.(page S48)

Figur e 2 Professional contact with farm animals or swimming or rafting in freshwater and Time RS less than 4 weeks. (Page S48)

Figur e 3 Sexual contacts with a new partner or injections received. (Page S48)

Figur e 4 Consumption of raw dairy products and symptoms for more than 7 days. (Page S49)

Figure 5 Jaundice. (Page S49)

Figure 6 Maculopapular rash. (Page S49)

Figure 7 Ulcerative skin lesion (excluding genitals). (Page S50)

Figure 8 Cough or dyspnea. (Page S50)

Figure 9 Sore throat. (Page S51)

Figure 10 Abdominal pain. (Page S51)

Figure 11 Diarrhea. (Page S51)

Figure 12 Hepatomegaly. (Page S52)

Figure 13 Splenomegaly. (Page S52)

Figur e 14 Eosinophils greater than $500/mm^3$. (Page S52)