Life Threatening Tropical Infections

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Abstract

Infectious diseases are among the most common pediatric illnesses and are frequently encountered in the pediatric intensive care unit. Tropical infections, on the other hand, are relatively uncommon in children in developed countries, except those with pertinent travel histories or recent immigration. Clinicians who participate in mission work and disaster relief work also encounter these diseases as they are endemic in many developing nations. For the most part these infections do not result in critical illness however some do and this chapter will focus on a few of the more common infections with potential to be acutely life threatening. The epidemiology, pathophysiology, clinical manifestations, and current clinical management are presented for severe malaria, dengue fever, typhoid, and leptospirosis.

Keywords

Severe malaria • Dengue fever • Typhoid • Leptospirosis • Critical illness • Pediatric

Introduction

Infectious diseases are among the most common pediatric illnesses and are frequently encountered in the pediatric intensive care unit (PICU). Tropical infections, on the other hand, are relatively uncommon in children in developed countries, except those with pertinent travel histories or recent immigration. With a few notable exceptions, most tropical infections seen in developed countries are likely to cause illnesses that do not result in the need for critical care. As a result, many pediatric intensivists have minimal exposure and training related to these diseases. There are two scenarios in which life-threatening tropical diseases are likely to be encountered in developed countries: (1) *Imported diseases* seen in returned travelers or immigrant children and (2) *Locally prevalent diseases* seen during mission trips to tropical countries. Of course, clinicians working in developing countries are likely to see many of these diseases and conditions almost daily. These clinicians likely will have a different level of experience and expertise with these diseases. As such, the chapter will be geared towards those clinicians working in developed countries, focusing on those diseases that either present in developed countries after travel/immigration or those that are encountered by healthcare providers who engage in disaster relief and/or mission work.

Imported Diseases

Millions of children travel internationally every year [1] to many developing countries. While most return home healthy, travel acquired illness should be included on the differential diagnosis of the acutely ill child, especially if presenting less than 30 days after returning from abroad. The largest multinational study to date [2] reporting on the clinical and epidemiological characteristics of 1,591 children who were ill after international travel

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D.S. Wheeler et al. (eds.), *Pediatric Critical Care Medicine*,
DOI 10.1007/978-1-4471-6416-6_37, © Springer-Verlag London 2014

Table 37.1 Incubation periods for potentially life-threatening tropical infections

<14 days
Bacterial diarrhea
Dengue
Malaria (falciparum)
Typhoid fever
Leptospirosis (average 1–2 weeks)
Rickettsial infection
Avian influenza
Viral hemorrhagic fever
Chikungunya
Yellow fever
14–30 days
Malaria (falciparum)
Typhoid fever (average 7–21 days)
Hepatitis A and E (2–6 weeks)
Acute schistosomiasis
Tuberculosis
>30 days
Malaria (ovale, vivax)
Hepatitis A, B and E
Acute schistosomiasis
Tuberculosis

found that the most common syndrome categories were diarrhea (28 %), dermatologic disorders (25 %), systemic febrile illnesses (25 %), and respiratory disorders (11 %) [2]. The group with the highest rate of hospitalization (36 %) was the systemic febrile illness group. Apart from the nonspecific viral illness syndrome, this group included malaria, typhoid fever, and dengue fever – two thirds of children presenting with these conditions required hospitalization. This finding is in keeping with previous observations that almost all life-threatening infections after travel present with fever [1, 3, 4].

In the approach to the pediatric febrile returned traveler, knowledge of incubation periods can give critical clues to the etiology of the underlying fever (Table 37.1) [3, 5–7].

In this chapter we will focus our discussion on the three most common tropical infections that may present with critical illness in the United States, which include malaria (there are approximately 225 pediatric cases every year in the US), dengue (there were 23 reported cases in children between 1999 and 2009, though dengue was not a reportable disease to the CDC until 2009, so this is likely a gross underestimation), typhoid fever (there were 21 pediatric cases reported to the CDC between 1999 and 2009 [8]), and leptospirosis. In addition, the practitioner should include rickettsial diseases and tuberculosis in their differential diagnosis of the sick febrile child returning from the tropics. Although these diseases have worldwide prevalence and specific risk factors related to various exposures, they are more commonly encountered in the tropical regions.

Locally Prevalent Diseases

In addition to the conditions listed above, the following is an abbreviated list of potentially life-threatening infectious diseases that are likely to be encountered while working overseas:

1. Severe diarrheal syndromes, notably cholera, amebiasis, *Clostridium perfringens*
2. Other hemorrhagic fevers, including yellow fever, Congo-Crimean fever, Lassa fever
3. Tuberculosis including meningoencephalitis, pericarditis, disseminated pulmonary disease leading to acute respiratory failure or a sepsis-like picture
4. Tetanus
5. Acute liver failure due to parasitic infestations or viral hepatidites
6. Heart failure due to Chagas disease (Trypanosoma infections)
7. Meningococcal disease
8. AIDS

Due to space limitations, we will not discuss these conditions, and the reader is referred to other textbooks on Tropical Medicine and Medical Microbiology/Parasitology as well as MMWR Geosurveillance Reports.

Malaria

Epidemiology

Malaria is the most important parasitic disease of man. Recognized since antiquity, it has a huge global impact – approximately 5 % of the world population is infected with malaria and almost two thirds of the world's population is exposed to malaria annually. In 2008, there were an estimated 243 million clinical cases globally and 863,000 deaths, mostly in children aged <5 years living in sub-Saharan Africa [9]. According to the CDC [10], from 1999 to 2008 there were 8,117 cases of travel-associated malaria with 43 fatalities among US residents. The majority of these infections (66 %) were acquired in sub-Saharan Africa with similar proportions of remaining cases from Asia (14 %) and Central/South America (12 %).

In its latest MMWR report [11], the CDC received reports of 1,484 cases of malaria in 2009, including two transfusion-related cases, three possible congenital cases, one transplant-associated case, and four fatal cases among persons in the United States. Sixteen percent of these – 225 cases – occurred in children (age <18 years). Of the 86 children for whom chemoprophylaxis information was known, 27 (31 %) were reported as having taken chemoprophylaxis – 18 of these (67 %) had taken an appropriate regimen, though only four (22 %) reported adherence. Physicians practicing in the US

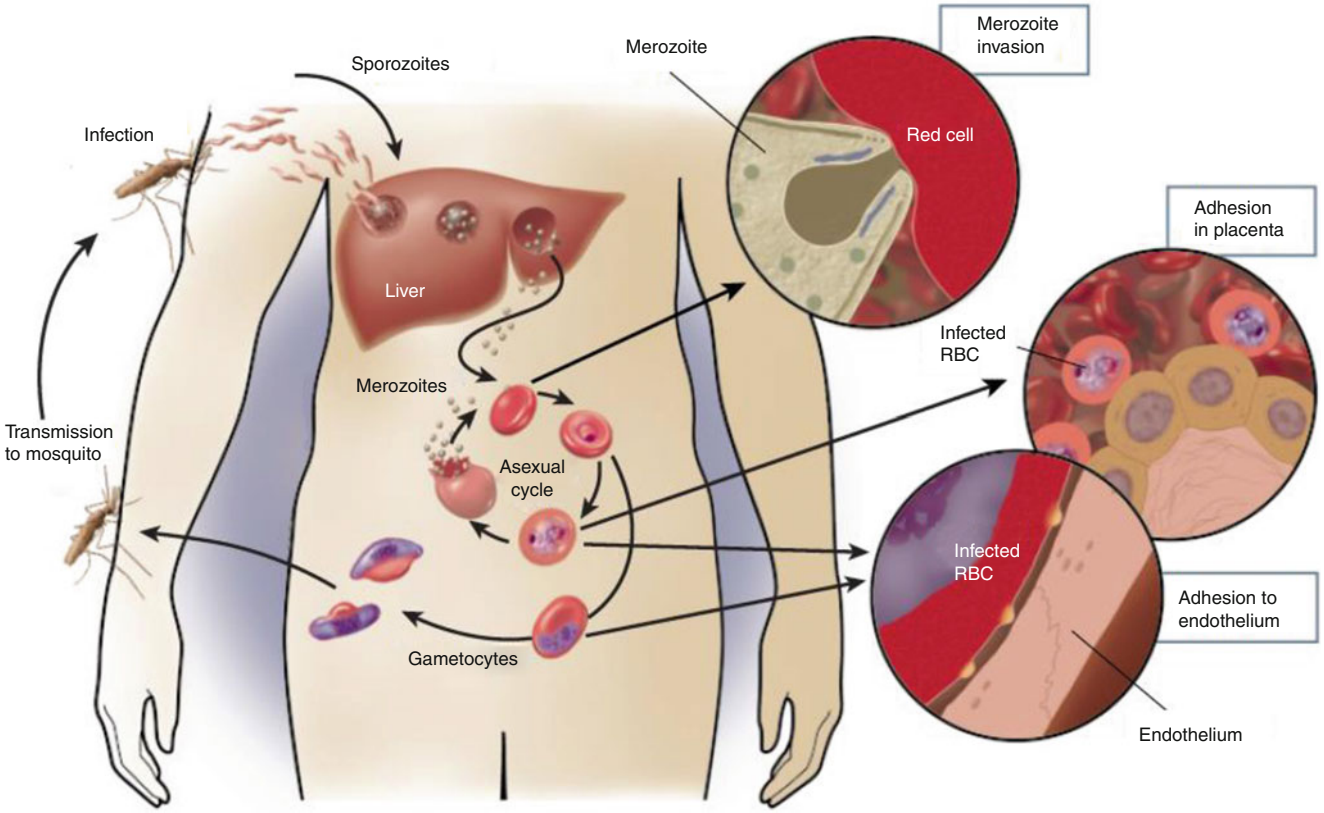

Fig. 37.1 Parasite life cycle and pathogenesis of falciparum malaria. The molecular and cellular events during the parasite life cycle influence the severity of the disease. Disease occurs only as a result of the asexual blood stage after the parasite leaves the liver and begins to invade and grow inside red blood cells (*RBCs*). All human Plasmodium spp. invade by the same mechanism, but P. falciparum reaches high parasitemia because of greater flexibility in the receptor pathways that it can use to invade all RBCs. RBCs infected with P. falciparum must bind to endothelium or placenta for the parasite to avoid spleen-dependent killing mechanisms, but this binding also leads to much of the pathology (Reprinted from Ref. [16]. With permission from Nature Publishing Group)

are unlikely to encounter malaria frequently, which can make it more difficult to include it in the differential diagnosis of fever. However, failure to consider a diagnosis of malaria in a febrile child returning from an endemic area can lead to significant delays in diagnosis – in different series, between 35 % [12] and 90 % [13] of pediatric cases were initially misdiagnosed. In children, acute malaria is often mistaken for a viral illness or acute gastroenteritis due to associated nausea, vomiting and diarrhea. This delay in recognition, compounded with lack of immediate availability of antimalarial drugs in some US hospitals, can contribute to significant morbidity and mortality.

Etiology

The malaria parasite, *Plasmodia*, is a sporozoan parasite of red blood cells (RBCs) transmitted to mammals by a mosquito vector. Human malaria is caused by five species of *Plasmodium*, namely *falciparum*, *ovale*, *vivax*, *malariae* and the recently characterized species *knowlesi* ("monkey malaria" – malaria of long-tailed and pig-tailed macaque monkeys, found on the island of Borneo and peninsular Malaysia, though it can also infect humans [14]). All of the species of *Plasmodium* causing malaria in humans are transmitted by mosquito species of the genus *Anopheles*. Only female mosquitoes bite, and the sporozoites are transmitted to the skin from the saliva of a biting female mosquito, after which they eventually make it into the bloodstream through the network of capillaries in the subcutaneous tissue. After the sporozoites are introduced to the blood through the mosquito bite, they remain in the circulation for approximately 45 min before infecting a hepatocyte [15]. For the next 6–15 days, the parasites develop in hepatocytes (the incubation period) (the sporozoites at this stage are known as schizonts) and are then released into the circulation as merozoites, where they infect RBCs. The life cycle of the *P. falciparum* is shown in Fig. 37.1 [16]. The sporozoites of both *P. vivax* and *P. ovale* can become dormant in the hepatocyte in a form referred to as a hypnozoite. The hypnozoite may emerge months to years after initial infection to cause the relapses that characterize infections with these two species [15].

