Severe Infections in the Returning Traveler

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The ease of air travel has made spread of infectious agents a global problem. There are a multitude of tropical diseases ranging from benign viral illnesses to highly contagious and life-threatening diseases and it is important to take a detailed clinical and travel history from the ill returning traveller, especially in the first 4 weeks of return.

The following article will concentrate on three major disease areas:

1. Falciparum malaria, which remains a very important infection because delays in diagnosis may be fatal.
2. Emerging or reemerging infections, such as severe acute respiratory syndrome (SARS) or avian influenza, have a serious impact on patients but also on staff, especially in a critical care environment.
3. There are highly contagious infections, such as viral hemorrhagic fever (VHF), with high mortality, which present occasionally in the United Kingdom. It is important to be familiar with those diseases and their common presentations to be able to deliver the best care in an environment safe for both patients and staff. Recognizing these diseases and instigating appropriate management protocols are essential for patient management and protection of staff.

Severe and Complicated Malaria

There are four human malarial parasites; Plasmodium falciparum, p. ovale, p. vivax, and p. malariae. Severe and complicated malaria is caused by p. falciparum and will be dealt with here. Malaria is estimated to cause 200 million clinical cases and approximately 1 million deaths mainly in sub-Saharan Africa each year. More than 75% of deaths are in children younger than 5 years old. In adults, severe falciparum malaria is more commonly seen in populations vulnerable because of war or famine, during pregnancy, and in nonimmune travellers to malarial endemic areas. In the United Kingdom, severe malaria is most often seen in travellers who have not taken chemoprophylaxis, those who present late, and those with underlying medical conditions. Malarial chemoprophylaxis does not provide absolute protection and, therefore, malaria must be excluded as a cause of febrile illness in all travellers returning from endemic areas.

Clinical and Laboratory Features

The incubation period for falciparum malaria is at least 7 days. Patients commonly present within 2 weeks of return to the United Kingdom. Occasionally, however, they may present later; up to 3 months after return, especially if chemoprophylaxis has been taken. The clinical presentation of severe malaria is very variable depending on the immunity of the infected person. The most common presentation is with fever, chills, malaise, headache, myalgia, anorexia, nausea, diarrhea, dry cough, impaired consciousness, and convulsion (cerebral malaria). They may be pale, dehydrated, jaundiced, hypotensive, confused, and may have tender hepatosplenomegaly. Some of the false localizing features (e.g., significant diarrhea) can cause diagnostic confusion. Table 9.1
lists the criteria for severe and complicated malaria. In nonimmune patients, severe malaria can occur without heavy parasitemia.

The most common laboratory abnormality is thrombocytopenia. Other abnormalities include anemia, deranged clotting, hyponatremia with or without renal impairment, raised liver transaminases, raised bilirubin, metabolic acidosis, and low blood glucose and hypoalbuminemia.

Remember: patients who present with fever lasting longer than 4 days and/or who have not taken any malaria prophylaxis may be severely ill, requiring critical care input at an early stage.

Pathogenesis

Several mechanisms are involved in the pathogenesis of complicated malaria.

Parasitized red blood cells (pRBC) develop “knobs” on the cell membrane, which adhere to capillary endothelial cells. In addition, the red cells may conglomerate around pRBC, causing a phenomenon called “rosetting.” The end result is sequestration of pRBC, causing blood flow obstruction and tissue anoxia. Release of cytokines, such as tumor necrosis factor (TNF), also have a role in the pathogenesis of cerebral malaria. Anemia is caused by bone marrow suppression and red cell destruction, either directly or immune mediated. Acidosis is a marker of severity of disease caused by lactic acid release from hypoperfusion and cytokine release.

