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A “Syndromic” Approach for Diagnosing and Managing Travel-Related Infectious Diseases in Children

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Primary care physicians practicing in the United States are often less familiar with many of the common as well as more exotic diseases that children can acquire when traveling abroad. This review will focus mainly on infectious diseases specifically associated with travel-related exposures. While having access to reference material to help guide diagnostic resources and therapy is useful, it is most useful to have a consistent well-organized approach to help identify specific risk factors associated with both the most common and the most severe illnesses potentially occurring in a child who has recently traveled internationally. According to the National Travel and Tourism Office the number of Americans traveling abroad increased to more than 61.9 million in 2013.1 The main areas of travel included Europe at 34.6%, the Caribbean at 24.8%, Asia at 18.8%, South America at 7.3%, Central America at 6.9%, Africa at 3.1%, the Middle East at 5.9%, and Oceania at 1.9%. Nearly 27% of travel was to visit friends and families. This category accounts for a significant portion of the travel in the pediatric age groups.2,3 Although travel to Asia and Africa accounted for only 21.9% of US traveler the majority of travel-related illnesses were acquired from Asia (32.6%) and sub-Saharan Africa (26.7%) according to a recent GeoSentinel illness surveillance of returned international travelers presenting to the GeoSentinel Network.4,5

The Critical Roles of a Detailed History and Assessment of Risk Factors

The initial assessment of an ill pediatric traveler begins with a rapid screen for acutely life-threatening...
symptoms requiring empiric management, as well as features that mandate an escalation of infection prevention and control procedures. Next, a detailed travel history is performed. Table 1 summarizes the most important historical factors to obtain to help identify risks and focus the assessment for serious disease after recent travel. The age of the patient should be taken into account as it may affect the types of exposures and risk behaviors. For example, while smaller children are more prone to animal bites as compared to adults, adolescents may be more likely to participate in high risk activities such as body piercing, tattoos, and sexual activity. As with pre-travel preparation, the exact geographic location(s) of recent travel is among the most important history to review, as the most serious diseases have very specific regional risks. Overall, malaria is known to be more prevalent in travelers returning from sub-Saharan Africa, dengue is more common after travel in Asia and the Caribbean, and diarrheal diseases more common after travel in northern Africa. The predominant disease categories identified in specific regions of the world are summarized in Table 2.

Travelers whose purpose is visiting friends and relatives (VFR) are less likely to have had visits to a travel medicine provider or other pre-trip preparation, are more likely to be staying in remote areas for longer time periods, and to have been in closer contact with local people, food, water, and animals. They also commonly and mistakenly believe that they are still immune to malaria as when they lived in a region in which they were constantly exposed. GeoSentinal surveillance data noted that travelers visiting friends and relatives returning from sub-Saharan Africa, south-central Asia, and Latin America were overall more likely to experience “fever” than any other group. In all travelers (and particularly the VFR families), the clinician must ascertain not only whether pre-travel advice was sought, but an appraisal of the degree to which a family complied with any pre-travel immunizations, recommended prophylactic medications, and other precautions. This information is important for all travelers but especially in the VFR families.

Incubation periods for the more common travel-acquired diseases are presented in Table 3, and can help focus the differential diagnosis. For instance, dengue has a short incubation period and generally presents during or upon initial return from travel, while Plasmodium falciparum infection typically presents within the first 30 days after departing an endemic region, and hypnozoites of Plasmodium vivax or Plasmodium ovale may result in infections up to a year later. It is important to try to determine the most accurate estimate of symptom onset from the time of exposure. Seasonality is also an important consideration, as risk for many diseases may vary significantly due to climate factors. While most of the risk factors for young children can be extrapolated from the actions and experiences reported by their adult caregivers, one must also ask if the children followed any different practices than the adults, such as swimming in freshwater, sleeping in different circumstances, or consuming different foods?

Patterns ( Syndromes) of Disease

Categorizing the illness according to a pattern of symptoms and findings, i.e., “syndrome” that the patient most closely fits; followed by a deliberate and systematic diagnostic approach to identify a specific infectious agent. This simultaneously leads to a more
TABLE 3. Syndromic Approach to Illness in Returning Travelers