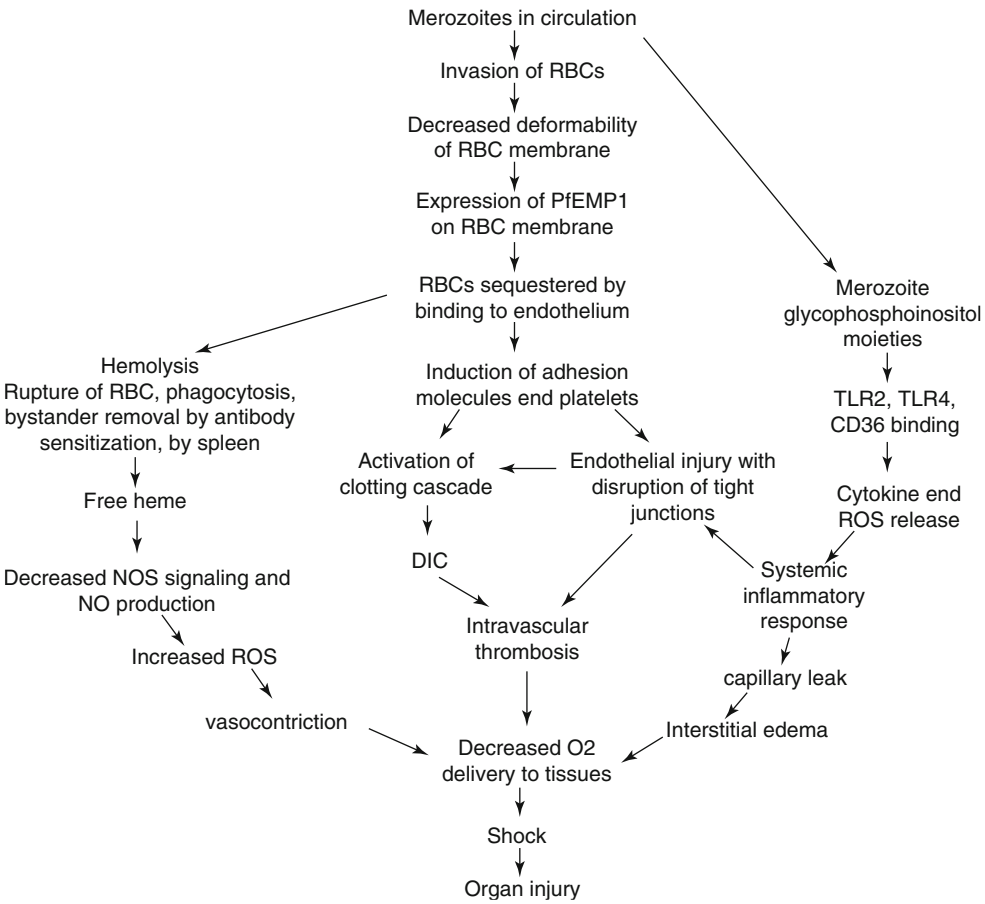

Fig. 37.2 Pathogenesis of malaria (Based on data from Ref. [23])

Within the RBCs, the sporozoites grow to form a trophozoite, dividing several times to produce new merozoites. The merozoites are released into the bloodstream, where they are free to invade new RBCs. The parasites feed on hemoglobin and other RBC materials, which causes damage and eventual destruction of the RBCs. Infection caused by *P. falciparum*, is associated with the worst morbidity and mortality due to the ability to sequester itself in the capillaries and cause major organ dysfunction [17]. Although classically viewed as "benign", infections with *P.vivax* and *ovale* can have severe clinical manifestations, such as acute respiratory distress syndrome (ARDS), severe anemia, spleen rupture [18], and in chronic untreated infections, severe malnutrition [19]. *P. malariae* can result in long-lasting infections and if untreated can persist asymptomatically in the human host for years, even a lifetime [9].

Pathophysiology of Severe Malaria

Plasmodia are parasites of RBCs, and as such the pathophysiology of malaria results from destruction of RBCs (both infected and uninfected [16]), followed by liberation of the parasite and its metabolic byproducts into the circulation, which can trigger the excessive production and release of pro-inflammatory cytokines [20–22]. As mentioned briefly above, a mechanism of disease specific to *P. falciparum* is sequestration of infected RBCs to the endothelium of various tissues, in a manner somewhat similar to sickling, leading to microvascular obstruction with decreases in the regional blood flow and perturbation of tissue metabolism. In spite of a growing body of literature on the pathophysiology of severe malaria, opinion is divided over which of these mechanisms – inflammation versus sequestration – represents the main driving force leading to disease and death in severe *P. falciparum* malaria (see Fig. 37.2) [23].

Inflammation

The idea that the characteristic febrile paroxysms of malaria are induced by parasite products released at the time of schizont rupture originated in the nineteenth century [24]. Malaria parasites induce the release of cytokines in a similar way as bacterial endotoxin [15], although they are much less potent. Merozoites contain (and release upon rupture) many glycophosphoinositol moieties that can activate the host inflammatory response in macrophages and dendritic cells via Toll like receptor 2 (TLR2) and to a lesser extent TLR4 as well as scavenger receptors such as CD36 [16, 20–22].

Tumor necrosis factor (TNF), interleukin (IL)-1 and gamma interferon (γ-IFN) are produced and, in turn, induce release of a cascade of other pro-inflammatory cytokines including IL-6, IL-8, IL-12, and IL-18. These are balanced by production of anti-inflammatory cytokines, notably IL-10 [15]. Cytokines are responsible for many of the signs and symptoms of infection, particularly fever and malaise. In addition, cytokines upregulate the endothelial expression of adhesion molecules such as intercellular adhesion molecule 1 through which *P. falciparum*-infected RBCs promoting cytoadherence, providing a pathogenic link between inflammation and adherence/sequestration. Some investigators have suggested that severe malaria and bacterial septicemia may have a common cytokine-mediated pathology [15, 24, 25]. Several studies have shown a positive correlation between blood cytokine levels and prognosis in severe *Falciparum* malaria, although the relationship is far from linear. For example, some authors [26] have found that appropriate levels of TNFα exhibit antiparasitic effects, and a high TNFα production capacity protects from severe malaria [27]. On the other hand, excessive TNFα levels are associated with complications such as severe anemia [28], and a low ratio of plasma levels IL–10/TNFα is associated with severe malarial anemia [29].

Interaction Between Malaria Parasites and RBCs

Parasite entry into erythrocytes is the key to the establishment of blood stage infection and thus is central to both acute and severe malaria. Infected RBCs have reduced deformability and altered surface characteristics and can be sequestered and destroyed by the spleen. In addition, once the parasites successfully complete the erythrocytic stage of their life-cycle, they replicate, and are released as merozoites with rupture of their host RBCs, leading to intravascular hemolysis [30]. In a recent study [31] from Mali, children with severe malarial anemia and markers of active intravascular hemolysis also demonstrated reduced whole blood levels of nitrite and increased NO consumption relative to controls, which is evidence of NO depletion. It is likely that the mechanism is similar to other hemolytic anemias, where free plasma hemoglobin reacts with NO produced by NO synthases to form biologically inactive nitrate. Because NO plays a critical role in downregulating the expression of adhesion molecules [32] and maintaining blood flow and vascular tone, the catabolism of NO and arginine from intravascular hemolysis in malaria likely promotes inflammation and endothelial activation [33], thus increasing the cytoadherence of abnormal RBCs.

Due to its complexity, erythrocyte invasion is an inefficient process and may be completed in only a small fraction of erythrocytes targeted for infection. Parasite antigens are shed during RBC entry, and many of these parasite encoded erythrocyte-adhesive proteins are present at high levels in plasma. They adhere to uninfected erythrocytes and resulting in IgG or complement binding to erythrocytes, leading to their clearance from circulation [34]. As a result of this binding, the direct Coombs test for immunoglobulins and/or complement deposited on the surface of the RBCs is frequently positive. The antibodies giving rise to the positive test are not autoimmune, but rather directed against adsorbed malarial antigens [35]. In addition to destruction of infected and uninfected erythrocytes, decreased erythrocyte production and/or suppression of the erythropoietic response contributes to the severe malarial anemia [34]. Although the cumulative data strongly support that there is imbalance of cytokines in malarial anemia, the cytokine pathways have not been fully characterized.

Sequestration

An important difference between *P. falciparum* and other human malarias is the way in which *P. falciparum* modifies the surface of the RBCs so that parasitized RBCs can adhere to the endothelium [16]. This phenomenon is called "cytoadherence" and it protects the parasite from destruction, as non-adherent, mature parasitized RBCs are cleared rapidly in the spleen [16]. As a result, only young forms ("ring") are found in the bloodstream, the rest of the parasite burden is "sequestered" in the microvascular beds of many organs. Sequestration occurs predominantly in the venules of vital organs, being greatest in the brain, heart, eyes, liver, kidneys, intestines, and adipose tissue [15]. This explains why some patients with heavy parasitemia are minimally symptomatic, whereas patients with less impressive bloodstream parasite numbers can be gravely ill, as blood parasitemia is an inaccurate marker of total body parasite burden in *P. falciparum* infections.

The mechanics of cytoadherence involve interaction between parasitized RBCs, endothelial cells, other RBCs, platelets and leukocytes. Parasitized RBCs express an adhesion molecule on their membrane, *P. falciparum erythrocyte membrane protein 1* (PfEMP1) [16]. This protein mediates adhesion to various membrane receptors, most importantly CD36 and ICAM 1, but also chondroitin sulphate A (CSA), vascular cell adhesion molecule 1 (VCAM 1), E selectin, platelet endothelial cell adhesion molecule 1 (PECAM 1), and integrins and selectins [15]. Parasitized red blood cells (pRBCs) and unparasitized RBCs (uRBCs) become less deformable during *P. falciparum* malaria and, consequently, plug the 3–7 μm-diameter capillaries with stiff RBCs, which have an average diameter of 7.5 μm [36]. The altered surface membrane of RBCs leads to micro-agglutination of parasitized RBCs as well as clumping of unparasitized RBCs around parasitized RBCs to form micro-thrombi ("rosettes") [36]. A role of complement receptor 1(CR1) in RBC rosette formation has been postulated as individuals with polymorphisms in the CR1 gene, who express low levels of CR1, show greatly reduced rosette formation, and are protected against

severe disease [37]. While the mechanisms responsible for cytoadherence and agglutination are well described, their pathologic consequences are less clear. Several mechanisms that might cause damage to host endothelium have been proposed, including mechanical obstruction of blood flow, with vascular leak and subendothelial hemorrhage, activation of endothelium, platelets and leukocytes [38], followed by systemic or local production and deposition of pro-inflammatory cytokines [16] that further upregulate the expression of the adhesion receptors, thus closing the loop between inflammation and sequestration.

The pathophysiology of severe malaria is therefore quite complex. Infection results in destruction of both infected and uninfected RBCs leading to anemia and decreased O2 carrying capacity, microvascular obstruction, and inflammation, all of which result in decreased tissue perfusion [16]. Parasite antigens are thought to activate platelets [38], which in turn provide adhesion receptors to microvascular beds originally devoid of these receptors [39]. The activated platelets contribute to the activation of the inflammatory response, increased levels of endothelial cell adhesion molecules, and sequestration. These events lead to disruption of the local microvasculature with ensuing vascular leak, potentially hemorrhage in various tissue beds.

Clinical Manifestations

The clinical manifestations of malaria are dependent on the previous immune status of the host, which varies with the age of the patient and the epidemiological context in which the infection is acquired. Holo-endemic areas (i.e. areas where essentially every individual in the population is infected) have high intensity, constant malaria transmission. Hypo-endemic or unstable transmission areas have a low, erratic, and markedly seasonal transmission pattern. In holo-endemic areas, infection is most severe in children between 1 and 3 years old. The severe manifestations, such as cerebral malaria, severe anemia, and shock are encountered in this age group and explain the high mortality rate in the pediatric population. Children less than 1 year of age are protected by passive maternal antibodies and by a higher percentage of hemoglobin F, which retards parasite development [40]. As children age, constant exposure to infection leads to a boost in immunity and a situation called "premonition", where infections cause little to no problem to the host and parasitemia may either be eradicated or continue asymptomatically. As a consequence, an individual may be parasitized, but not ill. In a symptomatic and parasitized individual, the parasites may be causing the fever or may be a "red herring" – there is no definitive means of distinguishing between malarial disease and incidental malarial infection as indicated by relative quantities of parasitemia. As a result, in endemic settings, a positive malaria test does not necessarily mean that malaria is the cause of the illness. In contrast, in hypo-endemic areas where transmission is too sporadic to promote "premonition", symptomatic infections are more common and the severe forms of disease, such as cerebral malaria, severe anemia, may be encountered at any age [15].

Malaria encountered in the United States follows similar patterns, according to the immune status of the patient. Imported malaria in travelers without previous exposure is much more likely to be symptomatic, and severe forms can be encountered in all patients irrespective of their age [15]. Conversely, children who are partially immune (e.g., newly arrived immigrants or refugees from areas where malaria is highly endemic) frequently present with signs of chronic infection, such as hepatosplenomegaly, anemia, and jaundice. It is not unusual for these patients to have very minimal symptoms, such as anorexia or decreased activity, or even to be asymptomatic [41]. A study [42] of Liberian children immigrating to Minnesota found that smears of blood from 28 to 43 patients were positive for malaria parasites. Of children with positive test results, one third were asymptomatic, and splenomegaly was the only manifestation of disease in one-third.

In most children, the first symptoms begin 10 days to 4 weeks after transmission by an infected mosquito. In exceptional cases presentation can be as early as 8 days or as late as 1 year, particularly in malaria caused by *P vivax*, *P ovale*, or *P malariae* or in children who have taken prophylaxis [43]. The first symptoms of malaria are nonspecific and similar to the symptoms of a minor systemic viral illness [44]. Signs and symptoms include headache, fatigue, abdominal discomfort, muscle and joint aches, usually followed by fever, chills, perspiration, anorexia, vomiting and worsening malaise. This leads to frequent over-diagnosis in endemic areas and conversely, under-diagnosis in non-endemic areas where many other more commonly encountered illnesses are considered first. If the infection continues untreated, the fever in *P. vivax* and *P. ovale* may regularize to a 2-day cycle (tertian malaria) and *P. malariae* to a 3-day cycle (quartan malaria). *P. falciparum* remains erratic for longer and usually doesn't regularize to a tertian pattern or, conversely, may turn into a daily fever cycle (quotidian malaria) [15] Older textbooks used to emphasize the diagnostic importance of these "fever charts", however many clinical studies have showed that these are neither sensitive nor specific for a diagnosis of malaria and reliance on the fever periodicity may miss a significant number of cases [30].

