lactate production by the parasites, and a failure of hepatic and renal lactate clearance. The prognosis of severe acidosis is poor.

Noncardiogenic Pulmonary Edema Adults with severe falciparum malaria may develop noncardiogenic pulmonary edema even after several days of antimalarial therapy. The pathogenesis of this variant of the adult respiratory distress syndrome is unclear. The mortality rate is >80%. This condition can be aggravated by overly vigorous administration of IV fluid. Noncardiogenic pulmonary edema can also develop in otherwise uncomplicated vivax malaria, where recovery is usual.

Renal Impairment Acute kidney injury is common in severe falciparum malaria, but oliguric renal failure is rare among children. The pathogenesis of renal failure is unclear but may be related to erythrocyte sequestration and agglutination interfering with renal microcirculatory flow and metabolism. Clinically and pathologically, this syndrome manifests as acute tubular necrosis. Renal cortical necrosis never develops. Acute renal failure may occur simultaneously with other vital-organ dysfunction (in which case the mortality risk is high) or may progress as other disease manifestations resolve. In survivors, urine flow resumes in a median of 4 days, and serum creatinine levels return to normal in a mean of 17 days (Chap. 334). Early dialysis or hemofiltration considerably enhances the likelihood of a patient's survival, particularly in acute hypercatabolic renal failure.

Hematologic Abnormalities Anemia results from accelerated RBC removal by the spleen, obligatory RBC destruction at parasite schizogony, and ineffective erythropoiesis. In severe malaria, both infected and uninfected RBCs show reduced deformability, which correlates with prognosis and development of anemia. Splenic clearance of all RBCs is increased. In nonimmune individuals and in areas with unstable transmission, anemia can develop rapidly and transfusion is often required. As a consequence of repeated malarial infections, children in many areas of Africa and on the island of New Guinea may develop severe anemia resulting from both shortened survival of uninfected RBCs and marked dyserythropoiesis. Anemia is a common consequence of antimalarial drug resistance, which results in repeated or continued infection.

Slight coagulation abnormalities are common in falciparum malaria, and mild thrombocytopenia is usual (a normal platelet count should raise questions about the diagnosis of malaria). Of patients with severe malaria, <5% have significant bleeding with evidence of disseminated intravascular coagulation. Hematemesis from stress ulceration or acute gastric erosions also may occur rarely.

Liver Dysfunction Mild hemolytic jaundice is common in malaria. Severe jaundice is associated with *P. falciparum* infections; is more common among adults than among children; and results from hemolysis, hepatocyte injury, and cholestasis. When accompanied by other vital-organ dysfunction (often renal impairment), liver dysfunction carries a poor prognosis. Hepatic dysfunction contributes to hypoglycemia, lactic acidosis, and impaired drug metabolism. Occasional patients with falciparum malaria may develop deep jaundice (with hemolytic, hepatic, and cholestatic components) without evidence of other vital-organ dysfunction, in which case the prognosis is good.

Other Complications HIV/AIDS and malnutrition predispose to more severe malaria in nonimmune individuals; malaria anemia is worsened by concurrent infections with intestinal helminths, hookworm in particular. Septicemia may complicate severe malaria, particularly in children. Differentiating severe malaria from sepsis with incidental parasitemia in childhood is very difficult. In endemic areas, *Salmonella* bacteremia has been associated specifically with *P. falciparum* infections. Chest infections and catheter-induced urinary tract infections are common among patients who are unconscious for >3 days. Aspiration pneumonia may follow generalized convulsions. The frequencies of complications of severe falciparum malaria are summarized in Table 248-4.

TABLE 248-4 RELATIVE INCIDENCE OF SEVERE COMPLICATIONS OF FALCIPARUM MALARIA

Complication	Nonpregnant Adults	Pregnant Women	Children
Anemia	+	++	+++
Convulsions	+	+	+++
Hypoglycemia	+	+++	+++
Jaundice	+++	+++	+
Renal failure	+++	+++	–
Pulmonary edema	++	+++	+

Note: –, rare; +, infrequent; ++, frequent; +++, very frequent.

MALARIA IN PREGNANCY

Malaria in early pregnancy causes abortion. In areas of high malaria transmission, falciparum malaria in primi- and secundigravid women is associated with low birth weight (average reduction, ~170 g) and consequently increased infant mortality rates. In general, infected mothers in areas of stable transmission remain asymptomatic despite intense accumulation of parasitized erythrocytes in the placental microcirculation. Maternal HIV infection predisposes pregnant women to more frequent and higher-density malaria infections, predisposes their newborns to congenital malarial infection, and exacerbates the reduction in birth weight associated with malaria.

In areas with unstable transmission of malaria, pregnant women are prone to severe infections and are particularly vulnerable to high parasitemias with anemia, hypoglycemia, and acute pulmonary edema. Fetal distress, premature labor, and stillbirth or low birth weight are common results. Fetal death is usual in severe malaria. Congenital malaria occurs in <5% of newborns whose mothers are infected; its frequency and the level of parasitemia are related directly to the parasite density in maternal blood and in the placenta. *P. vivax* malaria in pregnancy is also associated with a reduction in birth weight (average, 110 g), but, in contrast to the situation in falciparum malaria, this effect is more pronounced in multigravid than in primigravid women. About 350,000 women die in childbirth yearly, with most deaths occurring in low-income countries; maternal death from hemorrhage at childbirth is correlated with malaria-induced anemia.

MALARIA IN CHILDREN

Most of the 660,000 persons who die of falciparum malaria each year are young African children. Convulsions, coma, hypoglycemia, metabolic acidosis, and severe anemia are relatively common among children with severe malaria, whereas deep jaundice, oliguric acute kidney injury, and acute pulmonary edema are unusual. Severely anemic children may present with labored deep breathing, which in the past has been attributed incorrectly to "anemic congestive cardiac failure" but in fact is usually caused by metabolic acidosis, often compounded by hypovolemia. In general, children tolerate antimalarial drugs well and respond rapidly to treatment.

TRANSFUSION MALARIA

Malaria can be transmitted by blood transfusion, needle-stick injury, sharing of needles by infected injection drug users, or organ transplantation. The incubation period in these settings is often short because there is no preerythrocytic stage of development. The clinical features and management of these cases are the same as for naturally acquired infections. Radical chemotherapy with primaquine is unnecessary for transfusion-transmitted *P. vivax* and *P. ovale* infections.

CHRONIC COMPLICATIONS OF MALARIA

TROPICAL SPLENOMEGALY (HYPERREACTIVE MALARIAL SPLENOMEGALY)

Chronic or repeated malarial infections produce hypergammaglobulinemia; normochromic, normocytic anemia; and, in certain situations, splenomegaly. Some residents of malaria-endemic areas in tropical Africa and Asia exhibit an abnormal immunologic response to repeated infections that is characterized by massive splenomegaly, hepatomegaly, marked elevations in serum titers of IgM and malarial antibody, hepatic sinusoidal lymphocytosis, and (in Africa) peripheral B cell lymphocytosis. This syndrome has been associated with