| Syndrome Presentation | Possible Infectious Disease | Incubation (Range in Days) | Unique Risk Factors | Discriminating Physical Signs and Symptoms |
|-----------------------|-----------------------------|-----------------------------|---------------------|-------------------------------------------|
| **Systemic Febrile Illness with Non-Focal Symptoms** | Malaria | 7–30 (Most 12–14) | Endemic areas | Often none; focal signs rare in children, V/D, occasionally pallor, jaundice |
|                       | Dengue | 4–7 | Endemic areas | Macular rash, petechiae, lymphadenopathy |
|                       | Leptospirosis | 2–21 | Freshwater activities | Conjunctival suffusion, jaundice if severe |
|                       | Typhoid fever | 6–30 | Highest in S. Asia, vaccine only 50% effective | Evanscent macules – “Rose spots” |
|                       | Chikungunya | 3–7 | Up to 60% infected in endemic regions | Maculopulular rash, small joint arthritis |
|                       | Acute HIV Infection | 10–28 | Sexual contact, transfusion, piercings, recent tattoos | Lymphadenopathy, “mono-like” illness |
|                       | Rickettsial disease | 5–14 | Rural Africa, game parks | Petichial rashes, focal eschars |
|                       | East African Trypanosomiasis | 7–14 | African/Asian game parks | Inoculation chancre |
|                       | Schistosomiasis (Katayama fever) | 14–84 | Swimming/wading in fresh water - Africa | Pruritic papular rash within a day after water contact |
|                       | Ebola, other VHFs | 2–21 | Outbreaks, traditional burial practices, bush meat | Petichiae, purpura, conjunctival hemorrhage, other bleeding problems |
| **Fever with CNS Involvement** | Malaria | 7–30 (Most 12–14) | Endemic areas | Fundoscopy: papilledema, retinal pallor, hemorrhages |
|                       | Meningococcal meningitis | 3–4 | Meningitis belt (Africa) | Petichiae, purpura |
|                       | Japanese encephalitis | 5–15 | Rural areas of south and southeast Asia | Multi-focal encephalitis, extrapyramidal signs |
|                       | West Nile Virus | 3–14 | Americas, Africa, Europe, west and central Asia | Rash |
|                       | E. Africa Trypanosomiasis | 7–14 | E. Africa/Asia game parks | Inoculation chancre |
|                       | Angiostrongyliaasis | 7–21 | Raw vegetables, snails | Asymmetric paresthesias, fever rare |
|                       | Rabies | 21–60 | Animal bites, bat exposure | Paresthesias (at bite), progressive altered mental status, autonomic instability |
| **Fever with Respiratory Involvement** | Influenza | 1–4 | New serotype outbreaks, poultry, pig exposure | Cough, myalgias, hypoxemia if severe |
|                       | Bacterial pneumonia | 1–3 | | Cough, hypoxemia if severe |
|                       | Malaria | 7–30 (Most 12–14) | Endemic areas | Tachypnea, ARDS if severe |
|                       | Tuberculosis -primary | 2–12 Weeks for TST positivity | Expatriates, exposure to high risk groups, VFR | Hilar adenopathy, occasionally mild hepatomegaly |
|                       | Q Fever | 14–21 | Regional risk/farm animals | ‘Can occur without obvious animal exp. |
|                       | Dengue | 4–7 | Endemic areas | Macular rash, petichiae, lymphadenopathy |
| **Fever and Skin Rash** | Mononucleosis | 4–8 Weeks | Outbreaks, Still endemic in parts of Asia | Variable “morbilliform” rash |
|                       | Measles | 7–21 | | Oral Koplik spots early, then “Head to Toe” spread, |
|                       | Typhoid fever | 7–21 | Highest in S. Asia | Evanscent macules early, then “Rose spots” |
|                       | Chikungunya | 3–7 | Endemic regions | Maculopulular rash, small joint arthritis |
|                       | Rickettsia diseases | 5–14 | Rural areas, game parks | Petichiae or Eschar with most species |
|                       | Acute HIV infection | 10–28 | Sexual contact, transfusion, piercings, recent tattoos | Lymphadenopathy, “mono-like” illness; non-specific eczematous rash upper body |
| **Dermatologic Findings without Fever** | Bacterial Skin Infections/ Abscess | Varied | Skin injury, bites, eczema | Varied – erythema, pain |
|                       | Cutaneous larva migrans | 1–5 | Barefoot walking | Serpiginous “creeping” eruption |
|                       | Tungiasis | 1 day | Barefoot walking | Tender nodule, possible black center |
|                       | Myiasis | 1–12 Weeks | Africa, C. and S. America | Looks like and abscess, but “motile” |
|                       | Scabies | 2–6 Weeks | Crowded, poor hygiene | Serpiginous burrows |
|                       | Cutaneous leishmaniasis | 2–8 Weeks | Endemic regions, outdoor exposure | Progression of papule – painless ulcer; intranasal lesions in some new world inf. |
focused and productive evaluation, yet keeps the possibilities open for a variety of diagnoses to be considered. For example, after a careful history there are certain clues on physical exam that can aid in identification of types of illnesses, but rarely a specific diagnosis. Discriminating physical findings which may help further focus an evaluation are listed in Table 3. For example, jaundice could indicate severe malaria, severe leptospirosis, enteric fever, the viral hepatitides, or viral hemorrhagic fevers. An enlarged spleen, liver, or both may be associated with malaria, rickettsial infections, enteric fever, leptospirosis, Q fever, schistosomiasis (Katayama syndrome), visceral leishmaniasis (very enlarged spleen), dengue, hepatitis, or HIV. The pediatric patient presents a particular challenge, as common illnesses in pediatric patients such as CMV and EBV can also present with hepatosplenomegaly, but should be considered after excluding the life-threatening diseases associated with travel that require immediate therapy, or the more exotic etiologies that might require unique diagnostics and therapy. Another example is that of the numerous rashes which can be associated with travel-related diseases (discussed in more detail in the “Presentations of Rash” section), a common syndrome with many ubiquitous pediatric infections, but also with life-threatening travel-associated diseases. The flow chart presented in the Figure, as well as the content of Table 3 and, and the subsequent approach help guide a practitioner through these challenging differential diagnoses.