In a host without immunity and in the absence of effective treatment, the parasite burden continues to increase and severe malaria may ensue. The WHO definitions for severe malaria are listed in Table 37.2 [45]. This progression may occur within a few hours, although the risk factors and the specific pathogenic mechanisms of development of severe

Table 37.2 WHO definition of severe malaria is one or more of the following features

Clinical features
Cerebral malaria: coma/altered mental status/more than two seizures in 24 h
Respiratory distress (more likely from metabolic acidosis than true ARDS)
Circulatory collapse or shock, SBP <70 mmHg in adults and <50 mmHg in children
Cinical jaundice plus evidence of other vital organ dysfunction
Hemoglobinuria
Abnormal spontaneous bleeding
Pulmonary edema
Laboratory findings
Hypoglycemia (blood glucose <40 mg/dl)
Metabolic acidosis (plasma bicarbonate <15 mmol/l)
Severe normocytic anemia (Hb <5 g/dl, Ht <15 %)
Hyperparasitemia (>2 %–100,000/μl in low or >5 %–250,000/μl in high intensity transmission areas
Serum lactate >5 mmol/l
Renal impairment

Based on data from Refs. [44, 45]

malaria are still subject to controversy. Hyperparasitemia as a marker of disease severity should be interpreted with caution. Two patients with the same peripheral parasitemia may have as much as a 100-fold difference in the total number of parasites in the body. In "benign" malarias (non-falciparum) where there is no sequestration, blood parasitemia is a reliable estimate of total parasite biomass. However in *P. falciparum* malaria, only the first third of the asexual life cycle can be seen and the remaining two-thirds of the parasitized cells are sequestered. As a consequence there might be large discrepancies between the number of parasites in the peripheral (circulating) blood and the number of parasites in the body (the parasite burden) – sequestration "hides" the parasites causing harm. As such, some patients appear to tolerate high parasitemia with little adverse effect, whereas others die with low parasite counts [15] (notwithstanding the role of covert co-infections). The predominance of more mature parasites on the blood film suggests greater sequestered parasite biomass and carries a worse prognosis for any parasitemia than a predominance of younger forms. The presence of intra-neutrophilic phagocytosed malaria pigment (more than 5 % of the neutrophils) also reflects the degree of previous schizogony and is also a valuable prognostic index. Measurement of proteins released by the parasite such as Pf HRP2 in plasma provides a good method of assessing this hidden pathogenic sequestered biomass [46] – a useful addition in cases where the severity of the disease seems discrepant with the measured parasitemia. The case fatality in people receiving treatment for severe malaria is typically 10–20 % [44]. However, if left untreated, it is fatal in the majority of cases.

Cerebral Malaria

Cerebral malaria is one of the deadliest complications of severe malaria. It is defined by the WHO as "unarousable coma in a patient with *P falciparum* parasitemia in whom other causes of encephalopathy have been excluded" [44]. Although the term implies a distinct disease entity, the clinical syndrome is highly variable, with most cases falling into one of three main categories [20] characterized by coma with (or due to) (1) marked physiological derangement (severe anemia, metabolic acidosis, hypoglycemia, respiratory distress, shock; (2) protracted or multiple seizures, where unconsciousness might be caused by a long (>1 h) postictal state or by subclinical or subtle seizure activity; (3) a pure neurological syndrome of coma and abnormal motor posturing, which might be complicated by raised intracranial pressure and recurrent seizures.

The differential diagnosis of fever and encephalopathy in children is quite broad, including many infectious, metabolic, and oncologic processes. However, the positive predictive value of malarial parasitemia for cerebral malaria in the appropriate clinical context is quite high in a hypo-endemic or non-endemic area such as the US or Europe. On the other hand, as discussed above, in holo-endemic areas the presence of malaria parasitemia can be an incidental finding. In addition, "exclusion of other causes of encephalopathy" as required in the WHO definition of cerebral malaria may call for investigations that are not routinely available in developing countries. Without a standard diagnostic criterion for cerebral malaria, a useful clinical indicator is the presence of malarial retinopathy, which consists of retinal whitening – as a consequence of retinal ischemia, vessel changes (whitening, "tramlining"), retinal hemorrhages, and papilledema as seen in Fig. 37.3 [47]. In a prospective autopsy study [48] from Malawi, 24 % of the children who fulfilled the usual criteria for cerebral malaria before death had evidence at post mortem of an alternative cause for the coma. The presence of malarial retinopathy had a positive predictive value of 95 % and a negative predictive value of 90 % for fatal cerebral malaria in comatose parasitemic patients from Malawi [48, 49]. The absence of malarial retinopathy, or finding isolated papilledema or retinal hemorrhages should alert the clinician to the possibility of other causes of coma, particularly if the coma is prolonged.

Almost all patients with cerebral malaria present with fever, rigors, chills, headache, and vomiting. Altered sensorium might be present from the outset, or might develop slowly over a period of several days. Signs of irritability, restlessness or psychotic behavior can be the initial manifestations of cerebral involvement. In children with cerebral malaria, coma usually develops rapidly, and often follows seizures. In children with cerebral malaria, seizures occur in approximately 60–70 % of cases [50]. In a study [51] of 65 Kenyan children with cerebral malaria, 40 (62 %) had

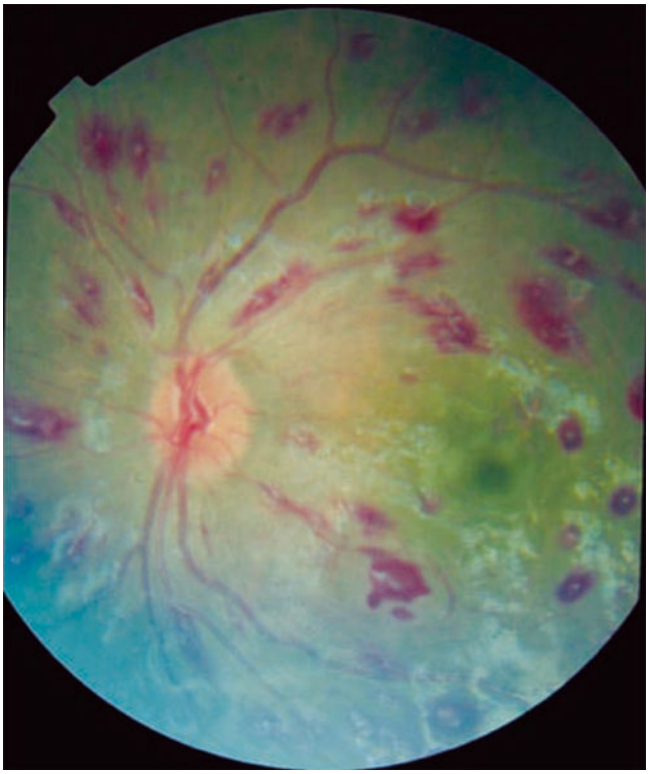

Fig. 37.3 Malarial retinopathy. Photograph of the retina in a patient with cerebral malaria, which shows exudates (i.e. retinal "whitening"), hemorrhages and changes in the color of the blood vessels (Reprinted from Ref. [47]. With permission from Nature Publishing Group)

seizures after admission and ten (15 %) had subtle seizures, manifesting as nystagmoid eye movements, irregular breathing, excessive salivation, and conjugate eye deviation. Seizures were often repetitive and prolonged, and 18 children (28 %) had an episode of status epilepticus. Brainstem signs are common and are associated with other features of high intracranial pressure [50]. Common signs include changes in pupillary size and reaction and disorders of conjugate gaze and eye movements. Other signs include abnormal respiratory patterns, motor abnormalities of tone and reflexes (usually upper motor neuron), posturing (decerebrate, decorticate, or opisthotonic posturing) – the latter usually associated with cerebral edema.

Intracranial hypertension occurs in virtually all children with cerebral malaria [47, 52]. While the etiology is multifactorial, the most likely cause is increased cerebral blood volume as a result of sequestration of infected and noninfected erythroctyes [50], coupled with an alteration of the blood – brain barrier [48]. Focal disruptions in the barrier at sites of sequestration could result in the exposure of sensitive perivascular neuronal cells to plasma proteins and increased concentrations of cytokines and metabolites caused by abnormalities in microcirculation. Although most children with cerebral malaria regain consciousness within 48 h and seem to make a full neurological recovery, approximately 20 % die and 10 % have persistent neurological sequelae [50].

Severe Malarial Anemia

Severe malarial anemia, defined as hemoglobin concentration <5 g/dL in the presence of *P. falciparum* parasitemia, is more common in children than in adults, with a peak incidence between 1 and 3 years of age [35]. The underlying causes of severe malarial anemia are multifactorial and involve both direct and indirect destruction of parasitized and nonparasitized erythrocytes, ineffective erythropoiesis, and dyserythropoiesis [34]. Mortality of children with asymptomatic severe malarial anemia is low (around 1 %), but rises to more than 30 % when anemia is complicated by severe respiratory distress and metabolic acidosis [53]. "Blackwater fever" is a rare, but feared complication. A rapid and massive intravascular hemolysis of parasitized and nonparasitized red blood cells results in hemoglobinuria and acute onset anemia and is accompanied by high fever, hepatic involvement, and renal failure. Unfortunately, even with aggressive treatment, this complication is often fatal [23]. Activation of the coagulation cascade and platelets has been widely reported in malaria [39]. Typical disseminated intravascular coagulation (DIC) with the presence of bleeding is reported in 5–10 % of severe malaria cases [23] – 1 % of all cases – probably less frequently in children. Thrombocytopenia is a common finding and is attributable to sequestration in the spleen or increased consumption secondary to activation of coagulation system.

Severe malaria is a complex syndrome affecting many organs and metabolic acidosis is both an important component of the syndrome and the major predictor of a poor outcome [54]. Table 37.3 lists some uncommon manifestations of severe malaria in children [45]. The etiology of the metabolic acidosis in this case is multifactorial and includes increased lactate production from the parasite, decreased hepatic metabolism [15], recent seizure activity, hypovolemia, cardiac dysfunction and sequestration obstructing the microvasculature causing tissue hypoxia. While the relative contribution of each of these factors is still subject to debate, it is likely that hypovolemia, by causing a volume concentrated and sluggish circulation, acts synergistically with other factors leading to cytoadhesion, increasing the likelihood of microvascular obstruction. In children, respiratory distress (deep breathing, Kussmaul's respiration, tachypnea) is usually a clinical sign of metabolic acidosis [15]. It can be misinterpreted as cardiac failure and circulatory overload, which rarely occurs in children [55].

A less common pulmonary manifestation of severe malaria is ARDS. Its pathogenesis includes cytoadherence with sequestration followed by changes in endothelial permeability, as well as immune/inflammatory mediated lung injury [23]. In addition, bacterial pneumonia or aspiration caused by impaired mental status may be aggravating factors of lung injury.

Hypoglycemia (blood glucose concentration <45 mg/dL) is associated with a poor outcome in children with malaria [24]. It results from impaired hepatic gluconeogenesis [15], however it can be compounded by quinine induced hyperinsulinemia. Severe hypoglycemia can lead to altered mental status and seizures. Current guidelines [44] recommend monitoring serum glucose concentration every 4 h, especially in unconscious patients.

Acute renal failure caused by acute tubular necrosis is a fairly frequent complication of severe malaria especially in non-immune European or US adults, but is rare in children. The postulated mechanism is thought to be sequestration of parasitized and nonparasitized RBCs with consequent microvascular ischemia leading to acute tubular necrosis [23], although other factors such as hypovolemia, intravascular hemolysis with hemoglobinuria, superimposed bacterial sepsis with DIC may also contribute. In some cases, immune complex deposition and/or autoimmune reactions to glomerular structures induced by the parasite are thought to result in glomerulonephritides or nephrotic syndrome, especially in children.

Table 37.3 Less frequent manifestations of severe malaria in children

CNS
Spontaneous subdural empyema
Subdural hemorrhage/intracranial hemorrhages
Central pontine myelinolysis
Acute disseminated encephalomyelitis
Pulmonary
Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)
Secondary bacterial pneumonia
Pleural effusion
Gastrointestinal and hepatic
Malarial hepatitis and jaundice
Acute liver failure
Spontaneous splenic rupture (especially with *P. vivax* and *P. ovale*)
Acute pancreatitis
Hematologic
Thrombocytopenia
Anemia
Purpura fulminans
Acquired hemophilia A
Hemophagocytic syndrome

Based on data from Ref. [23]

Laboratory Findings and Diagnosis

There are several methods for detecting malaria parasites in the blood, including direct microscopy, rapid antigen detection testing (RDT), and polymerase chain reaction (PCR). Light microscopy has long been considered the gold standard for making the diagnosis of malaria. Parasites are directly observed in thick or thin blood smears as seen in Fig. 37.4 [56]. The thick film preparation is more sensitive, but is more difficult to interpret by inexperienced examiners [30]. The thin smear is used to identify the *Plasmodium* species and to perform a quantitative assessment of parasite burden. While considered a "gold standard", the sensitivity and specificity of direct microscopy is variable. In resource poor settings, a study [57] found 25–100 % sensitivity and 56–100 % specificity of microscopy done at rural health centers in Zambia compared with reference laboratory microscopy. In non-endemic areas, where access to equipment is less of a concern, lack of experienced microscopists and the relative rarity of the diagnosis also can result in significant delays and errors in diagnosis [58].

"Rapid Diagnostic Tests" (RDTs) are immunological antigen detection tests in a dipstick or cassette format that can give a diagnosis in minutes. The sensitivity and specificity of the RDT's vary with the species and the antigen targeted [59]. In a recent meta-analysis comparing performance of RDTs with the reference standard – microscopy – with or without PCR, the average sensitivities of the most commonly used RDTs were 93–95 %, while the average specificities where 95–98 % [60]. Caution needs to be exercised when translating these performance characteristics from an

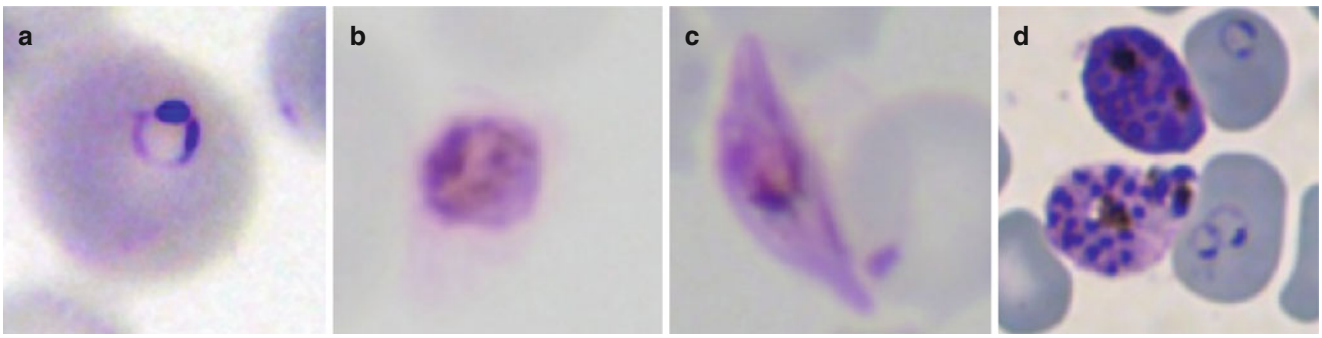

Fig. 37.4 Direct microscopic diagnosis of malaria. (**a**) *P. falciparum* ring, (**b**) trophozoite, (**c**) gametocyte, (**d**) schizont (Reprinted from Ref. [56]. With permission from BioMed Central, Ltd)

Table 37.4 Parenteral treatment options for malaria by severity

Uncomplicated malaria
Atovaquone plus proguanil (once a day for 3 days)
Artemether plus lumefantrine
Dihydroartemisinin plus piperaquine
Quinine plus doxycycline or clindamycin
Severe malaria
Artesunate 2.4 mg/kg IV or IM is given on admission (time = 0), then at 12 h and 24 h, then once a day for a minimum of 24 h or until clinical improvement occurs.
Artemether or quinine are acceptable alternatives if parenteral artesunate is not available:
Artemether 3.2 mg/kg IM is given on admission then 1.6 mg/kg per day
Quinine 20 mg salt/kg on admission loading dose (IV infusion or divided IM injection), then 10 mg/kg/dose every 8 h; infusion rate should not exceed 5 mg salt/kg/h

endemic to a non-endemic area, because the sensitivity of the RDTs decreases sharply when parasite density is below 200/μl, as may be the case with imported malaria. A positive test is useful, though a negative test should be confirmed by serial microscopy [61]. In the US, there is only one RDT approved by the FDA, *Binax Now*®. Its use is unlikely to become widespread, because the manufacturer requires that the laboratory prepare a positive test with known malaria infected blood for quality assurance each time a sample is tested with the RDT and malaria infected blood is not routinely stocked in most laboratories [59]. While potentially useful in the acute setting where an urgent diagnosis is needed, the RDTs cannot be used to monitor response to therapy as the malarial antigens persist up to 3 weeks in spite of successful treatment [61].