Management

Management should include specialist advice from Regional Infections Disease Units. Severe falciparum malaria (Table 9.1) should be managed in the high dependency unit (HDU) or intensive therapy unit (ITU). The definitive diagnosis is made by finding *P. falciparum* on a blood film (Figure 9.1). A rapid antigen test specific for *P. falciparum* is available, which may help in the initial management of the patient while waiting for the microscopy result. An assessment of severity must be performed (see Table 9.1). Recommended treatment regimens are shown in Table 9.2. Artemisinin-based combination therapy has now been shown to be as effective as quinine in treating severe and complicated malaria, and intravenous artesunate has been shown to be more efficacious with reduced complications and mortality. In the United Kingdom, quinine is still recommended by the British Infection Society guidelines, but intravenous artesunate may be used in certain circumstances, although it is not easily available. In some parts of the world, such as Southeast Asia, there is widespread quinine resistance and so these new drugs are of great importance.

Exchange transfusion can be used in heavy parasitemia (>10%) to increase parasite clearance, although there is no randomized trial for this form of therapy. Introduction of intravenous artesunate may reduce the need for plasma exchange transfusion because it reduces parasitemia much
more rapidly than quinine. Patients may develop acute renal failure and severe lactic acidosis, requiring hemofiltration or hemodialysis. Fluid management is crucial because dehydration is common but overly liberal infusion can cause pulmonary or cerebral edema. Empiric antibiotics may be necessary when sepsis cannot be excluded. Occasionally, patients may develop hypoxic events or cardiomyopathy after severe malaria and these should be considered when recovery, despite parasite clearance, does not proceed as expected.

### Severe Malaria in Pregnancy

Pregnancy is a risk factor for severe malaria in endemic areas as well as for visitors. Malaria-related maternal mortality is particularly high in low-malaria transmission areas where natural immunity is low. Death may be directly related to severe falciparum malaria, or indirectly from malaria-related severe anemia. In addition, malaria in pregnancy can result in stillbirth, spontaneous abortion, intrauterine growth retardation, low birth weight (<2.5 kg), and neonatal death.

The increase susceptibility to malaria is probable caused by waning of immunity during pregnancy compared with nonpregnant women. In areas of low transmission and epidemics, pregnant women are prone to malaria infection developing severe disease because of lack of protective immunity. Additionally nonimmune pregnant travellers are at the highest risk. PRBC are sequestrated in the placenta, resulting in impairment of function. Management of severe malaria in pregnancy requires multidisciplinary input from obstetricians, pediatric intensivists, adult intensivists, and infectious diseases specialists, but should follow otherwise the same management as outlined above (Table 9.2). Particular problems during treatment in pregnancy are hypoglycemia from both the infection and quinine, and pulmonary edema. Quinine is recommended in severe malaria with clindamycin (doxycycline is contraindicated). Artemisinin derivatives are currently not recommended because the teratogenic risk in humans has not been fully assessed. Other drugs used commonly for symptom control, such as nonsteroidal anti-inflammatory drugs (NSAIDs), are relatively contraindicated in pregnancy.

Remember: falciparum malaria in pregnancy is worse in the nonimmune patient and may be associated with serious disease to both mother and child and require early critical care input.

### SARS as an Example of an Emerging Contagious Disease with High Morbidity and Mortality

SARS is caused by SARS-associated coronavirus (SARS-CoV), a novel coronavirus that first caused human illness in the Southern Chinese province of Gaungdong toward the end of November 2002. It may have originated as a zoonosis. It spread to Hong Kong in February 2003, when an infected doctor fell ill while staying at a hotel. From this index case, the disease spread in the local population as well as to other Asian countries, Canada, the United States, and Germany. The mortality rate ranged from 0% in mild cases to 50% in those with severe disease. The World Health Organization (WHO) announced an end of SARS transmission in July 2003, by which time, there were more than 8000 probable cases of SARS and 774 deaths in 29 countries, with a case fatality rate of 10%. A significant number of medical and paramedical staff were affected, particularly those involved in
airways management. Introduction of new rigorous infection control mechanisms in acute and critical care setting were necessary. Since July 2003, there have been no new outbreaks of infections, but this new disease entity has the potential to reemerge and exemplifies the problems faced by clinicians in the coming years.