### Stepwise Approach to Diagnostic Studies

The pediatric provider is challenged by both the need for a thorough exam and an open-minded approach to unusual disease presentations, which must be simultaneously balanced by the level of acuity and disease severity. In addition, though it is a relatively rare possibility, the risk of contagiousness of certain diseases, such as meningococcemia or viral hemorrhagic fevers, cause great anxiety among health care providers and their institutions. At the time of the preparation of this article, the world is hopefully seeing the resolution of the largest single epidemic of Ebola virus infections,23 which has led to great challenges in rationally assessing the risk of this highly fatal infection in travelers from the affected regions. A general approach to ill and/or febrile children returning from travel, which addresses these concerns, is described in a detailed clinical flow chart in the Figure. The most important tasks are in simultaneously identifying illnesses which could prove to be potentially life-threatening due to shock, hemorrhage, altered mental status (such as malaria, meningococcemia, VHF, etc.), as well as any illnesses that may require isolation precautions to prevent spread such as meningococcemia or the viral hemorrhagic fevers.14,24,25 First and foremost is the rapid stabilization of circulation, respiration, and any hemorrhagic complications; any of which may require intensive care support as depicted in the Figure. Any child with serious neurological complications should bring up the consideration of the need and safety of a lumbar puncture, and in the same case rapid malarial diagnostics must be performed immediately if there is consideration of the possibility of cerebral malaria such as recent travel to an endemic area.14,20,26 As with any severe pediatric illness, empiric antibiotics may be used early in the resuscitation, though in the recent traveler antibacterial agents may be augmented by consideration of anti-malarial agents if life-threatening complications of malaria are a possibility.8,27–29 If a traveler has been to a malarial endemic region, rapid
Febrile/Ill Child Post-Travel

- Signs of hemorrhage, petechiae, meningismus, shock, altered mental status, or other life-threatening illness?

Yes

- Risks for meningococcemia, VHF? = Isolation and careful specimen-handling until ruled out
- Consider empiric antibiotics
- Aggressive supportive therapy

Additional Risk Factors Identified

History, physical, labs

No

Likelihood of malaria?

Malaria more likely (high endemicity areas, Not taking/poor adherence to prophylaxis, Poor vector control/mosquito exposure/bites, Appropriate timing of symptoms)

- Serial thick and thin smears, and RDTS until malaria confirmed or other diagnosis identified, or clinically resolving
- Consider empiric therapy if evidence of end-organ involvement, other serious symptoms

Malaria Less Likely

Likelihood of dengue

Dengue more likely (high endemicity areas, appropriate timing of symptoms)

- RDT / serology / PCR - Supportive treatment with emphasis on fluid replacement

Dengue less likely

Did child receive routine pediatric and geographic specific pre-travel immunizations?

Yes

Syndromic approach to differential diagnosis

Fever without a focus

- Meningococcal meningitis
- Arboviral Encephalitis
- Japanese Encephalitis
- West Nile Virus
- Trypanosomiasis
- Angiostrongylsis
- Rabies

(Rearss for malaria/dengue)
- Influenza
- Leptospirosis
- Typhoid Fever
- Chikungunya
- Acute HIV
- Arbovirus
- Rickettsiae spp.
- Trypanosomiasis

Fever + CNS symptoms

- Influenza
- Bacterial PNA
- Histoplasmosis
- Coccidiomycosis
- Tuberculosis
- Q fever
- Tularemia
- Plague

Fever + respiratory symptoms

- Meningococcal meningitis
- Arboviral Encephalitis
- Chikungunya
- West Nile Virus
- Trypanosomiasis
- Angiostrongylsis
- Rabies

Rash ± fever

Diffuse:
- Measles
- Typhoid (transient)
- Chikungunya
- Rickettsiae
- Varicella
- Parvovirus B19
- Mononucleosis
- Acute HIV