Polymerase chain reaction (PCR) is increasingly being used as the "gold standard", being capable of detecting parasites below the threshold for microscopic identification [62]. PCR is particularly advantageous in patients who have very low parasite levels, have taken chemoprophylaxis with consequent alteration in the morphology of the parasites, or in non-endemic settings where experience with direct microscopy is not as extensive. Other ancillary tests supporting a diagnosis of malaria include an elevated C-reactive protein, an elevated procalcitonin, thrombocytopenia, anemia, neutropenia, elevated liver function tests, and albuminuria [17].

Treatment

The first step in managing a child with suspected malaria is to determine whether the infection is uncomplicated, in which case the patient may be managed on a general pediatric ward or even as an outpatient. Alternatively, if the infection is a severe case (cerebral malaria or severe malarial anemia), treatment in a closely monitored setting is usually recommended. Additional factors to consider in triaging children towards admission to a closely monitored or ICU setting include evidence of dehydration, inability to take or comply with oral medications requiring parenteral antimalarial treatment, or coexistence of malaria and sickle cell anemia [43]. In holo-endemic areas in particular, with high rates of asymptomatic malarial infections, coexisting or alternative illnesses causing a clinical picture suggestive of severe malarial anemia should be aggressively pursued. The most common differential diagnoses include meningoencephalitis, pneumonia, infectious or metabolic encephalopathy, other causes of severe anemia, and septic shock. In this epidemiological context, falciparum malaria is a diagnosis of exclusion, in which three negative blood smears at 8–12 h intervals are required before the diagnosis can be ruled out. In the meantime, the systemically ill patient is started on empiric parenteral antimalarial therapy as detailed below, in addition to broad-spectrum antibiotic therapy as clinically indicated. The WHO guidelines for therapy and particularly parental treatment options for malaria by severity are listed in Table 37.4 [44, 45].

Severe malaria is a medical emergency because the mortality of untreated severe malaria (particularly cerebral malaria) is thought to approach 100 %. Death from severe malaria often occurs within hours of admission, so it is essential that therapeutic concentrations of a highly effective antimalarial are achieved as soon as possible. According to the WHO guidelines, after rapid clinical assessment and a strong suspicion of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with *any effective antimalarial first available* [44, 45]. The mainstay of therapy was intravenous quinine or quinidine until the results of a randomized controlled trial comparing standard therapy – parenteral quinine versus artesunate were published in 2011 [63]. This study recruited 5,425 participants in an open-label randomized trial. Artesunate treatment was shown to significantly reduce the risk of death from severe malaria compared to intravenous quinine: RR 0.76, 95 % CI 0.65–0.9. No difference was found in the risk of serious neurological sequelae at day 28. Artesunate therapy was also associated with a lower risk of hypoglycemia compared to quinine. Artesunate also

Table 37.5 Parenteral to enteral options for full treatment course of severe malaria

Severe malaria options for parenteral to enteral transition
Artemether plus lumefantrine,
Artesunate plus amodiaquine
Dihydroartemisinin plus piperaquine
Artesunate plus sulfadoxine-pyrimethamine
Artesunate plus clindamycin or doxycycline
Quinine plus clindamycin or doxycycline

has the advantage of not requiring rate controlled infusion or cardiac monitoring during administration and no need for dose modification in renal failure [23]. Conversely, administration of parenteral quinine is fraught with the potential dangers of cardiac arrhythmias – cardiac telemetry is mandatory. If the QRS becomes prolonged more than 50 % its baseline value, or QTc > 600 msecs or >25 % baseline, the infusion should be stopped [23]. As mentioned above, quinine can also cause hypoglycemia through direct stimulation of insulin secretion. The loading dose of quinine should not be given if the patient has received quinine, quinidine, or mefloquine during the previous 24 h [44]. Quinidine commonly causes hypotension and concentration-dependent prolongation of ventricular repolarization (QT prolongation). Quinidine is thus considered more toxic than quinine and should only be used if no other effective parenteral drugs are available. Parenteral chloroquine is no longer recommended for the treatment of severe malaria, because of widespread resistance. Intramuscular sulfadoxine-pyrimethamine is also not recommended [44]. Parenteral antimalarials should be administered for a minimum of 24 h, once started (irrespective of the patient's ability to tolerate oral medication earlier), and, thereafter, a 7 day treatment course should be completed with the enteral combinations listed in Table 37.5 as described by the WHO [44, 45]. Treatment should be monitored closely. Along with clinical improvement, parasite clearance should also be demonstrated by following daily parasite counts. In the first 24–36 h of therapy, it is possible for the parasite count to rise and this does not indicate failure of therapy [23]. However if the counts do not start to fall by 48 h and/or do not clear by day 7, resistance to the chosen course of chemotherapy is likely.

Adjuvant Management

Initial management is based on that of any acutely and severely ill patient. A rapid clinical assessment should focus on airway patency, early recognition of impending respiratory failure and shock, and neurological assessment. Hypoglycemia should be ruled out or treated empirically. The following discussion will focus on specific complications of severe malaria.

Cerebral Malaria

Children presenting with fever and altered mental status, even with a positive malaria parasitemia, should have further investigations performed in parallel with starting parenteral antimalarial treatment. Most authorities [23, 44, 45, 52, 64] recommend obtaining a lumbar puncture and starting empiric antibiotics at meningitic dosing, pending culture results. The cerebrospinal fluid (CSF) findings in cerebral malaria are generally unremarkable – mild pleocytosis, slightly elevated protein, and a normal glucose level [41]. In a child with neck stiffness or a full fontanel, other infections of the CNS or intracranial hemorrhage should be considered rather than cerebral malaria [43]. Other investigations, such as head imaging, viral studies, tuberculosis testing, toxic or metabolic screening should be performed as clinically indicated. Given the high incidence of seizures in cerebral malaria and the possible occurrence of subclinical status, EEG monitoring should be strongly considered.

Supportive treatment of cerebral malaria follows the general management principles of non-traumatic intracranial hypertension – support of the airway with mechanical ventilation as needed, maintenance of normocapnia, isotonic fluids, seizure control, aggressive fever control (preferably avoiding NSAIDS), avoidance of hypoxia, hypotension and hypoglycemia. Given that most cases of cerebral malaria in children are cared for in severely limited resource settings, there is scarce literature on using advanced therapies such as controlled mechanical ventilation, use of osmolar agents, or intracranial pressure monitoring. In a small study from Kenya [52], mannitol was successful in transiently reducing intracranial pressure but no convincing clinical evidence emerged supporting its use. However patients in this study were not ventilated and they were supported with hypotonic fluids (1/8 saline in Dextrose 4 % solution according to the local protocol), hence the results are difficult to evaluate in reference to the standard management of intracranial hypertension in resource-rich ICUs.

Severe Malarial Anemia

In the sickest children with severe malarial anemia and lactic acidosis, early transfusion, preferably of whole fresh blood, is indicated [15]. In children with severe malarial anemia but no signs of decompensation, the indications for transfusion are less well defined. The WHO recommends using a cutoff of Hb < 5 g/dL in high transmission settings and less than 7 g/dL in low transmission settings [44]. However, these general recommendations still need to be tailored to the individual, as the pathological consequences of rapid development of anemia are worse than those of acute on chronic anemia, where there has been adaptation and a compensatory right shift in the oxygen dissociation curve.

Exchange transfusion has been initially tried for patients with hyperparasitemia and multi-organ failure in adult ICU

settings. The rationale [44] for exchange blood transfusion has been proposed as:

- removing infected RBCs from the circulation and, therefore, lowering the parasite burden (although only the circulating relatively non-pathogenic stages are removed; this is also achieved rapidly with artemisinin derivatives);
- reducing rapidly both the antigen load and the burden of parasite-derived toxins, metabolites and toxic mediators produced by the host; and
- replacing the rigid unparasitized red cells by more deformable cells, therefore alleviating microcirculatory obstruction.

A meta-analysis of 12 studies concluded that adjunct RBC exchange transfusion did not improve survival as compared to antimalarial chemotherapy alone [65]. The current WHO guidelines [44] do not make any recommendation about exchange transfusion for management of severe malaria. Some authors of a proposed guideline [43] for the management of imported pediatric malaria in the UK suggested that exchange transfusion might be considered in patients with persistent acidosis and multi-organ impairment who are not responsive to resuscitation and adequate anti-infective treatment. The authors caution that exchange transfusion remains an experimental treatment and there is no consensus on the indications, benefits and dangers involved, or on practical details such as the volume of blood that should be exchanged.

Metabolic acidosis is a consistent feature of severe malaria but differs fundamentally from that associated with sepsis [15]. The relative importance of hypovolemia versus microvascular obstruction in the pathophysiology of acidosis is controversial. Small studies [54] have found evidence for hypovolemia in children with severe malaria. Standard fluid resuscitation (20 mL/kg aliquots rapid infusion as typically used in pediatric septic shock) resulted in improvement in hemodynamic parameters and clinical condition in small series. These findings are contradictory to classical teachings that urge caution with vigorous intravenous volume expansion in severe malaria, specifically with concerns of precipitating pulmonary edema and/or intracranial hypertension.

In an effort to address the controversies surrounding fluid resuscitation in severely ill children with malaria and other conditions, a recent large randomized trial – the Fluid Expansion As a Supportive Therapy (FEAST) trial [66] included 3,141 children in Uganda, Kenya and Tanzania with febrile illnesses and signs of poor perfusion. Importantly, 57 % of the patients in this study had severe malaria. The investigators found that bolus fluid resuscitation consisting of 20–40 mL/kg of either albumin or saline, as compared with controls – 2–4 mL/kg/h maintenance fluids (i.e. no fluid bolus), increased the absolute risk of death at 48 h by 3.3 % and the risk of death, neurologic sequelae, or both at 4 weeks by 4 %. In the subgroup of children with severe malaria, fluid resuscitation increased mortality as well – OR 1.59 (1.10–2.31). The trial included children with malaria, sepsis, pneumonia and meningitis, randomizing all children across treatment arms, even though recommendations for fluid resuscitation are different among these conditions. The authors argue that in sub-Saharan Africa, where resources are very limited, positive diagnosis is not possible at the time of admission to the hospital, and a uniform approach has to be employed for treating severely ill children with very different clinical conditions that present in a similar manner. While the results of this study caution against liberal fluid resuscitation where facilities for advanced diagnostics and monitoring are unavailable, their applicability is probably somewhat limited to those same settings. Conversely, at least for now, in more resource-rich settings, it seems reasonable to identify and treat hypovolemia and/or distributive shock according to the usual Pediatric Advanced Life Support (PALS) guidelines and employ the usual parameters to guide treatment (restoration of peripheral perfusion and urine output, central venous pressure, artificial ventilation as necessary). In children presenting with coma, a more cautious approach to volume expansion should be employed [43], maintaining the fine balance between risk of aggravating cerebral edema and the necessity of an adequate cerebral perfusion pressure.

In cases of refractory shock or unexplained clinical deterioration, "algid malaria" which is a bacterial infection superimposed on acute malaria should be aggressively searched for and treated. In a recent study [67] from rural Kenya, the prevalence of bacteremia was 11.7 % among children presenting with malaria, the most frequent isolate being non-typhoidal salmonella, followed by *Staphylococcus aureus* bacteremia. Broad-spectrum antibiotic therapy should be used, especially for severely ill children, until a bacterial infection is excluded. In addition, nosocomial infections such as UTIs or ventilator-associated pneumonias can occur and should be treated according to the local guidelines.

Dengue

Epidemiology

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, the incidence of dengue has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings. The rising incidence over the last 50 years can be seen in Fig. 37.5 [68]. The reasons for the global resurgence of epidemics of dengue include large scale population growth and migration of viremic humans to new geographic settings with a suitable vector and susceptible population [69]. In addition, the uncontrolled urbanization that has occurred in the last 30 years, as well as the tremendous growth in international trade have facilitated transmission and increased densities of *Aedes* – borne disease [70, 71].