**Clinical and Laboratory Features**

The incubation period of SARS ranges from 2 to 16 days (median, 10 d). The clinical features range from mild respiratory symptoms to very severe disease with pneumonia and respiratory failure. SARS commonly presents with fever, chills, rigors, myalgia, sore throat, and headache followed by a nonproductive cough and breathlessness. In the second week of illness, watery diarrhea may occur and chest signs worsen. Signs may be minimal initially and progress to consolidation and pleural effusion. Approximately 20% of patients develop acute respiratory distress syndrome (ARDS), necessitating ventilatory support, and a high proportion will develop nosocomial sepsis and multiorgan failure with a high mortality rate.

The clinical case definition of suspected, probable, and confirmed cases in the event of reemergences of SARS is listed in Table 9.3. The diagnosis of SARS is made by either isolation of virus by cell culture or by reverse transcriptase (RT) polymerase chain reaction (PCR), or by four-fold rise in antibody titers.

Laboratory findings at presentation include anemia, lymphopenia, thrombocytopenia, hyponatremia, hypocalcemia, raised lactate dehydrogenase (LDH) levels, and elevated liver transaminases. The raised LDH level indicates severity.

An abnormal chest X-ray is present in up to 80% of patients at onset of fever, initially as unilateral patchy shadowing, which progress to bilateral involvement. Early computed tomographic (CT) scans show subpleural focal consolidation.

**Management**

It is vital to consider SARS as a possible diagnosis during an active outbreak here or elsewhere in the world. Symptomatic “probable” cases of SARS require urgent assessment and negative pressure isolation facilities. Clear guidance for admission to a critical care unit needs to be established within each hospital setting. Empiric antibiotic should be used to cover community-acquired pneumonia because clinical presentation is nonspecific and rapid laboratory diagnosis is difficult.

During the SARS outbreak in 2003, ribavirin, a broad-spectrum antiviral was used widely but there is no randomized control trial to assess its efficacy. However, in the absence of alternative agents, this should be considered early in management. Systemic steroids are suggested on the

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**Table 9.3.** UK SARS case definition, if SARS reemerges (once verified by WHO)

| Suspect case of SARS                                                                                   |
|--------------------------------------------------------------------------------------------------------|
| Respiratory illness requiring hospitalization characterized by:                                       |
| • Fever (>38°C) and                                                                                  |
| • Cough or breathing difficulty and                                                                   |
| • One or more of the following exposure during the 10 days before onset of symptoms:                  |
|   ◦ Close contact with a suspect or probable case of SARS                                            |
|   ◦ History of travel to area with recent local transmission of SARS                                   |
|   ◦ Residing in an area with recent local transmission of SARS                                         |
|   ◦ History of exposure to laboratories that have retained SARS virus isolates and/or diagnostic specimens from SARS patients |
|--------------------------------------------------------------------------------------------------------|
| Probable case of SARS                                                                                 |
| A suspected case with:                                                                               |
| • Radiological evidence of infiltrates consistent with pneumonia or respiratory distress syndrome (RDS) or |
| • Autopsy finding consistent with the pathology of pneumonia or RDS without an identifiable cause     |
| • No alternative diagnosis to fully explain their illness                                              |
|--------------------------------------------------------------------------------------------------------|
| Confirmed case of SARS                                                                               |
| Symptoms and signs that are clinically suggestive of SARS and:                                        |
| • Laboratory evidence of SARS-CoV infection based on one or more of the following:                   |
|   ◦ PCR positive for SARS-CoV (validated method) from at least two different specimens (respiratory, stool) |
|   ◦ Same clinical specimen collected on two or more occasions                                         |
|   ◦ Two different assays or repeat PCR using new RNA extract                                          |
|   ◦ Seroconversion by enzyme-linked immunosorbent assay (ELISA) or immunofluorescence assay (IFA)    |
| • Positive antibody test during convalescent phase after negative test during acute illness           |
| • Four-fold rise in antibody titers between acute and convalescent sera                               |
| • Virus isolation                                                                                    |
| • Isolation in cell culture of SARS-CoV from any specimen, plus                                       |
| • PCR confirmation using validated method                                                            |
|--------------------------------------------------------------------------------------------------------|

Source: Lim et al., 2004.
basis of experience in Hong Kong and Toronto as part of a three-pronged approach (Table 9.4). The rationale was that, despite decreases in SARS-CoV viral load and rises in SARS-specific IgG toward the third week of illness, clinical deterioration was observed, probably related to cytokine release induced by the virus. Currently interferon has no use in clinical practice.