Focal:
- Bacterial Infection
- CLM, insect bite

Diarrhea ± fever

Malaria more likely (high endemicity areas, Not taking/poor adherence to prophylaxis, Poor vector control/mosquito exposure/bites, Appropriate timing of symptoms)

Malaria Less Likely

No

Increased risk for childhood and/or travel associated Rotavirus, Pneumococcus, Measles, Rubella, Hepatitis A, Hepatitis B, Polio; Yellow Fever, Influenza, JEV, Typhoid Fever, Rabies

Key:
- VHF = Viral hemorrhagic fever
- RDT = Rapid diagnostic test
- JE = Japanese Encephalitis
- PNA = Pneumonia
- AGE = Acute gastroenteritis

FIG. A clinical approach to the child presenting with a serious illness during or after travel.
diagnostic tests (RDT) for malaria and blood smears should be obtained immediately and repeated 8–12 h later if the first set is negative. After severe infections with pathogens such as meningococccemia, and malaria have been determined less likely by expedited diagnostic tests, or “empirically covered” pending diagnostics, the sequential evaluation may then follow that for dengue or other viral hemorrhagic fevers. A tiered approach to laboratory diagnostic studies can be utilized. General screening lab studies can be justified initially for nearly all ill children, while specific further studies should be considered on a more focused basis, after the initial history, physical, and screening lab studies are obtained. This again includes the consideration of risk factors (geographic regions visited, as well as symptoms), physical findings, and early laboratory findings. As noted in the Figure and in Table 4, more specific diagnostic tests should be obtained but may realistically take days to provide conclusive clinical information. Other laboratory-specific tests should be used more selectively, based upon specific syndromes. These may include hepatitis serologies, HIV tests, CMV and EBV serology, dengue titers, rapid influenza diagnostics and/or a multiplex respiratory panel, and a chest radiograph.\textsuperscript{12,18,25} Common general and specific diagnostic tests, and therapeutic approaches for the more common and serious travel-associated illnesses are discussed in the following section and are summarized in Table 4.

### Specific Categories of Illness in the Ill Pediatric Traveler

**Diarrhea—With or Without Fever**

The most common category of illnesses presenting in child travelers in the GeoSentinel Surveillance Network cohort are gastrointestinal illnesses.\textsuperscript{4} Traveler’s diarrhea in children most often presents with loose non-bloody stools associated with abdominal pain/cramps, nausea, and occasional vomiting. Severe manifestations include fever, tenesmus, and passage of mucous and/or blood in the stool represents the colorectal inflammation seen in dysentery. Alternately, severe watery diarrhea leading to dehydration may also occur. While primary causes of diarrhea in children that have not traveled are viral, bacterial causes are most common. The bacteria most commonly identified as causes of traveler’s diarrhea include enterotoxigenic \textit{Escherichia coli} (ETEC), \textit{Campylobacter jejuni}, \textit{Shigella} spp., non-typhoid \textit{Salmonella} spp.\textsuperscript{30,31} Clinicians should be aware that ETEC is not identified on routine stool culture and requires either PCR or toxin assays typically only available in the research lab setting. Shigatoxin producing \textit{E. coli} (STEC) can be diagnosed with either a specialized selective media, PCR, or toxin assays that are in use in most clinical laboratories; however, this pathogen is rare among travelers to the developing world. The duration of symptoms as well as other risk factors should direct the need for further diagnostics. An acute onset of diarrhea during or after travel can always justify sending a stool for culture, but stool collection for ova and parasitic examination should be reserved for more chronic persistent diarrhea.\textsuperscript{32} The relatively high prevalence of giardia among GeoSentinel data reflects a selection bias for causes that were not self-treated or self-resolved while still traveling.\textsuperscript{5} Examination for parasites should be considered in all immunocompromised those with acute diarrhea that have already failed one attempt at antibiotic therapy, and those with severe watery or chronic diarrhea. This should entail at least 3 samples collected on 3 different