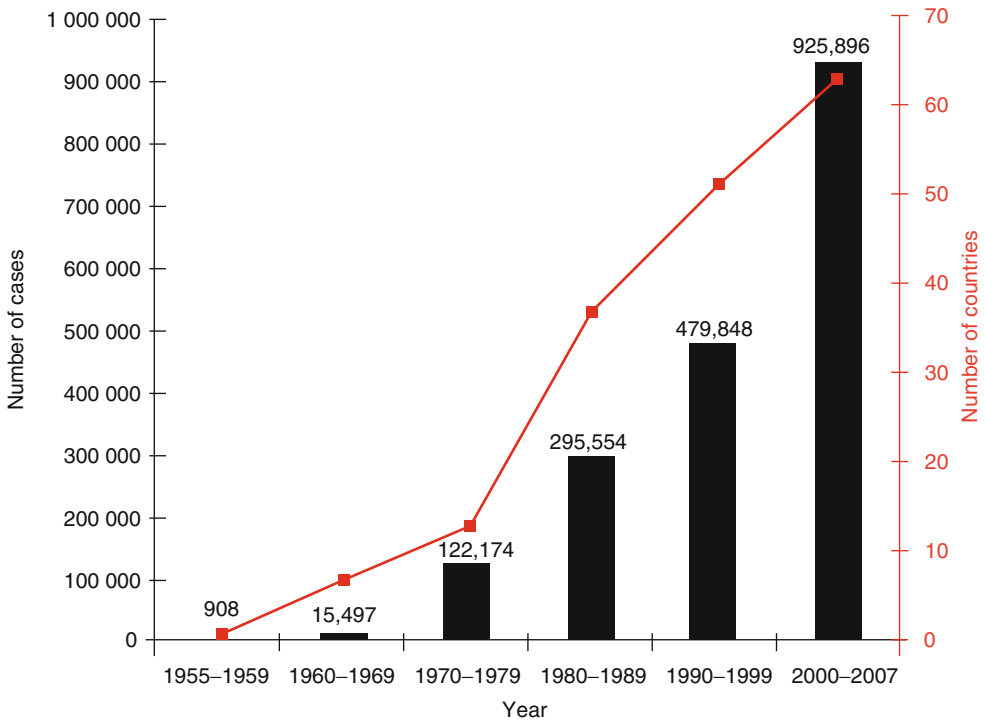

Fig. 37.5 Average annual number of dengue fever and dengue hemorrhagic fever reported to WHO and of countries reporting dengue, 1955–2007 (Reprinted from Ref. [68]. With permission from World Health Organization (WHO))

Dengue infections span a spectrum of illness ranging from asymptomatic to life-threatening severe dengue which also is known as Grade III-IV DHF and in the past has been referred to as dengue shock syndrome (DSS) [72]. Each year there are an estimated 50–100 million dengue infections worldwide, of which 500,000 are cases of DHF with 20,000 deaths, mainly in children [15]. Case fatality rates vary from 1 to 5 % but can be less than 1 % with appropriate treatment [68]. An important detail in the reported epidemiology of this disease is that the cases reported likely represent only a percentage of the true incidence, as in many countries dengue only became a reportable disease since 2000. For instance, in the USA dengue fever first became a reportable disease in 2009.

Dengue is a worldwide condition spread through the tropical and subtropical zones, where environmental conditions are optimal for dengue virus transmission by the highly "domesticated" *Aedes* mosquitoes, classically *Aedes aegypti*. The most seriously affected regions are South East Asia and the Western Pacific region, followed by Central and South America, Africa and the Eastern Mediterranean regions. According to the WHO [68], the majority of notified cases of dengue in Canada and the US are persons who had travelled to endemic areas. From 2001 to 2007, 796 cases of dengue were reported in the US, the majority imported. The diagnosis should be considered in any patient developing fever within 14 days after even a brief trip to the tropics or subtropics, including those regions where dengue has not traditionally been considered an endemic disease [69].

It is important to note however that not all US cases of dengue are imported. Outbreaks of dengue in Hawaii and southern Texas have been reported [68]. A serological survey [73] in Brownsville, Texas a city on the border with Mexico, found that 38 % of surveyed residents had IgG antibodies to dengue, indicating that a substantial proportion of the city population had been infected with the dengue virus transmitted locally. The introduction and spread of a secondary dengue virus vector into the US in 1985, the *Aedes albopictus* mosquito, means that wide-spread appearance of dengue in the continental US could be a real possibility [74].

Etiology

Dengue is an acute, febrile infection caused by one of four dengue viruses (DENV-1, DENV-2, DENV-3 and DENV-4), members of the family Flaviviridae (same genus as yellow fever virus, West Nile virus, St. Louis encephalitis virus, and Japanese encephalitis virus), belonging to the Arboviruses. Dengue virus is transmitted from human to human by mosquito bites – the vector is the female *Aedes* mosquito, which, once infected, remains infective for life (30–45 days). Man is the main reservoir of the virus [15]. Viremia in susceptible humans begins between 3 and 6 days after subcutaneous injection, lasts for another 3–6 days, and ends as the fever resolves [71, 75]. Dengue can essentially be excluded as the cause of symptoms in a traveler who develops an illness more than 14 days after returning from a tropical or subtropical country [76]. Lifetime immunity follows infection by one serotype, but immunity to the other serotypes is short-lived [15] and is actually involved in the pathogenesis of severe

dengue when reinfection with a different serotype occurs (see below). Infectious virus and the virus-encoded non-structural protein 1 (NS1) are present in the blood during the acute (febrile) phase, and high-level early viremia and NS1 antigenemia have been associated with more severe clinical presentations [15, 77, 78].

Pathophysiology

All four dengue serotypes are capable of causing a clinical spectrum of illness ranging from undifferentiated febrile illness (dengue fever) to severe DHF/DSS, depending on the immune status and age of the host, primary vs. secondary infection, and an array of other putative factors. DHF/DSS occurs predominantly in children under the age of 16 years and is generally associated with secondary dengue infections [15]. Both the undifferentiated viral syndrome, seen in young children (from first-time infection) and the classic dengue fever or "breakbone fever" seen in older children and adults (from secondary infections), are self-limited diseases that require minimal supportive therapy and have with excellent prognosis [15]. The focus of our discussion will therefore be severe dengue also known as DHF/DSS in the old classification scheme (see further discussion below).

The major pathophysiological processes that distinguish severe DHF from mild dengue are an abrupt onset of vascular leakage, with effusions, ascites and ensuing hypovolemic shock, accompanied by thrombocytopenia and a hemorrhagic diathesis [79]. The acute onset of hypovolemic shock – usually due to low plasma volume and less frequently due to hemorrhage – and the often dramatic clinical recovery with fluid resuscitation, argue in favor of a transient functional increase in plasma vascular permeability that results in plasma leakage [15]. A characteristic feature of severe DHF is that it manifests clinically between days 4 and 6 of the illness, a time when the viremia is in steep decline and the host immune response is well established. The timing of these events suggests the host proinflammatory response, rather than direct virus-mediated effects, mediates the vascular permeability syndrome leading to DSS [80]. However, in spite of extensive research, little is known of the exact mechanisms underlying the change in vascular permeability. The prevailing view is that dengue infection triggers an immunopathogenic cascade that alters microvascular structure or function in some as yet undefined way, resulting in a transient, spontaneously-reversible increase in permeability [81].

In the first few days of clinically apparent infection, there is an innate immune response in all patients [69, 82]. Gene expression studies have shown that blood leukocytes in the early acute phase of dengue relative to the late convalescence phase overexpress genes related to antiviral responses, innate immune responses and inflammatory pathways [80]. Overproduction of cytokines by dengue virus-infected cells or by activated lymphocytes is believed to be critical in pathogenesis [83, 84]. In addition, NS1, the major nonstructural dengue virus protein, which can be either expressed on the surface of infected cells or released in the plasma, is an important trigger for complement activation [79]. Together, complement activation products and cytokines may act synergistically to produce vasoactive and cytotoxic effects by directly targeting the vascular endothelium, resulting in vascular leakage.

Serologic-epidemiological studies in Cuba [85] and Thailand [86] consistently support the role of secondary infection with a different serotype as a risk factor for severe dengue, which is also regularly observed during primary infection of infants born to dengue-immune mothers. This immunopathogenic model hypothesizes that low circulating antibody titers from a primary infection bind to epitopes on the heterologous infecting virus and facilitate its entry into Fc-receptor-bearing cells [68]. This paradoxically results in an increased number of infected cells, a higher viral burden, and induction of a "cytokine storm" that will contribute to the syndrome of increased capillary permeability that characterizes severe dengue.

There is still controversy as to whether direct infection of endothelial cells with the dengue virus contributes to the pathogenesis of the increased vascular permeability. Infection of endothelial cells by dengue virus has been studied *in vitro* but has resulted in conflicting findings; the role of endothelial cells in dengue disease pathogenesis remains incompletely understood [87]. A postulated mechanism includes activation and apoptosis of human microvascular endothelial cells, with disruption of the inter-endothelial cell junctions [88]. Other studies have suggested a role for vascular endothelial growth factor (VEGF) [82] or alterations in β integrin expression on the surface of the infected endothelium [89]. Another plausible pathophysiological mechanism for the increased vascular permeability characteristic of severe dengue is a transient disruption in the function of the endothelial gylcocalyx layer [69]. This layer covers the luminal surface of vascular endothelium throughout the body and is composed of a hydrated mesh, rich in carbohydrates and in dynamic equilibrium with plasma constituents. The endothelial glycocalyx has important roles in transduction of shear stress, regulation of leukocyte-endothelial cell interactions, regulation of clotting and complement cascade and it contributes to the permeability of the capillary wall [90]. Supporting the hypothesis of increased systemic permeability due to damaged glycocalyx is the observation that urinary clearance of albumin and other macromolecules is increased in children with active dengue infection [91]. In addition, both the virus itself and dengue non-structural protein (NS1) are known to adhere to heparan sulfate, a key structural element of the glycocalyx [69], and increased urinary

heparan sulfate excretion has been detected in children with severe infection [92, 93]9392.

In spite of its name (DHF), hemorrhage is not the major determinant of shock in severe dengue hemorrhagic fever. Self-limited muco-cutaneous hemorrhage is common, while overwhelming hemorrhage occurs less often. When it does occur, it can involve the gastrointestinal tract, skin, heart (pericardium), pleura, lungs or periadrenal tissue [94]. The pathogenesis of hemorrhage includes vascular changes, including capillary fragility (the basis of the tourniquet test), thrombocytopenia – due to both decreased marrow production and increased consumption, platelet dysfunction and disseminated intravascular coagulation (DIC) [95], the latter usually in the setting of prolonged shock. While all these changes have been noted, they are seldom severe enough to cause the overwhelming hemorrhage that can occur in DHF [96]. An alternative explanation comes from studying the Ebola virus, another arbovirus belonging to the Filoviridae family. Recent work has demonstrated that Ebola virus produces a viral glycoprotein that infects endothelial cells and causes vascular cytotoxicity, leading to entothelial loss and vascular leak and hemorrhage [97]. Some authors speculate that this mechanism may be shared by other arboviruses causing viral hemorrhagic fevers, including dengue [96]. Others are circumspect, given the lack of direct evidence [98, 99].

Disease Classification and Clinical Course

Dengue virus infection may be asymptomatic or may cause undifferentiated febrile illness, dengue fever (DF), or dengue hemorrhagic fever (DHF). In addition, a few patients experience unusual manifestations that are grouped under the name of "expanded dengue syndrome". The clinical course of the infection is often unpredictable in an individual patient, although certain risk factors have been identified. The classification of dengue infections has undergone many revisions, all with the same goal of proper triage of cases that are potentially life threatening and thus require more intensive monitoring and therapeutic management in areas with limited resources. In 2012 the WHO differentiated dengue fever into uncomplicated dengue and severe dengue. Warning signs were described to help identify clinical changes indicative of a transition to the severe classification. This WHO classification is shown in Table 37.6 [72].

Most cases of dengue fever have no signs of bleeding, except a positive tourniquet test (also known as the Rumpel-Leede Capillary-Fragility Test – a blood pressure cuff is inflated to the midpoint between systolic blood pressure and diastolic blood pressure for 5 min), which is defined by the presence of 10–20 petechiae per a 1 in. diameter circle, as seen in Fig. 37.6 [100]. Despite the name DHF and DF is not hemorrhage but rather the presence of capillary leak.

Table 37.6 WHO 2009 dengue classification

Dengue fever	Reside or travel to endemic area
	Fever and 2 of the following:
	Nausea, vomiting
	Headache
	Rash
	Myalgias, arthralgias
	Tourniquet test positive
	Leukopenia (<5,000 cells/mm^2)
	Mild thrombocytopenia (<150,000 cells/mm^2)
	Mild elevation in HCT (5–10 %)
	No other evidence of plasma leakage
Warning signs	Abdominal pain
	Persistent vomiting
	Edema, other fluid accumulation
	Mucosal bleeding
	Lethargy or restlessness
	Hepatomegaly (>2 cm)
	Increase in HCT and decreased platelet count
Severe dengue	Severe plasma leakage
	Shock (DSS)
	Edema, pulmonary edema, effusions, ascites, hypoalbuminemia
	Severe bleeding
	Severe organ dysfunction including:
	Altered mental status
	Transaminitis (AST or ALT >1,000)
	Multiple organ failure

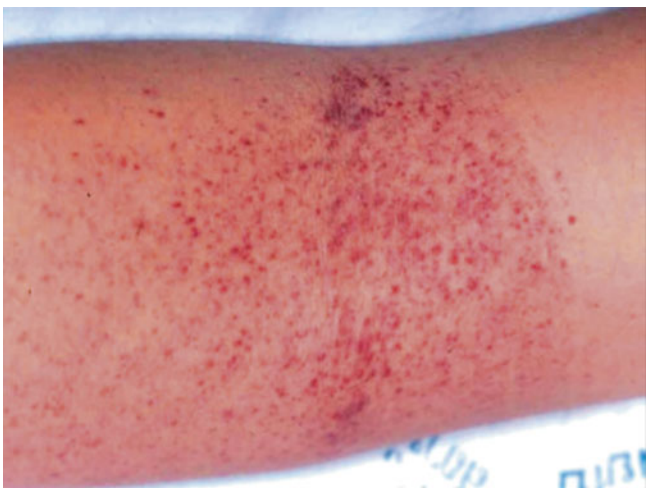

Fig. 37.6 Positive tourniquet test (Reprinted from Ref. [100]. With permission from Oxford University Press)

Evidence of plasma leakage includes hemoconcentration (10–20 % from baseline (if available), hypoproteinemia, and/or pleural effusion and ascites which are the most objective signs of plasma leakage [101]. Severe plasma leakage will result in shock and DHF III, IV are characterized by

Table 37.7 WHO classification of dengue hemorrhagic fever severity

DF/DHF	Grade	Signs and symptoms	Laboratory
DHF	I	Fever	Platelets <100,000 cells/mm^2
		Positive tourniquet test	HCT rise by ≥20 %
		Evidence of plasma leakage	
DHF	II	Grade I and spontaneous bleeding	Platelets <100,000 cells/mm^2
			HCT rise by ≥20 %
DHF[a]	III	Grade II and shock	Platelets <100,000 cells/mm^2
			HCT rise by ≥20 %
DHF[a]	IV	Grade III and profound shock (moribund)	Platelets <100,000 cells/mm^2
			HCT rise by ≥20 %

[a]DHF III and IV are DHF with shock, formerly called dengue shock syndrome

Table 37.8 Complications of severe dengue fever

Expanded dengue syndrome	Dengue hemorrhagic fever with shock with complications due to co-infection, severe shock, or pre-existing conditions
	Single organ dysfunction including
	CNS: encephalitis, encephalopathy, CNS bleed, ADEM
	GI: hepatitis, acute liver failure, pancreatitis, parotitis
	Renal: hemolytic uremic syndrome
	Cardiac: dysrhythmia, myocarditis, pericarditis
	Respiratory: ARDS, pulmonary hemorrhage
	Musculoskeletal: rhabdomyolysis
	Opthalmic: macular hemorrhage, optic neuritis
Immune dysregulation syndromes	Hemophagocytic histiocytosis syndrome
	Immune thrombocytopenia
Shock without capillary leak	Unclear etiology

shock in addition to the other criteria. Previously, DHF with shock was referred to as DSS however this terminology has been eliminated from the current classifications. The WHO classification of DHF by severity (Grades I–IV) is shown in Table 37.7 [101].

