parasite densities. In Melanesia, children with α-thalassemia appear to have more frequent malaria (both vivax and falciparum) in the early years of life, and this pattern of infection appears to protect them against severe disease. In Melanesian ovalocytosis, rigid erythrocytes resist merozoite invasion, and the intraerythrocytic milieu is hostile.

Nonspecific host defense mechanisms stop the infection's expansion, and the subsequent strain-specific immune response then controls the infection. Eventually, exposure to sufficient strains confers protection from high-level parasitemia and disease but not from infection. As a result of this state of infection without illness (*premunition*), asymptomatic parasitemia is common among adults and older children living in regions with stable and intense transmission (i.e., holo- or hyperendemic areas) and also in parts of low-transmission areas. Immunity is mainly specific for both the species and the strain of infecting malarial parasite. Both humoral immunity and cellular immunity are necessary for protection, but the mechanisms of each are incompletely understood (Fig. 248-1). Immune individuals have a polyclonal increase in serum levels of IgM, IgG, and IgA, although much of this antibody is unrelated to protection. Antibodies to a variety of parasitic antigens presumably act in concert to limit in vivo replication of the parasite. In the case of falciparum malaria, the most important of these antigens is the surface adhesin—the variant protein PfEMP1. Passively transferred IgG from immune adults has been shown to reduce levels of parasitemia in children. Passive transfer of maternal antibody contributes to the relative (but not complete) protection of infants from severe malaria in the first months of life. This complex immunity to disease declines when a person lives outside an endemic area for several months or longer.

Several factors retard the development of cellular immunity to malaria. These factors include the absence of major histocompatibility antigens on the surface of infected RBCs, which precludes direct T cell recognition; malaria antigen–specific immune unresponsiveness; and the enormous strain diversity of malarial parasites, along with the ability of the parasites to express variant immunodominant antigens on the erythrocyte surface that change during the course of infection. Parasites may persist in the blood for months or years (or, in the case of *P. malariae*, for decades) if treatment is not given. The complexity of the immune response in malaria, the sophistication of the parasites' evasion mechanisms, and the lack of a good in vitro correlate with clinical immunity have all slowed progress toward an effective vaccine.

CLINICAL FEATURES

Malaria is a very common cause of fever in tropical countries. The first symptoms of malaria are nonspecific; the lack of a sense of well-being, headache, fatigue, abdominal discomfort, and muscle aches followed by fever are all similar to the symptoms of a minor viral illness. In some instances, a prominence of headache, chest pain, abdominal pain, cough, arthralgia, myalgia, or diarrhea may suggest another diagnosis. Although headache may be severe in malaria, the neck stiffness and photophobia seen in meningitis do not occur. While myalgia may be prominent, it is not usually as severe as in dengue fever, and the muscles are not tender as in leptospirosis or typhus. Nausea, vomiting, and orthostatic hypotension are common. The classic malarial paroxysms, in which fever spikes, chills, and rigors occur at regular intervals, are relatively unusual and suggest infection with *P. vivax* or *P. ovale*. The fever is usually irregular at first (that of falciparum malaria may never become regular); the temperature of nonimmune individuals and children often rises above 40°C (104°F) in conjunction with tachycardia and sometimes delirium. Although childhood febrile convulsions may occur with any of the malarias, generalized seizures are specifically associated with falciparum malaria and may herald the development of encephalopathy (cerebral malaria). Many clinical abnormalities have been described in acute malaria, but most patients with uncomplicated infections have few abnormal physical findings other than fever, malaise, mild anemia, and (in some cases) a palpable spleen. Anemia is common among young children living in areas with stable transmission, particularly where resistance has compromised the efficacy of antimalarial drugs. In nonimmune individuals with acute malaria, the spleen takes several days to become palpable, but splenic enlargement is found in a high proportion of otherwise healthy individuals in malaria-endemic areas and reflects repeated infections. Slight enlargement of the liver is also common, particularly among young children. Mild jaundice is common among adults; it may develop in patients with otherwise uncomplicated malaria and usually resolves over 1–3 weeks. Malaria is not associated with a rash like those seen in meningococcal septicemia, typhus, enteric fever, viral exanthems, and drug reactions. Petechial hemorrhages in the skin or mucous membranes—features of viral hemorrhagic fevers and leptospirosis—develop only very rarely in severe falciparum malaria.

SEVERE FALCIPARUM MALARIA

Appropriately and promptly treated, uncomplicated falciparum malaria (i.e., the patient can swallow medicines and food) carries a mortality rate of <0.1%. However, once vital-organ dysfunction occurs or the total proportion of erythrocytes infected increases to >2% (a level corresponding to $>10^{12}$ parasites in an adult), mortality risk rises steeply. The major manifestations of severe falciparum malaria are shown in Table 248-2, and features indicating a poor prognosis are listed in Table 248-3.

TABLE 248-2 MANIFESTATIONS OF SEVERE FALCIPARUM MALARIA

Signs	Manifestations
Major	
Unarousable coma/ cerebral malaria	Failure to localize or respond appropriately to noxious stimuli; coma persisting for >30 min after generalized convulsion
Acidemia/acidosis	Arterial pH of <7.25 or plasma bicarbonate level of <15 mmol/L; venous lactate level of >5 mmol/L; manifests as labored deep breathing, often termed "respiratory distress"
Severe normochromic, normocytic anemia	Hematocrit of <15% or hemoglobin level of <50 g/L (<5 g/dL) with parasitemia <10,000/μL
Renal failure	Serum or plasma creatinine level of >265 μmol/L (>3 mg/dL); urine output (24 h) of <400 mL in adults or <12 mL/kg in children; no improvement with rehydration
Pulmonary edema/adult respiratory distress syndrome	Noncardiogenic pulmonary edema, often aggravated by overhydration
Hypoglycemia	Plasma glucose level of <2.2 mmol/L (<40 mg/dL)
Hypotension/shock	Systolic blood pressure of <50 mmHg in children 1–5 years or <80 mmHg in adults; core/skin temperature difference of >10°C; capillary refill >2 s
Bleeding/disseminated intravascular coagulation	Significant bleeding and hemorrhage from the gums, nose, and gastrointestinal tract and/or evidence of disseminated intravascular coagulation
Convulsions	More than two generalized seizures in 24 h; signs of continued seizure activity, sometimes subtle (e.g., tonic-clonic eye movements without limb or face movement)
Other	
Hemoglobinuria[a]	Macroscopic black, brown, or red urine; not associated with effects of oxidant drugs and red blood cell enzyme defects (such as G6PD deficiency)
Extreme weakness	Prostration; inability to sit unaided[b]
Hyperparasitemia	Parasitemia level of >5% in nonimmune patients (>10% in any patient)
Jaundice	Serum bilirubin level of >50 mmol/L (>3 mg/dL) if combined with a parasite density of 100,000/μL or other evidence of vital-organ dysfunction

[a]Hemoglobinuria may also occur in uncomplicated malaria and in patients with G6PD deficiency who take primaquine. [b]In children who are normally able to sit.

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.