### TABLE 4. Common laboratory diagnostics and therapy\textsuperscript{7,8,12,16,24–26}

| Infection   | Supporting laboratory findings                                      | Diagnostics*                                                                 | Therapy                                                                 |
|-------------|---------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Malaria     | Anemia, thrombocytopenia, ↑LFTs                                    | Thick and thin blood smears, RDT, PCR                                        | IV/PO antimalarials                                                    |
| Dengue      | Lymphopenia, thrombocytopenia, ↑H/H, ↑LFTs, ↑PT/PTT                 | RDT, serology, PCR                                                           | Supportive                                                             |
| Typhoid fever| Lymphopenia, thrombocytopenia                                       | Culture                                                                      | IV/PO antibiotics                                                      |
| Chikungunya | Lymphopenia, thrombocytopenia<sup>\textsuperscript{50}</sup>        | Serology, PCR                                                                | Supportive                                                             |
| Acute HIV   | Lymphopenia, thrombocytopenia                                       | Serology (ELISA-1-WB), PCR                                                  | Antiretrovirals                                                       |
| Helminths   | Eosinophilia                                                       | Stool O&P, blood smear, serology, PCR                                        | Anthelmintics                                                         |
| Viral hepatitis | ↑↑ LFTs                                                            | Serology                                                                     | Supportive, antivirals                                                  |
| Ebola       | Thrombocytopenia, lymphopenia, ↑LFTs, ↑PT/PTT                       | Serology, PCR, viral culture: special handling and lab support required      | Isolation, supportive                                                  |
| Rickettsiae | Leukopenia, thrombocytopenia, azotemia, hyponatremia               | Serology, PCR, complement fixation                                           | Antibiotics                                                           |
| Yellow fever| ↑LFTs, ↑PT/PTT, leukopenia, azotemia, acidosis                     | Serology, PCR                                                                | Supportive                                                            |
| Influenza   | Mild leukopenia and thrombocytopenia, ↑a gradient                  | RDT, PCR, culture                                                            | Symptomatic, antivirals                                                |

* RDT = rapid diagnostic test, PCR = polymerase chain reaction, WB = western blot.
days to be reviewed microscopically for intestinal protozoa such as *giardia*, amebiasis, *cryptosporidium*, and *cyclospora*. Depending on the laboratory protocol, a routine “O&P” may primarily target helminth eggs by way of iodine staining, yet not be optimized for protozoa with trichrome and modified acid fast stains to identify protozoal pathogens. Antigen assays are also available for *giardia*, *entamoeba histolytica*, and *cryptosporidium* and can increase sensitivity.

For an acute presentation of pediatric travelers, with onset during or less than 7 days after return from a trip, collection of a stool culture followed by empiric therapy with azithromycin is a reasonable strategy. Quinolone antibiotics can be considered for adolescent patients if indicated by stool culture results. However, quinolone resistance is increasingly common among enteric gram negative infections acquired in South and Southeast Asia. Empiric protozoa therapy is generally not recommended both due to the low prevalence of these infections and the fact that trimethoprim-sulfamethoxazole, metronidazole, or tinidazole are among the optimal therapies for various pathogens. The differential diagnosis for chronic or relapsing diarrhea includes non infectious causes such as irritable bowel disease and inflammatory bowel disease. Dehydration is the most common complication with pediatric diarrheal illness.

**Fever Without a Focus**

Perhaps the most challenging disease syndrome during or after travel includes the presentations of “fever without a specific focus.” By definition these involve some of the most serious travel-acquired diseases, which will require a wide array of diagnostic tools and an efficient approach to provide timely and appropriate care for pediatric travelers. The most important diseases in this category are as follows:

**Malaria**

Malaria is a common cause of systemic febrile illness and must be considered in children returning from travel to an endemic area regardless of whether or not children were receiving any type of prophylaxis. It is one of the true life-threatening emergencies associated with travel. Malaria represented 8% of childhood illnesses of pediatric ill returning pediatric travelers seen at GeoSentinel Surveillance sites but accounted for 69% of the hospital admissions. Families visiting friends and relatives (VFR), and travel to Africa are the most common known risk factors. Of the 98 pediatric cases treated at a single site over a recent 8-year period in the Washington DC area, the majority of patients were from West Africa (85%), the purpose of the visit was VFR, and prophylaxis was not used in 70% of patients. *P. falciparum* was the malaria species predominant in sub-Saharan Africa in all age travelers returning with illness to GeoSentinel surveillance clinics from 2007 to 2011.

Recognition of the disease can be challenging without an appropriate index of suspicion as common presentations for malaria include nonspecific symptoms of fever, lethargy, nausea, abdominal pain, or emesis. In a study of 107 children diagnosed with malaria in Canada, the most common symptoms described on history were fever (100%), vomiting (32%), headache (22%), and chills (20%). The most common symptoms noted on physical exam in this study were fever documented in 40%, followed by tachycardia in 20%, hepatosplenomegaly in 20%, hypotension in 5%, and CNS impairment in 3%. A similar study in the US found that fever (97.6%) followed by vomiting (34%) were the most common symptoms. Periodicity of fevers is not typically observed among travelers and young children. Younger children and infants, may present with only vomiting and fever, yet are at highest risk of developing severe disease. Perhaps the most challenging cases occur in very recent immigrants who may have some natural immunity and therefore display less severe disease findings.