Up to 30% of SARS patients required intensive care admission. Of these, 10 to 20% needed mechanical ventilation. Noninvasive ventilation was used widely and was estimated to prevent intubation and mechanical ventilation in two-thirds of severe cases, but infection risk associated with aerosol generation is greatest in noninvasive intermittent ventilation (NIV) and during intubation.

**Control of Infection**

Healthcare workers (HCWs) are at great risk of contracting SARS, and it was estimated to have affected up to 30% of staff in the Hong Kong outbreak, with occasional fatalities. In particular, HCWs involved in airways management, such as critical care staff, are at high risk of exposure. After the SARS outbreaks in 2003, each hospital should have developed their own protocols to prevent disease transmission. It is, however, important to realize that infection control measures should be applied to every patient. United Kingdom recommendations are shown in Table 9.5.

**Other Issues Relating to New or Emerging Infections**

The critical care staff are under increased stress during the management of a highly infectious patient and require close monitoring and support. SARS reminds us that there are other potentially serious infections that require all members of staff to be on high alert.

**Viral Hemorrhagic Fever**

VHF encompasses a wide range of viruses that cause febrile hemorrhagic illness with high case fatality rates. There are four main viruses, which are predominantly zoonotic but can cause human disease (Table 9.6). They are highly infectious agents that can spread by direct contact with blood, secretions, organs, or other bodily fluids of infected persons.

**Pathogenesis**

Each VHF may present a different disease spectrum, but there are common pathophysiological processes. There is vascular endothelial damage

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**Table 9.5.** Infection control in hospital management of SARS

| Measure                                                                 |
|------------------------------------------------------------------------|
| Patient to wear surgical mask continuously unless on face mask for oxygen |
| Admit to a negative-pressure room (single room if unavailable)          |
| Transfer to designated center with facility for isolation (negative pressure) |
| Ensure HCWs adhere to control measures: gown, gloves, goggles or visors, respirator masks (EN149:2001, FFP3), and strict hand washing |
| Inform hospital infection control, regional disease control center (CCDC), designated SARS infectious disease unit, and maintain list of all staff in contact with the patient |
| All staff to be vigilant for symptoms after contact with patient and not to turn up for work if develop symptoms up to 10 days after exposure |
| Visitors to be restricted (except for immediate family)                  |

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**Table 9.4.** Modified treatment protocol for probable or confirmed SARS

| Standard treatment protocol for SARS in adult patients (Hong Kong) |
|--------------------------------------------------------------------|
| Antibiotic (according to local protocol for community-acquired pneumonia) |
| • 500 mg levofloxacin daily, intravenously or orally; or |
| • 500 mg clarithromycin twice daily plus |
| • 375 mg Amoxiclav (amoxicillin and clavulanic acid) three times daily, orally |
| Antiviral (10–14 d) |
| • 400 mg Ribavirin every 8 hours intravenously for 3 days, or when stable; then |
| • 1200 mg Ribavirin twice daily |
| Corticosteroid regime (21 d) |
| • 1 mg/kg methylprednisolone every 8 hours for 5 days; then |
| • 1 mg/kg methylprednisolone every 12 hours for 5 days; then |
| • 0.5 mg/kg prednisolone twice daily for 5 days; then |
| • 0.5 mg/kg prednisolone daily orally for 3 days; then |
| • 0.25 mg/kg prednisolone daily orally for 3 days; then |
| • Stop |
| • Pulsed 500 mg methylprednisolone twice daily intravenously for 2 days (if worsening) |
| Ventilation |

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caused by both direct viral injury and indirect effects or from inflammatory cytokines and immune activation. In addition, there is disruption of coagulation system, leading to disseminated intravascular coagulation.

