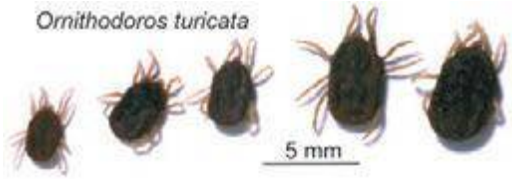

FIGURE 209-1 ***Ornithodoros turicata*** **soft ticks** of different ages.

presence inside cells likely represents a dead end for the bacteria after phagocytosis. Binding of the spirochetes to erythrocytes leads to aggregation of red blood cells, their sequestration in the spleen and liver, and hepatosplenomegaly and anemia. A bleeding disorder is probably the consequence of thrombocytopenia, impaired hepatic production of clotting factors, and/or blockage of small vessels by aggregates of spirochetes, erythrocytes, and platelets. Some species are neurotropic and frequently enter the brain, where they are comparatively sheltered from host immunity. Relapsing fever spirochetes can cross the maternal-fetal barrier and cause placental damage and inflammation, leading to intrauterine growth retardation and congenital infection.

Although *Borrelia* species do not have potent exotoxins or a lipopolysaccharide endotoxin, they have abundant membrane-associated lipoproteins whose recognition and binding by Toll-like receptors on host cells can lead to a proinflammatory process similar to that in endotoxemia, with elevations of tumor necrosis factor α, interleukin 6, and interleukin 8 concentrations.

IgM antibodies specific for the serotype-defining surface lipoprotein appear after a few days of infection and soon reach a concentration that causes lysis of bacteria in the blood through either direct bactericidal action or opsonization. The release of large amounts of lipoproteins and other bacterial products from dying bacteria provokes a "crisis," during which there can be an increase in temperature, hypotension, and other signs of shock. A similar phenomenon occurring in some patients soon after the initiation of antibiotic treatment is characterized by the abrupt worsening of the condition, which is called a Jarisch-Herxheimer reaction (JHR).

CLINICAL MANIFESTATIONS

Relapsing fever presents with the sudden onset of fever. Febrile periods are punctuated by intervening afebrile periods of a few days; this pattern occurs at least twice. The patient's temperature is ≥39°C and may be as high as 43°C. The first fever episode often ends in a crisis lasting ~15–30 min and consisting of rigors, a further elevation in temperature, and increases in pulse and blood pressure. The crisis phase is followed by profuse diaphoresis, falling temperature, and hypotension, which usually persist for several hours. In LBRF, the first episode of fever is unremitting for 3–6 days; it is usually followed by a single milder episode. In TBRF, multiple febrile periods last 1–3 days each. In both forms, the interval between fevers ranges from 4 to 14 days, sometimes with symptoms of malaise and fatigue.

The symptoms that accompany the fevers are usually nonspecific. Headache, neck stiffness, arthralgia, myalgia, and nausea may accompany the first and subsequent febrile episodes. An enlarging spleen and liver cause abdominal pain. A nonproductive cough is common during LBRF and—in combination with fever and myalgias—may suggest influenza. Acute respiratory distress syndrome may occur during TBRF.

On physical examination, the patient may be delirious or apathetic. There may be body lice in the patient's clothes or signs of insect bites. In regions with *B. miyamotoi* infection, a hard tick may be embedded in the skin. Epistaxis, petechiae, and ecchymoses are common during LBRF but not in TBRF. Splenomegaly or spleen tenderness is common in both forms of relapsing fever. The majority of patients with LBRF and ~10% of patients with TBRF have discernible hepatomegaly.

Localizing neurologic findings are more common in TBRF than in LBRF. In North America, *B. turicatae* infection has neurologic manifestations more often than *B. hermsii* infection. Meningoencephalitis can result in residual hemiplegia or aphasia. Myelitis and radiculopathy may develop. Unilateral or bilateral Bell's palsy and deafness from seventh or eighth cranial nerve involvement are the most common forms of cranial neuritis and typically present in the second or third febrile episode, not the first. Visual impairment from unilateral or bilateral iridocyclitis or panophthalmitis may be permanent. In LBRF, neurologic manifestations such as altered mental state or stiff neck are thought to be secondary to spirochetemia and systemic inflammation rather than to direct invasion of the nervous system.

Myocarditis appears to be common in both forms of relapsing fever and accounts for some deaths. Most commonly, myocarditis is evidenced by gallops on cardiac auscultation, a prolonged QT_c interval, and cardiomegaly and pulmonary edema on chest radiography.

General laboratory studies are not specific. Mild to moderate normocytic anemia is common, but frank hemolysis and hemoglobinuria do not develop. Leukocyte counts are usually in the normal range or only slightly elevated, and leukopenia can occur during the crisis. Platelet counts can fall below 50,000/μL. Laboratory evidence of hepatitis can be found, with elevated serum concentrations of unconjugated bilirubin and aminotransferases; the prothrombin and partial thromboplastin times may be moderately prolonged.

Analysis of the cerebrospinal fluid (CSF) is indicated in cases of suspected relapsing fever with signs of meningitis or meningoencephalitis. The presence of mononuclear pleocytosis and mildly to moderately elevated protein levels justifies intravenous antibiotic therapy in TBRF.

The manifestations and course of *B. miyamotoi* infection remain incompletely characterized, but reports to date indicate that the sign most often reported by patients at presentation is fever without respiratory symptoms starting 1–2 weeks after a tick bite and recurring once or twice in some cases. Meningoencephalitis with spirochetes in the CSF was documented in one immunodeficient adult.

DIAGNOSIS

Relapsing fever should be considered in a patient with the characteristic fever pattern and a history of recent exposure—i.e., within 1–2 weeks before illness onset—to body lice or soft-bodied ticks in geographic areas with documented current or past transmission. Because of the longevity of the ticks and the transovarial transmission of the pathogen in the ticks, a case of relapsing fever may be diagnosed many years after the last case reported in that locale.

The bedrock for laboratory diagnosis remains the same as it has been for a century: direct detection of the spirochetes by microscopy of the blood. Manual differential counts of white blood cells by Wright or Giemsa stain usually reveal spirochetes in thin blood smears if their concentration is $\geq 10^5$/mL and several oil-immersion fields are examined (Fig. 209-2). The preferred time to obtain a blood specimen is between the fever's onset and its peak. Lower concentrations of spirochetes may be revealed by a thick blood smear that is either directly stained with acridine orange and then examined by fluorescence microscopy or treated with 0.5% acetic acid before Giemsa or Wright staining. An alternative to a fixed blood smear is a wet mount of anticoagulated blood mixed with saline and examined by phase-contrast or dark-field microscopy for motile spirochetes.

Polymerase chain reaction (PCR) and similar DNA amplification procedures are increasingly used for examination of an extract of blood. PCR may reveal spirochetes between febrile episodes, since there are already escape variants in the population when the first wave of bacteria is neutralized.

Culture of blood or CSF in Barbour-Stoenner-Kelly broth medium is an option for isolation of *Borrelia* species except for *B. miyamotoi*, which is noncultivable or poorly cultivable. However, few laboratories offer this service. An alternative for tick-borne *Borrelia* species, including *B. miyamotoi*, is inoculation of blood or CSF into immunodeficient mice and examination of the animal's blood after a few days.

Options for serologic confirmation of infection are limited. Most assays that are available commercially or in reference laboratories are based on whole cells of a single *Borrelia* species. These assays may not detect the major variant antigens to which the patient is mainly responding or may yield false-positive results due to antibodies to cross-reactive antigens of related bacteria, including *B. burgdorferi*. The most