In the non-immune patient, malaria can rapidly progress to a fatal outcome. The most severe presentations are associated with hypoglycemia, lactic acidosis with associated respiratory distress, profound anemia renal failure, pulmonary edema, seizures, coma, and even death. Infections by *P. falciparum*, which causes the majority of severe cases, and is most associated with drug-resistance, account for approximately 80% of total malaria cases seen in child travelers. Resulting from high parasite burdens and sequestering within capillary beds of tissues, *P. falciparum* impairs end organ perfusion and oxygenation and can rapidly progress to death if appropriate therapy is not initiated. Other species of malaria such as *P. vivax* and *P. ovale*, are rarely fatal, but offer a different challenge by presenting months to years after returning from travel to endemic regions, due to relapses from hypnozoites that remain dormant in the liver.

Diagnosis of malaria is typically based upon detection of *Plasmodium* parasites on 3 sets of Giemsa-stained thick and thin blood smears over a 12–24-h
Dengue

Dengue is a flavivirus with 4 different serotypes that is transmitted by the daytime biting Aedes mosquito. The WHO estimates that at least 50 million dengue infections occur worldwide each year. It is the second most common specific diagnosis in all traveling children with systemic febrile illness without a clear focus yet is frequently misdiagnosed, which can lead to inadequate treatment. In fact, it is a more frequent cause of serious febrile illness than malaria in all regions of the developing world, except sub-Saharan Africa and Central America. Primary infection with the virus will often remain asymptomatic in up to 50% of primary infections, or present as a nonspecific febrile illness with mild symptoms. Dengue infection can present anywhere along a wide clinical spectrum ranging from asymptomatic, to the life-threatening forms of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), both of which only occur after secondary infections with different serotypes of the virus, and should be considered in a frequent traveler or immigrant. Travelers present within the first two weeks of return, or even toward the end of a multi-week trip with arthralgia, myalgia, headache, and a diffuse erythematous maculopapular rash that usually appears as the fever subsides. The more dramatic dengue hemorrhagic fever (DHF) marked by leukopenia, thrombocytopenia, and hemorrhagic manifestations (scattered petechiae and easy bruising); and increased capillary permeability with edema and pleural effusions; and finally to dengue shock syndrome (DSS) with end organ dysfunction. Clinical signs of impending severe dengue can include severe abdominal pain, persistent vomiting, rapid breathing, mucosal bleeding, fatigue, restlessness and blood in vomit, liver enlargement (≥2 cm), and increases in hematocrit concurrent with rapid decrease in platelet count. The diagnosis of dengue is based upon serological testing, PCR, or other antigen tests. PCR is the preferred method of confirming the disease during the febrile period and is available from the CDC. Initial serologic titers should be drawn early, as most titers become positive after 5 days of illness, though confirmation may require comparison of acute and convalescent titers. Treatment of dengue is supportive, often requiring more careful fluid management, and if progressing to DHF or DSS, support in an intensive care setting.

Chikungunya

Chikungunya virus presents with symptoms similar to dengue and is transmitted by the same vector. The geographic distribution has progressively spread from its traditional range in East Africa, spreading to Asia, Europe, and Indian and Pacific Oceans. Chikungunya was first reported in the Caribbean in 2013 and the case burden has expanded dramatically enough that the majority of reported cases of the virus are now from travelers returning from the Caribbean. Chikungunya virus has similar symptoms compared to dengue but is characterized not only with and acute onset of fever and malaise, but more severe and prolonged complaints of arthralgias, joint stiffness, and the finding of arthritis with a predilection for affecting distal small joints; full convalescence may take months.

Dengue fever and severe dengue, if left untreated, can result in fatal outcomes. In addition, patients with severe dengue can also exhibit signs of dengue hemorrhagic fever, which can include severe abdominal pain, persistent vomiting, rapid breathing, mucosal bleeding, fatigue, restlessness and blood in vomit, liver enlargement (≥2 cm), and increases in hematocrit concurrent with rapid decrease in platelet count. The diagnosis of dengue is based upon serological testing, PCR, or other antigen tests. PCR is the preferred method of confirming the disease during the febrile period and is available from the CDC. Initial serologic titers should be drawn early, as most titers become positive after 5 days of illness, though confirmation may require comparison of acute and convalescent titers. Treatment of dengue is supportive, often requiring more careful fluid management, and if progressing to DHF or DSS, support in an intensive care setting.
Enteric Fever