Most patients infected with dengue experience a self-limited, mild illness and only about 5–10 % [102] progress to severe disease, mostly characterized by hypovolemic shock due to plasma leakage, with or without hemorrhage [68]. In some cases however, the clinical course of dengue is beyond that of typical severe dengue. Other features of severe dengue that have been reported include those listed in Table 37.8. Such entities may occur either as a complication of severe shock, preexisting conditions, or possibly co-infections [103, 104]. Typically, the clinical course is characterized by three well-defined phases: febrile, critical and recovery.

Febrile Phase

The *febrile phase* lasts 2–7 days and is characterized by sudden onset, high-grade fever. The clinical manifestations are relatively similar to many other viral syndromes – making the early diagnosis of dengue challenging. Common signs and symptoms include facial flushing, skin erythema/rash, generalized body aches, myalgia, arthralgia, headache, conjunctival injection, and pharyngeal erythema. Anorexia and nausea are common and lead to dehydration. Young children and infants can develop febrile seizures and they present more often with encephalopathy than older children [105]. There is often tender hepatomegaly [100].

A positive tourniquet test in this phase increases the probability of dengue. In a prospective study in Thailand, the positive predictive value of a positive tourniquet test done during the febrile phase was 57 % in distinguishing dengue from nonspecific viral infection [106]. The combination of a positive tourniquet test plus leukopenia (WBC <5,000/mm^3) increases the positive predictive value to 70–83 % [100]. Mild mucocutaneous hemorrhage can be seen – reported frequencies vary between 9.7 % of serologically confirmed cases in a retrospective study in Puerto Rico [107] to 68 % in a prospective study in Thailand [106]. Leukopenia is one of the first laboratory abnormalities observed, while thrombocytopenia usually ensues shortly thereafter.

Critical Phase

Defervescence occurs between day 3 and 7 of illness, accompanied by worsening thrombocytopenia and the onset of plasma leakage, as evidenced by a rising hematocrit level. This *critical phase* lasts 24–48 h [108]. It is postulated that patients without a marked increase in capillary permeability will improve, while those with increased permeability will progress onto severe dengue which is essentially DHF Grade III–IV [68]. Since it is difficult to know which patients will progress onto this critical phase, it is important for the clinician to be aware of warning signs that clinically significant vascular leakage may be developing [69, 72]. Although rare, true hemorrhage can occur, and is more often seen in adult patients [109].

Hypovolemic shock occurs when a critical volume of plasma is lost through leakage, although less commonly it might occur due to severe hemorrhage. Before intravenous fluid therapy, it may be difficult to detect objective signs of plasma leakage such as pleural effusions and ascites. During the initial stage of shock, the usual compensatory mechanisms come into play, with tachycardia, peripheral vasoconstriction and cool extremities. These mechanisms maintain a "normal" or even elevated diastolic blood pressure with a narrow pulse pressure (less than 20 mmHg). As opposed to many cases of bacterial septic shock, DSS is reversible and

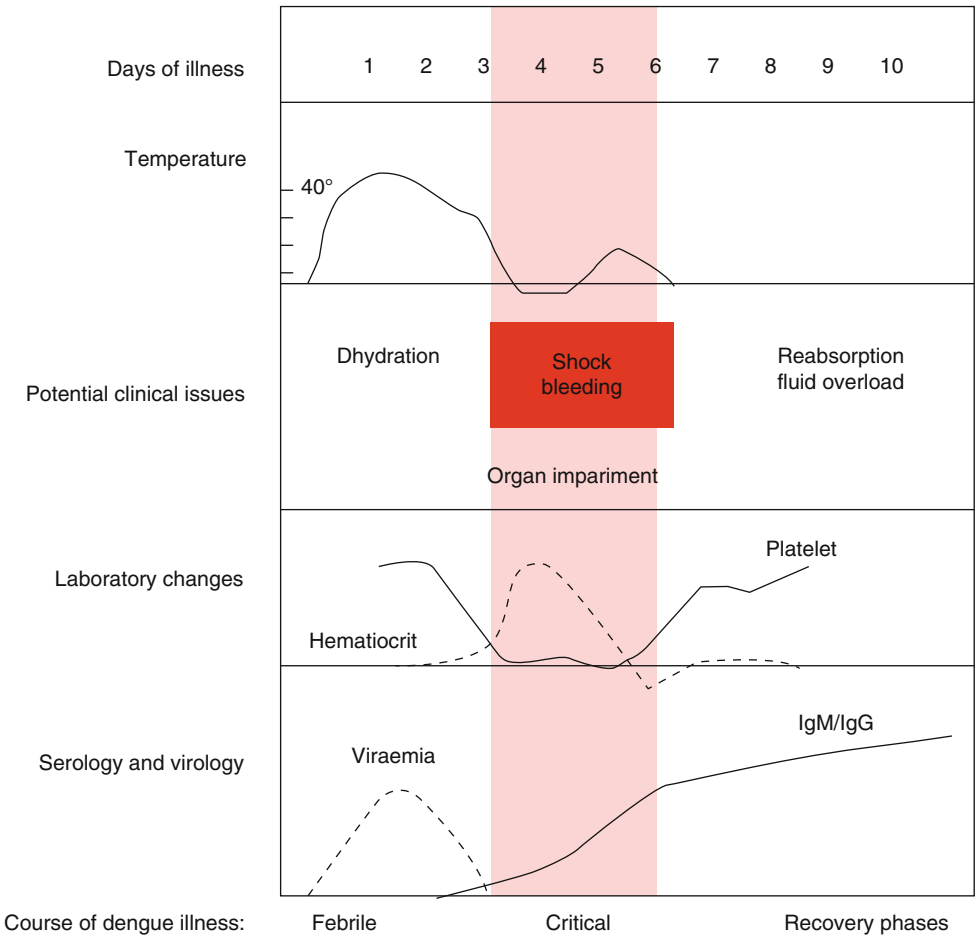

Fig. 37.7 The clinical course of dengue illness and laboratory studies (Reprinted from Ref. [68]. With permission from World Health Organization (WHO))

of short duration if timely and adequate volume resuscitation is administered [101]. Prolonged uncorrected shock progresses in the usual fashion, with hypoperfusion leading to multiorgan failure, metabolic acidosis and DIC and a high mortality rate.

Respiratory distress may be due to diffuse capillary leak or it may result from massive pleural effusions. Ascites may progress to abdominal compartment syndrome [110]. In addition, excessive administration of intravenous fluids, especially during the transition period from critical to recovery phase may lead to pulmonary edema and potentially to congestive heart failure. Clinical observations [105] have suggested that the degree and duration of plasma leakage is shorter in infants than in children, thus predisposing them to iatrogenic fluid overload with its attendant complications.

Recovery Phase

If the patient survives the 24–48 h *critical phase*, the capillary leak resolves, followed by a gradual reabsorption of edema fluid in the next 48–72 h [68]. Brisk diuresis ensues, with decrease of hematocrit towards baseline level, followed by stabilization of hemodynamic parameters and improvement in the general condition. Some patients may have a particular rash, described as "isles of white in the sea of red" [111], that may be pruritic. Even cases with profound shock that receive adequate and timely treatment recover within 2–3 days, however those who have prolonged shock and multiorgan failure will take longer to recover [101].

The typical course of dengue infection is summarized in Fig. 37.7 [68].

Diagnosis

Early in its course, dengue infection is often indistinguishable from other viral syndromes, parasitic infections, or bacterial sepsis. In addition, other conditions leading to a systemic inflammatory response should be considered in the differential diagnosis. Laboratory methods for confirming dengue vary depending on the stage of the illness. In the early stages – the first 4–5 days of illness – diagnosis relies on detection of the virus, viral nucleic acid or viral antigens (especially non-structural antigen 1 – NS1) that can be detected within the first 24 h to 5–7 days. These are called "direct" methods and although they provide an early and accurate diagnosis, they are not widely available in resource-limited countries. As the patient

Table 37.9 WHO guidelines for dengue laboratory diagnosis

Probable dengue	Clinical features
	Positive IgM or IgM
	Occurrence at same location/time as confirmed dengue cases
Confirmed dengue	Isolation of whole virus, detection of genomic sequence by RT-PCR or antigen from serum, CSF or autopsy samples
	Fourfold increase in serum IgG or increase in IgM between paired sera

Based on data from Ref. [101]

progresses into the critical/recovery phases, serology becomes the method of choice [68] – while serology is widely available, it is also less accurate. The antibody response varies according to the immune status of the host. A first dengue infection in a person who has not been infected with or immunized against another *Flavivirus* (e.g. yellow fever, Japanese encephalitis, etc.) leads to the appearance of specific IgM antibodies in the serum between day 5 and 10 of illness. These IgM antibodies disappear after 2–3 months. Anti-dengue serum IgG becomes detectable at the end of the first week of illness, increasing slowly thereafter, with levels detectable for months and possibly longer. During a secondary dengue infection, or in a person previously infected with or immunized against another *Flavivirus*, antibody titers rise rapidly but cross-react with many viruses from the *Flavivirus* group. The predominant antibody type of secondary dengue infection is IgG, which rises as early as day 5 of illness and persists from months to life. Early IgM levels are much lower than in the primary infection and may even be undetectable [69]. Given these intricacies and the variable performance characteristics of commercially available ELISA tests, studies have shown that combining a direct method such as NS1 detection (day 1 to 7–9) with a serologic method such as IgM/IgG detection (after day 4–5) allows for dengue diagnosis throughout the normal temporal spectrum of patient presentation [112] (Table 37.9).

Treatment

Management of dengue is centered around careful fluid administration and supportive management, as no effective antiviral agents to treat dengue infection are available [69]. After making a presumptive diagnosis of dengue, management priorities include [102]:

- Establish the phase of the disease – febrile, critical or convalescence
- Recognize the presence of warning signs that prompt the need for hospitalization
- Recognize and reverse the shock state, using iv fluids and blood as needed
- Titrate fluid administration aiming to preserve an effective circulating blood volume but simultaneously avoiding fluid overload

Management of Dengue Hemorrhagic Fever Grade 1 and 2 (Without Shock)

The goal of therapy is to judiciously match the ongoing losses due to plasma leakage that occur during the 24–48 h of the critical phase. Clinical experience, synthesized in the most current guidelines [101], has shown that fluid needs during this period are about maintenance plus 5 % deficit, without the need for more aggressive fluid boluses [101]. Isotonic, dextrose-containing fluids are recommended. The hourly fluid administration rate is titrated according to the projected stage of the illness, i.e. a slower initial rate if the plasma leakage is just beginning. A useful clinical correlate is the severity of thrombocytopenia – a platelet count of 50–100,000/mm^3 is usually seen in the "initial" stages of leakage, whereas a platelet count <50,000 usually indicates that it has been ongoing for some time [108]. The rate of iv fluid should be adjusted according to the clinical vital signs, hematocrit – measured at least every 4–6 h during the critical phase – and urine output (target at least 0.5 mL/kg/h). Worsening of the clinical condition and/or inability to decrease the rate of iv fluids as predicted should prompt consideration of:

- Accelerated plasma leak with transition to DHF Grade III–IV – management described below
- Occult bleeding: whole blood or PRBCs are indicated, 10 ml/kg aliquots
- Liver or kidney dysfunction
- Myocardial dysfunction – one study [113] notes an incidence of systolic dysfunction from 14 % in pediatric patients with DHF non-shock to 36 % in DHF with shock. The clinical significance of these findings is not clear, as this seems to be a different phenomenon than the myocardial depression in septic shock [102]. The use of inotropes and vasopressors is rarely employed in clinical practice, outside of the situation of late presenting, decompensated shock [101]

- Presence of co-infections, such as bacterial sepsis, meningitis, malaria or underlying medical conditions
- Expanded dengue syndrome: occurrence of unusual manifestations, such as myocarditis or pericarditis, pancreatitis, encephalopathy, HLH, etc.

Management of DHF Grades 3 and 4 (Dengue Shock Syndrome)

More aggressive fluid strategy, with initial boluses of 10 mL/kg/h for the first 2–3 h is the mainstay of treatment for patients with grades 3 and 4 DHF (DSS). In case of low blood pressure/critically decreased perfusion of vital organs, the guidelines do recommend larger fluid boluses of 20 mL/kg, but only until blood pressure is restored. The hematocrit should be checked before and after the fluid boluses [101]. The presence of hypotension should alert the practitioner to the possibility of concealed hemorrhage. After the initial resuscitation, fluid administration is titrated according to the clinical response and gradual return of the hematocrit towards baseline levels. A suggested algorithm is presented in Fig. 37.8 [68].