**Clinical and Laboratory Features**

VHF is considered in a patient with fever who has visited a known endemic area or has been in contact with a suspected or confirmed case up to 21 days before onset of symptoms. Table 9.7 summarizes the risk category for VHF. Clinical presentation of VHF ranges from mild nonspecific symptoms to severe life-threatening manifestations. In severe disease, capillary leakage leads to shock. Bleeding may be extensive from gums, puncture sites, and orifices. Multiorgan failure occurs commonly, including encephalopathy, renal, and hepatic failure.

Laboratory specimens are extremely biohazardous and need to be sent in secure containers to specific Category 4 laboratories. Common initial abnormalities include raised hematocrit, leucopenia, thrombocytopenia, raised transaminases, and disseminated intravascular coagulation. Diagnosis is made by isolation of the virus or raising antibody levels.

It is important that treatable infections that are more common, such as malaria and typhoid, are considered and treated or excluded.

**Management**

Because VHF cases are managed in a center with the appropriate expertise and isolation facilities. In the United Kingdom, there are only two such units that use Trexler isolators for patient containment (Royal Free Hospital, London; and Newcastle General Hospital, Newcastle upon Tyne; Figure 9.2). It is, therefore, important to consider the diagnosis of VHF in patients carefully and seek advise early to prevent spread of infection. Supportive treatment and management of complications is important in all cases of VHF. Ribavirin is beneficial in the treatment of Lassa fever and Crimean-Congo hemorrhagic fever.

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**Table 9.6. Main features of VHF**

| Disease/virus                    | Family Genus      | Vector/route of transmission          | Geographical area | Mortality rate |
|---------------------------------|-------------------|---------------------------------------|-------------------|---------------|
| Ebola hemorrhagic fever         | Filoviridae       | Unknown Human to human Nosocomial spread | Sub-Saharan Africa | 25–90%        |
| Marburg hemorrhagic fever       | Filoviridae       | Unknown Human to human Nosocomial spread | Sub-Saharan Africa | 25–90%        |
| Lassa fever                     | Arenaviridae      | Rodent excreta Human to human          | Western Africa    | 2–15%         |
| Crimean-Congo hemorrhagic fever | Bunyaviridae      | Tick bite Blood of infected animal Human to human | Eastern Europe, Asia, Africa | 15–30% |

**Table 9.7. Risk categorization for VHF**

| Minimum (febrile patient)       |                                                               |
|---------------------------------|                                                               |
| • Not been in endemic area before onset of illness; or |                                                               |
| • Onset of illness longer than 21 days after being in endemic area or contact with suspected or confirm case of VHF |                                                               |

| Moderate (febrile patient)      |                                                               |
|---------------------------------|                                                               |
| • Been in endemic area during the 21 days before onset of illness (no additional risk factors); or |                                                               |
| • Been to adjacent area during the 21 days before onset of illness, and have severe disease, e.g., multiorgan failure, with no alternative cause |                                                               |

| Severe (febrile patient who has been to an endemic area during the 21 d before illness) |                                                               |
|---------------------------------|                                                               |
| • Stayed in house longer than 4 hours with confirmed or strongly suspected case of VHF |                                                               |
| • Nursed or cared for confirmed or strongly suspected case of VHF |                                                               |
| • Laboratory or HCW likely to come in contact with body fluid, tissue, or dead body of VHF patient or animal |                                                               |
| • Febrile patient not been to endemic area but in contact with confirmed or strongly suspected case or secretions/clinical specimens from such a case |                                                               |
Summary

Modern travel broadens the spectrum of diseases imported to the United Kingdom. Tropical or subtropical diseases may be brought back well within their incubation period, adding to diagnostic difficulties. Failure to take an adequate travel history is the commonest cause of “missed” diagnoses. Falciparum malaria, SARS, and VHF are examples of infections with high morbidity and mortality rates, often requiring critical care support. These diseases are uncommon and the general intensivist requires regular updates of knowledge, and procedures for infection control are essential. Up-to-date management will lead to better outcomes for patients and will also reduce the risks to staff. In the future, we may see more patients with tropical illness because of rising travel to increasingly exotic destinations and more travel by at-risk groups, such as the elderly and those with preexisting medical problems.

Suggested Reading

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