The enteric fevers include both the classic “Typhoid Fever,” caused by Salmonella typhi, and “paratyphoid fever,” caused by Salmonella paratyphi. It is estimated that each year in the US 400 cases of typhoid fever and 100 cases of paratyphoid fever are reported in returning travelers. Both have incubation periods of approximately 7–14 days. Children commonly present with fever, headache, malaise, and anorexia; splenomegaly is an occasional manifestation and the pathognomonic rash of “rose spots” is infrequently observed. Counter-intuitively, children often present with constipation rather than diarrhea. Diagnosis is best made by isolating the bacteria from blood cultures. Recovery of this organism is enhanced by obtaining more than one blood culture, as well as obtaining larger volumes of blood than typically obtained for pediatric cultures. Vaccine efficacy ranges from 50% to 80% for both the oral live-attenuated vaccine and the parenteral capsular polysaccharide vaccine. Many travelers to endemic regions fail to obtain the typhoid vaccine. Of 1027 travelers diagnosed with typhoid, only 36 reported having received the typhoid vaccine in the 5 years preceding travel. In fact, according to GeoSentinel surveillance data, the two most common illnesses occurring in pediatric travelers, which are vaccine-preventable, include those caused by S. typhi and the Hepatitis A virus. Antibiotic choices for therapy include ceftriaxone, ciprofloxacin, and azithromycin, but treatment for typhoid depends on the resistance patterns of the area visited, as in many regions, including southeast Asia, where resistance to fluoroquinolones has become prevalent. The ability to specifically test the antibiotic resistance pattern of an isolate is a compelling reason that attempts should be maximized to recover the specific organism.

Leptospirosis

Leptospirosis is a globally endemic zoonotic infection found in both temperate and tropical regions but travelers with eco-tourism and adventure itineraries have the highest risk of exposure. Human exposure usually occurs through contact of soil or water contaminated with urine from infected animals, or contact with the tissues from infected animals. The clinical presentation is classically described by the 2 distinct phases of illness; which may begin with an early, often abrupt initial septicemic phase, characterized by fever, chills, headache, nausea, vomiting, and a transient petechial or purpuric rash. A second immune-mediated stage is characterized by hepatomegaly, headache, aseptic meningitis, myalgia, rash, and conjunctival suffusion. Severe disease is described in approximately 10% of cases and when these manifestations include jaundice and renal failure is called “Weil Syndrome.” Diagnosis is based either upon 4-fold rise in antileptospiral antibodies or recovery from blood (more common in the septicemic phase) or urine but requires specialized lab techniques and results will not be available in a timely manner. Individuals with appropriate risk factors and compatible clinical manifestations should be treated empirically. Treatment for mild leptospirosis is doxycycline or, in young children, amoxicillin. Intravenous penicillin is the drug of choice for patients with severe infection.

Fever With CNS Symptoms

Neisseria meningitidis

N. meningitidis infections are among the most fulminant childhood bacterial infections affecting young children and residents of dormitories and barracks. Outbreaks, typically serogroup A, in the “meningitis belt” of sub-Saharan Africa, particularly during the dry season, occur frequently and there is a threat to travelers in the region. While vaccination is the principal control measure utilized, not all serotypes are covered through routinely recommended vaccinations. In particular, vaccines to protect against serogroup B meningococcal disease, which emerged among the U.S.-based school and college outbreaks in recent years, have only recently been licensed in the United States. Regardless of immunization status, it is important to quickly start empiric therapy for meningococcemia if one suspects this diagnosis, as outlined in the Figure. Children can present insidiously with nonspecific signs such as fever, chills, malaise, prostration, and rash (maculopapular to purpuric) yet often progress within hours to coma and death. Treatment relies on early suspicion and empiric antibiotic therapy with a broad-spectrum antibiotic (such as ceftriaxone), supportive treatment for shock, and when present, symptomatic therapy to reduce increased intracranial pressure. This obviously requires a highly capable intensive care environment.

Rabies

Fortunately, the acquisition of rabies during travel, as well as at home, remains an extremely rare occurrence, though a fatal outcome from the disease still occurs nearly 100% of the time. It should be considered in the...
differential diagnosis of any traveler presenting with fever and encephalitis. Additionally GeoSentinel surveillance data have identified children especially the 0–11 year old as being more prone to animal bites as compared to adults. The more common challenge for travelers is the need for obtaining early and appropriate post-exposure prophylaxis to prevent rabies, which is a tremendous logistical challenge in many regions of the world. Patients surveyed after an animal bite exposure, which occurred while traveling, demonstrated that rabies immune globulin (RIG) and rabies vaccine were not always readily available at their destination. In the unfortunate situation of seeking post-exposure prophylaxis in less developed regions of the world, travelers should look for providers using vaccines and rabies immunoglobulin (RIG) that conforms to WHO guidelines. One important resource is that US Embassies, as well as the International Society of Travel Medicine (ISTM.org), maintain lists of clinics and hospitals where rabies post-exposure prophylaxis is available, as discussed in the article on preparation for international travel.

Children who will spend long periods of time in rabies endemic regions (especially VFR travelers and expatriate residents) should be considered to be at increased risk of exposure, and consideration should be given for pre-travel administration of the 3 dose pre-exposure regimen both for added safety and, though still needing a vaccine booster, avoiding the difficulties of obtaining RIG.