The choice of resuscitation fluid – colloid versus crystalloid – has been the subject of many controversies. A few prospective, randomized controlled trials have been performed in the last decade [114, 115] and have shown that that neither crystalloids nor colloids had a distinct advantage over the other in terms of recurrence of shock, the need for rescue colloids after initial resuscitation, the subsequent need for diuretics, or mortality. The guidelines currently recommend crystalloid for the initial resuscitation of DHF Grade III and a choice between crystalloid or colloid for the initial resuscitation of DHF Grade IV [101].

As discussed in the management of grades 1 and 2 DHF, changes in hematocrit are a useful guide to treatment. A rising or persistently high hematocrit in an unstable patient indicates ongoing plasma leakage and the need for a further bolus of fluid. The same hematocrit in a patient who is improving clinically and has good urine output only calls for continuation of the current regimen and the expectation that the plasma leakage will stop in the next 24 h. Conversely, a decrease in hematocrit in an unstable patient indicates major hemorrhage [68] and the need for urgent transfusion. The same hematocrit in an improving patient indicates relative hemodilution due to reabsorption of extravasated edema fluid, signaling transition into convalescence, so in this case intravenous fluids should be discontinued to avoid iatrogenic fluid overload.

In contrast to the PALS guidelines for pediatric septic shock that emphasize early and aggressive fluid resuscitation, often with more than 60 mL/kg of fluid in the first few hours, the strategy for dengue shock is quite different and many authors and guidelines call attention to the need for hourly titration of iv fluids. While the pathophysiology of the two shock states may be different, it is important to note that in western countries mechanical ventilation is easily accessible if patients develop signs and symptoms of fluid overload and respiratory compromise. However in countries where dengue is endemic, respiratory compromise secondary to fluid overload is a major contributor to mortality in settings with poor resources, few personnel, and limited equipment [115]. It is thus incumbent upon critical care physicians to adjust their practice to the appropriate setting and keep parenteral fluid therapy to the minimum required to maintain cardiovascular stability, until plasma leakage ceases [69]. Patients with severe dengue shock, especially if presenting late in the course, should also receive supportive care as clinically indicated, to include renal replacement therapy, use of inotropes and vasopressors, management of liver failure or encephalopathy.

Typhoid and Paratyphoid Fever

Epidemiology

Typhoid fever has an estimated annual incidence of 20 million cases worldwide, causing 200,000 deaths. Paratyphoid fever contributes about five million cases annually [116], with fewer deaths. The regions with the highest incidence of typhoid fever (>100/100,000 cases/year) include South-Central and South-East Asia. Regions with medium incidence (10–100/100,000 cases/year) are the rest of Asia, Africa, Latin America and the Caribbean, while countries in the "developed" world – North America, Europe, Australia and New Zealand have a low incidence of typhoid fever (<10/100,000 cases/year) [116]. In regions with an increased burden of disease, the highest incidence of typhoid fever is observed in children less than 5 years of age [117], whereas in low incidence regions, where the disease is primarily travel- acquired [118], children and young adults are equally affected, with the incidence gradually decreasing in people above 30–40 years of age [116].

Since typhoid fever is an exclusively human disease, with a fecal – oral mode of transmission, the improvement in food hygiene and water sanitation in developed countries that took place in the twentieth century led to a marked decline in the incidence of the disease. For example, in the US the annual incidence dropped from 7.5/100,000 in 1940 to 0.2/100,000 in the 1990s [119]. In addition, the proportion of cases related to foreign travel increased from 33 % in the 1960s to

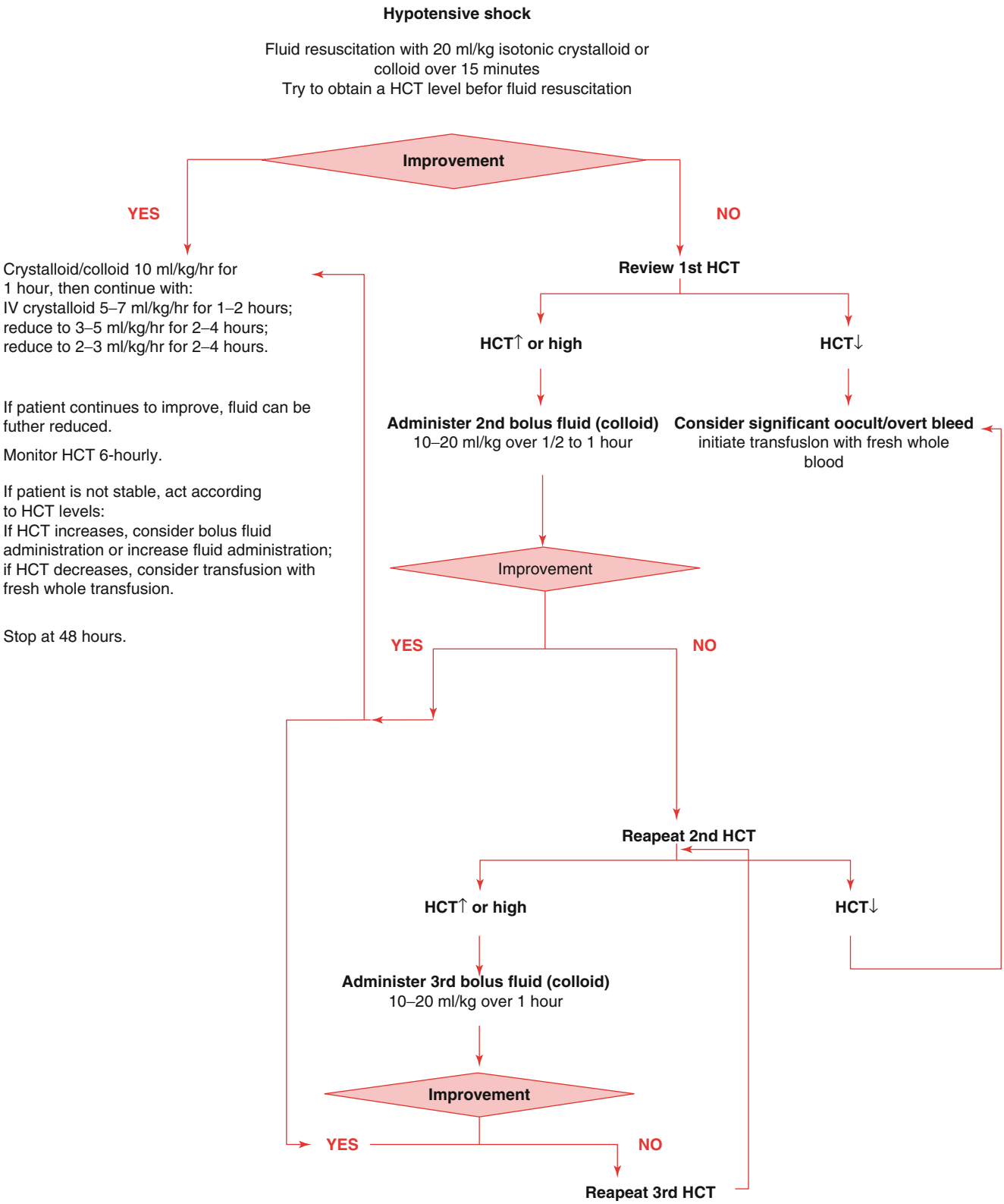

Fig. 37.8 Algorithm for fluid replacement in severe dengue with hypotensive shock (Reprinted from Ref. [68]. With permission from World Health Organization (WHO))

80 % in the 1990s. In the latest surveillance study from the US [120], during 1999–2006 there were 1,902 typhoid fever cases. Less than half of the patients were children – 4 % were younger than 2 years old, 12 % were between 2 and 5 years old, and 25 % between 6 and 17 years of age. Three quarters of these patients were hospitalized, with a case fatality rate of 0.2 %. About 80 % of cases were travel related (mostly to the Indian subcontinent) – notably, only 5 % of the travelers had received typhoid vaccine. Of the domestically acquired cases, the illness was traced either to a typhoid carrier or to food related outbreaks.

Etiology

Typhoid fever and its close cousin, paratyphoid fever, constitute the "enteric fever" group. They are systemic bacterial illnesses caused by the bacterium *Salmonella enterica*, serotype Typhi and respectively, Paratyphi A, B and C. These pathogens are exclusively human and the infection is transmitted through food or water contaminated with feces or urine of a patient or a carrier [15]. Typhoid fever is therefore primarily a disease of overcrowding, poor sanitation, and undertreated water. In highly endemic countries the ratio of typhoid to paratyphoid fever is about 8–10 to 1 [116], whereas, among travelers, the incidence of the disease caused by *S. paratyphi* may be more important, probably due to a vaccine effect, which gives protection only for *S. typhi* [119].

Pathophysiology

Typhoid bacilli are ingested and then penetrate the intestinal mucosa. In order to produce disease in healthy individuals, the infectious dose has to be large, between 1,000 and one million organisms in volunteers. The infectious dose is decreased in the presence of the capsular Vi antigen, decreased stomach acidity, and food (which protects the bacterium) [121]. Once in the small intestine, the organisms penetrate the mucosa – likely through the specialized epithelial M cells – and are taken up by the macrophages resident in the submucosa and travel to the local lymph nodes [122]. In contrast to the non-typhoidal Salmonella serotypes resulting in gastroenteritis, which cause a significant neutrophil influx in the intestinal mucosa and localized infection, the typhoidal Salmonella evade this local defense mechanism. Recent evidence suggests that typhoidal strains evade pattern recognition receptors and induce a less vigorous inflammatory response [123]. A short bacteremic phase ensues, which carries the Salmonella to the reticuloendothelial system of the liver and spleen, where massive multiplication of the organisms occurs. The incubation period lasts 7–14 days, followed by a severe secondary bacteremia which marks the onset of clinical illness [122]. During this phase, virtually all organs can be invaded, but of particular importance are the infection of the Peyer's patches and the gallbladder. The Peyer's patches become hyperplastic, with superficial necrosis that leads to superficial ovoid ulcers, a hallmark of typhoid fever. Located along the longitudinal axis of the gut, these do not heal with stricture formation, however when such an ulcer erodes into a mural vessel, severe hemorrhage and/or perforation leading to peritonitis can occur [122]. Infection of the gallbladder can result in a chronic, subclinical cholecystitis with persistent fecal carriage.

Clinical Manifestations

The incubation period averages 10–20 days (range 3–56 days) and is dependent on the infecting dose and the virulence of the Salmonella serotype. Paratyphoid fever has a shorter incubation period and has a similar, sometimes milder clinical course [122]. The classic description of the untreated typhoid fever of average severity is a protracted illness spanning about 4 weeks. The first week is characterized by non-specific, flu-like symptoms, a "coated" tongue, intermittent or low grade fevers, constipation in adults, diarrhea in children or HIV positive adults [124]. During the second week, the overall condition of the patient declines, with sustained high fevers and a characteristic "relative bradycardia." Patients appear systemically ill with abdominal distention and splenomegaly. In about 30–50 % of cases "rose spots" appear – these are pink, maculopapular lesions, 2–4 mm in diameter that develop in crops over the upper abdomen and lower thorax. These are not specific for typhoid, as they may also occur in invasive non-typhoidal salmonellosis and shigellosis [122]. They may be difficult to see in dark skinned individuals and may also be difficult to differentiate from other bacterial or viral exanthems. During the third week, the overall condition of the patient declines further, with continuous sustained high fever, neuropsychiatric manifestations, worsened abdominal distention, and diarrhea. Significant complications occur in about 10–15 % of patients and include overwhelming septic shock, myocarditis, intestinal perforation or hemorrhage, and typhoid encephalopathy. Gastro-intestinal bleeding is the most frequent complication and is usually mild, however in about 2 % of cases the bleeding can be life threatening. Intestinal perforation is the most serious complication, occurring in about 2 % of cases and it doesn't always present with an acute abdomen but rather in a more subtle manner, with worsening abdominal pain, tachycardia and altered mental status. Encephalopathy and shock carry a high mortality [121]. Neuropsychiatric symptoms include apathy, severe agitation, and delirium, although deep coma is unusual. For unclear reasons, the incidence of encephalopathy varies by country, from 10 to 40 % of

Table 37.10 Antibiotic recommendations for typhoid fever

	Optimal treatment	Alternative treatment
Typhoid fever		
Sensitive	Fluoroquinolone	Chloramphenicol, Amoxicillin, TMP-SMX
MDR	Fluoroquinolone or Cefixime	Azithromycin, Cefixime
Quinolone resistant	Azithromycin or Ceftriaxone	Cefixime
Severe typhoid fever		
Sensitive	Fluoroquinolone	Chloramphenicol, Amoxicillin, TMP-SMX
MDR	Fluoroquinolone	Ceftriaxone or Cefotaxime
Quinolone resistant	Ceftriaxone or Cefotaxime	High dose fluoroquinolone, ceftriaxone, azithromycin[a]

[a]Unclear effectiveness however treatment for quinolone resistance is not well defined

patients in Indonesia [125] to less than 2 % of patients in Vietnam [126]. Patients who survive into the fourth week start to improve, defervesce, abdominal distention also improves slowly, although the danger of perforation and hemorrhage persists well into the fourth week. Variations from this classic picture are often seen and with the widespread use of antibiotics, the clinical course is much shorter. In fact, community-based studies in areas of endemic disease indicate that many patients, especially children less than 5 years of age, may have a non-specific febrile illness that is not recognized clinically as typhoid [124].

Relapse occurs in about 1.5–20 % of patients treated with antibiotics, usually 2–3 weeks after the resolution of fever. The blood culture becomes positive again and the isolate usually has the same antibiotic susceptibility pattern as the isolate from the original episode [121]. The relapse has a shorter and milder clinical course than the original episode and occurs in spite of high titers of O, H and Vi antibodies. Reinfection may also occur and can only be distinguished from relapse by molecular typing techniques [127].