Fever With Respiratory Symptoms

Respiratory illnesses, influenza-like illness, bronchitis, and pneumonia are common among child travelers and occur at rates similar to adults. Among cases reported in the GeoSentinel cohort, influenza was specifically diagnosed in 8% of ill travelers, and Legionella in 0.7%. The majority of respiratory illnesses in children returning from travel are due to the commonly encountered viruses and bacterial agents found globally. However, one must still consider the risk of less common sources endemic to specific geographic regions or unusual exposures. As discussed previously, consideration should be given to the travel history, any specific activities (such as exposures to birds and their droppings, parturient animals, etc.) and the recent patterns of respiratory disease in the specific geographic regions visited. Depending on identification of specific and risk factors, one must consider more unique etiologies such as histoplasmosis, Legionella pneumophila, melioidosis, and Q fever, as well as emerging viruses such as SARS coronavirus and MERS-CoV. These novel organisms highlight that nothing should be “taken for granted,” and clinicians should be quick to consult with the continuously updated on-line resources regarding outbreaks and emerging infections discussed elsewhere in this supplement when evaluating unexplained serious respiratory disease in a recent traveler. For pediatric travelers, the use of a rapid diagnostic test for influenza and RSV are beneficial in the initial evaluation and should be performed on febrile children returning with respiratory complaints. One caveat is that viral infections such as influenza and RSV are prevalent throughout the year in many tropical climates, and do not follow the same seasonality observed in temperate climates. Tuberculosis should be considered especially in those travelers who are traveling to areas of high endemicity where risks may approach those of local populations or those who were working or volunteering in health care roles involving direct patient care.

Presentations of Rash (With or Without Fever)

Focal Disease

The GeoSentinel surveillance of children presenting with focal or localized skin lesions noted that nonfebrile skin lesions are much more common than febrile, and included a variety of complaints ranging from cutaneous larva migrans, tungiasis, and myiasis to animal bites. Other rarer focal dermatological conditions include ulcers from cutaneous leishmaniasis, and presence of focal ulcer with fever may be indicative of bacterial infections or anthrax. It is beyond the scope of this review to present an extensive discussion, other than to offer the practical advice that consultation with a dermatologist with experience in global and tropical diseases is invaluable in these situations.

Systemic Disease

Dermatological manifestations as part of the presentation of systemic infectious diseases are also very common. As stressed in the Figure, fever in the presence of petechial or hemorrhagic skin lesions must be addressed immediately as the differential diagnosis can include meningococcemia, dengue fever, leptospirosis, or rickettsial infections, many discussed previously in this article. Macular rashes can
be associated with measles, which is still endemic in many parts of the world, as well as Dengue and Chikungunya.  

Rickettsial diseases may present with a variety of skin manifestations including macular or, in the case of rickettsialpox, vesicular rashes, as well as the petechial lesions. The classic inoculation eschar is a painless black skin lesion surrounded by a red halo that can develop at the site of an infective tick bite. The presence of an eschar lesion plus a red halo that can develop at the site of an infective tick eschar is a painless black skin lesion surrounded by a well as the petechial lesions. The classic inoculation eschar, or, in the case of rickettsialpox, vesicular rashes, as well as with a variety of skin manifestations including macular

Eschars, often with surrounding edema, are also associated with anthrax, though infection in travelers is rare and typically involves direct contact with animals or their hides. As discussed previously, though classic “rose spots” are less common in children, are indicative of typhoid fever. Urticarial rash, fever and peripheral eosinophilia in a traveler with freshwater exposure (particularly in sub-Saharan Africa) would be highly suggestive of Katayama fever or acute Schistosomiasis. However, in some case reports up to 33% of patients can be asymptomatic and consideration for schistosomiasis should be strongly considered in expatriates, missionaries, volunteers, and researchers, and aid workers who tend to remain in areas for longer periods and have a two-fold greater risk of schistosomiasis.  

Presentation of a maculopapular rash within 21 days of exposure may be indicative of a viral hemorrhagic disease, for example Lassa fever or Ebola, and must be correlated with specific travel history (i.e., consumption of bush meat, or participation in traditional burial rituals) and knowledge of regional outbreaks. Once more exotic causes for rash have been ruled out it is important to consider common viral illnesses such as parvovirus, mononucleosis, roseola, and enteroviral disease.

Summary

It is impossible to discuss in detail all potential etiologies of every category of presenting illness. This article has focused on a logical approach that prioritizes the evaluation of an ill pediatric traveler based on a combination of the pattern and severity of illness and the most likely exposures occurring in the region visited, while taking into account all risk factors which can be identified. The reader is recommended to pursue the excellent references cited, especially the readily available and constantly updated on-line resources made freely available to practitioners everywhere.

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