Diagnosis

Laboratory diagnosis of typhoid fever has remained very challenging for decades. The clinical diagnosis can be difficult depending on the timing of presentation relative to the natural history of the clinical disease. The gold standard confirmatory test is a blood culture – however the sensitivity of a blood culture can be as low as 40–80 % early in the disease when bacteremia is highest and even lower later in the clinical course [128]. Stool and urine cultures become positive after the first week. However, sensitivity for stool and urine cultures is also low. Bone marrow culture is quite sensitive (55–67 %), though bone marrow aspiration is invasive and impractical in many cases. Multiple serologic tests are as widely used as microbiologic culture, but also with problematic performance. The Widal test is the classic test and is based on detecting antibodies to the O and H antigens of *S. typhi*. Other tests such as the Typhidot or Tubex tests directly detect IgM antibodies to multiple *S. typhi* antigens. These tests have also underperformed and overall show roughly a 70–90 % sensitivity and 70–90 % specificity. Despite their limitations they still are used clinically. Nested polymerase chain reaction is exquisitely sensitive and specific and remains promising as the next gold standard for diagnosis where laboratory resources are available. In the end, diagnosis of Typhoid is made largely on a clinical basis. Other common laboratory abnormalities are mild and nonspecific including leukopenia and thrombocytopenia in adults, whereas leukocytosis frequently occurs in children. Hepatic enzymes may also be mildly elevated [128, 129].

Treatment

Significant drug resistance issues have arisen with regard to the Salmonella serotypes responsible for typhoid and paratyphoid. Drug choices should be made based on the severity of illness, geographic resistance patterns, or laboratory sensitivities from clinical isolates. Historically, treatment with amoxicillin or trimethoprim-sulfamethoxazole was the standard of care for many years. Unfortunately, resistance to these agents has become very common. In some areas of China and India 50–80 % of isolates are multidrug resistant [119]. Fluoroquinolones have been an excellent alternative supported by multiple clinical trials. Unfortunately in many areas of central and South East Asia, decreased susceptibility to fluoroquinolones is as high as 75–80 % in Tajikistan and Vietnam in the late 1990s [119]. Many prospective trials have also demonstrated significant success with azithromycin and ceftriaxone, and treatment with these agents is becoming more widespread. Unfortunately, recently extended-spectrum beta-lactamases have been identified in typhoidal Salmonella serotypes that will greatly limit the therapeutic options for this widespread tropical disease [130]. At this point, for invasive infections fluoroquinolones or third generation cephalosporins are recommended empirically until sensitivities are available [121, 129, 130]. Table 37.10 contains some treatment options for resistant serotypes although in the case of quinolone resistance, multidrug regimens are being studied but data is lacking at this point [128, 131]. Other adjunctive therapy includes dexamethasone has been

used as an adjunctive therapy for severe disease characterized by shock and obtundation/coma. Reportedly, the use of dexamethasone reduced mortality in a severe cohort from 35–55 to 10 % [125, 132, 133].

Some reports have described different clinical features in multidrug resistant typhoid fever (MDRTF) and rising overall mortality up to 16 % in this cohort. These patients are more toxic in appearance, with a higher fever (up to 40 °C in some cases), more frequent (and more severe) abdominal distention and tenderness, and hepatomegaly and splenomegaly [134]. Several hypotheses have been suggested to explain this including delay in starting effective antibiotics, high bacterial load, and possibly higher microbial virulence.

Leptospirosis

Epidemiology

Leptospirosis is the most widespread zoonosis in the world and it is caused by a spirochete of the genus *Leptospira*. The annual incidence of leptospirosis in tropical endemic areas is 10–100/100,000 people whereas it is 0.1–1/100,000 people in temperate areas [135]. In the end there are more than 500,000 cases of leptospirosis reported per year with an overall mortality rate of 10 % [136]. Although leptospirosis is seen in tropical, subtropical, and temperate climates, it is endemic in much of the tropics, especially in South East Asia. The incidence of the disease is associated with the lack of proper sanitation, poor water quality, flooding, and the presence of maintenance hosts such as rats, dogs, cattle, and swine who excrete leptospira in the urine [137]. Infected rats shed the pathogen for life and most other animals shed for 6–12 months, thereby preventing pathogen eradication from the soil and water. In the past two decades the epidemiology of this disease is changing to include more poor urban settings, especially those with high rainfall and flooding. In addition, there have been multiple, limited outbreaks in nonendemic areas such as the USA, Canada, and continental Europe [138]. Many of these outbreaks were related to recreational contact with contaminated natural settings [137, 138]. The disease is contracted via contact with contaminated water or soil, as well as direct contact with infected animal urine. As such, the risk (and incidence) of leptospirosis is increased in many occupations, including farmers, butchers, and veterinarians because of direct contact with hosts. Also, sewer workers, construction workers, flood relief workers, and military personnel are at risk due to indirect contact with contaminated waters. In addition, recreational activities resulting in exposure to contaminated fresh water bodies (lakes, streams, ponds) are at risk for contracting the disease [139]. With increased incidence in endemic areas as well as nonendemic areas, leptospirosis is now considered an emerging global disease [137].

Etiology

Leptospira are spirochetes belonging to the same genus as *Borrelia* and *Treponema*, the pathogens responsible for Lyme disease and syphilis, respectively. Leptospira can be saprophytic or pathogenic and the pathogenic species are within the *L. interrogans* subgroup. There are many serogroups and serovars within this pathogenic category. The organism is morphologically unique with a thin and highly coiled shape with flagella present. The organism shares features with both Gram-positive and Gram-negative organisms in that its surface contains peptidoglycan, phospholipids, outer membrane proteins, and lipopolysaccharide [136, 137].

Pathophysiology

Leptospira are extracellular organisms and are highly invasive. The pathogen invades the body by contact with skin abrasions, mucous membranes (conjunctiva and nasopharynx), and possibly through intact skin [138, 140]. They invade tissues by adhering to a wide range of extracellular matrix components, endothelial cells, leukocytes, and kidney epithelial cells thereby gaining access to the bloodstream [136, 138]. Once the pathogen has invaded the entry point such as the conjunctiva, there is rapid penetration and dissemination of the organism throughout the body and particularly the kidney [141]. An early finding of diffuse endothelial injury or vasculitis is the main mechanism of tissue damage [142]. Although the exact cause of the vascular inflammation is not yet understood, there are many data showing evidence of small vessel disease in the lung and kidney, as well as the aorta, coronary arteries, and cerebral vessels. Other mechanisms of injury in addition to direct endothelial injury are parenchymal cell injury and increased vascular permeability [142]. Whether the vasculitis demonstrated in leptospirosis is of an autoimmune nature is controversial. Many of the features of common vasculitides such as immune complex deposition have not been shown in leptospirosis, leading some to maintain that the endothelial activation/injury is sepsis-like rather than autoimmune mediated [142, 143].

Acute kidney injury is common in leptospirosis and histopathologically the abnormality is an interstitial nephritis with interstitial edema and mononuclear infiltration. Large numbers of leptospires are found throughout the tubules, interstitium, and in some cases within glomeruli. Typically, AKI in this setting is non-oliguric and presents with evidence of tubular dysfunction with hypokalemia, hypomagnesemia, and hypophosphatemia. Rhabdomyolysis can add to the severity of AKI as well.

Severe lung injury and pulmonary hemorrhage is commonly observed in leptospirosis. By histopathology, the lung is edematous with moderate monocyte infiltration into the

Table 37.11 Clinical forms of leptospirosis

Anicteric	Fever, headache, chills, abdominal pain, conjunctival suffusion, severe myalgias, normal CSF
Aseptic meningitis	Can follow anicteric form, CSF pleocytosis, self limited, often mistaken for viral
Weil syndrome	Jaundice, severe renal dysfunction, hemorrhagic manifestations
Severe pulmonary form	Hemorrhagic pneumonitis, ARDS, massive pulmonary hemorrhage, +/− jaundice

alveolar septum. In addition, leptospiral antigen was demonstrated on the luminal surface and in the cytoplasm of endothelial cells in the alveolar septal capillaries. There are several experimental reports demonstrating Goodpasture's-like findings in the lung with linear deposits of immunoglobulin and complement along the alveolar septa. These findings suggest the presence of antiglomerular basement membrane antibodies, which could cross-react with lung septal matrix causing massive hemoptysis [142, 143]. In addition, experimentally abnormalities of multiple ion transporters are seen in leptospirosis models, and it is thought that these alterations of pulmonary permeability are important in ARDS seen in leptospirosis [141].

Clinical Manifestations

In most cases Leptospirosis is a mild nonspecific self-limited illness with initial symptoms presenting 2–30 days (average 10 days) after exposure to the bacteria [137, 139, 144]. There are four forms of leptospirosis. The *anicteric form* accounts for 85–90 % of cases and is a nonspecific febrile illness. The *aseptic meningitis form* can present concurrent with the anicteric form. *Weil's form* is characterized jaundice and the features are listed in Table 37.11 [142]. Lastly, the *severe pulmonary form of leptospirosis* (*SPFL*) may occur with or without jaundice. The mortality from Weil syndrome and SPFL is >10 and >50 % respectively [135, 141].

The clinical course is biphasic, with the initial phase lasting for 3–9 days characterized by leptospiremia and presenting with the sudden onset of high fever, headache, severe myalgias (lower limbs), chills, conjunctival suffusion, abdominal pain, nausea, vomiting, diarrhea, and malaise. At this point symptoms can resolve. In approximately 20 % of cases, after 1–3 days the second phase begins which is coincident with the appearance of circulating IgM and is thus called the "immune phase" [135, 140, 141, 145]. During this time fever is much less or absent. However, headache, myalgias, conjunctival suffusion, aseptic meningitis (80 % in children), hepatomegaly, and interstitial nephritis are the common during this phase, which can last up to a month. It is also called the leptospiruric phase because after the first week, leptospires are eliminated in the urine [141].

The severe form of leptospirosis – Weil's Syndrome can begin after an initial anicteric phase or the jaundice can be seen within the first 4–6 days. This presentation occurs in less than 10 % of leptospirosis patients. The liver is enlarged and tender and the jaundice is due to hepatocellular injury, cholestasis, and increased bilirubin load from tissue hemorrhage reabsorption. A hallmark of this disease is significantly elevated bilirubin out of proportion to the mildly elevated transaminases [138]. Despite this significant liver injury, it is recoverable and as such is rarely the cause of death in this disease. Renal failure can occur in 40–60 % with oliguria developing within the first 2 weeks. AKI can occur and can vary from urine sediment changes to anuric renal failure [141]. As stated above, the injury pattern is that of interstitial nephritis. Most develop nonoliguric AKI and those with some preservation of kidney function have better survival. Typically resolution of AKI in adults is near complete by 6 months. In one cohort of 43 children the incidence of AKI was 79 % however only two such children required dialysis and one died. These data show that children with AKI fare much better who also present mostly with nonoliguric AKI with hypokalemia [146].

Cardiac issues can arise with arrhythmias, myocarditis, and pericarditis. Coronary arteritis was found in 70 % and aortitis was found in 50 % of a reported cohort [139]. In addition, neurologic issues can be present, including altered mental status, meningoencephalitis, and cranial nerve palsy [135]. Severe hemorrhagic complications can occur in Weil's Syndrome, including ocular suffusion, petechiae, pulmonary hemorrhage, GI hemorrhage, and hematuria. Thrombocytopenia is present in up to 70 % of patients. In fact, hemorrhage has become the most serious manifestation of leptospirosis and the incidence of significant hemorrhage is increasing worldwide [141].

Severe pulmonary disease can manifest with or without jaundice. The incidence of pulmonary disease ranges from 20 to 70 % and has been increasing worldwide over the last two decades. There is no apparent relationship between the severity of lung disease and the severity of jaundice and liver injury. The spectrum of pulmonary disease can range from dyspnea, cough, tachypnea, chest pain, hemoptysis to ARDS and massive pulmonary hemorrhage. Recently, a cohort of Weil's Syndrome patients were described with a 69 % incidence of pulmonary hemorrhage at autopsy and pulmonary hemorrhage is now the leading cause of death from leptospirosis [135, 147]. A typical CXR is characterized by diffuse small opacifications that are disseminiated or coalesce [135]. Although the mortality for Weil's Syndrome is 10 %, the mortality for leptospirosis associated pulmonary hemorrhage is >50 % [148]. At autopsy, the lung reveals extensive pulmonary hemorrhage from numerous

sites, congestion, edema, and hyaline membranes [135]. In children the incidence of Weil's Syndrome and pulmonary hemorrhage is lower and mortality also is lower compared to adults. In a recent study of 139 pediatric cases the most common symptom was fever, headache, and myalgia. Jaundice was present in 18 % and renal failure in 2 %. Shock was present in 9 % and meningitis in 7 % [149].

Diagnosis

The most important aspect of this diagnosis is clinical suspicion followed by the limited laboratory studies available. Isolation of leptospira from the blood or CSF during the leptospiremic phase in the first 2 weeks is possible and from the urine thereafter for many weeks [144]. Serological methods rely on detection of IgM specific for leptospira in the early "immune phase" of the illness; however, false negatives can confound if obtained prior to 5–7 days. This serology is much more reliable in the second week of illness. The gold standard is the microscopic agglutination test (MAT) showing at least a fourfold rise in titers or a single titer of >1:800 [138, 139, 144]. Sensitivity for this test is not perfect and reaches 82 % after the second week and 96 % after the fourth week. PCR based diagnostics are being investigated.

Treatment

Antibiotic therapy is effective if initiated within 5 days of the onset of symptoms according to the WHO. Other clinicians report benefit from antibiotics started later in the course of illness [150]. Unfortunately given the nonspecific signs and symptoms and minimal laboratory diagnostic options, the diagnosis is often made as the disease is beginning to resolve. The antibiotics typically used are penicillin for severe disease and doxycycline for milder disease. Cephalosporins and macrolides can also be used. The Jarisch-Herxheimer reaction can occur shortly after starting any bacteriocidal antibiotic treatment of a spirochete. Typically it occurs within 1–2 h and is characterized by fever, tachycardia, rigors, and hypotension [139].

Because of the autoimmune-like findings, steroids have been tried in severe disease. The data remain conflicting and controversial.

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