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BABESIOSIS: AN UPDATE

INTRODUCTION

Babesiosis is a worldwide tick-borne hemolytic disease of wild and domestic animals that is caused by intraerythrocytic protozoan parasites of the genus *Babesia*.
Of the more than 70 species of Babesia, *Babesia microti* and *Babesia divergens* are the two that cause most human infections. An unknown species of Babesia (WA-1) was isolated from an immunocompetent man in Washington State with clinical babesiosis. Also, Herwaldt *et al*. described a probably new etiologic agent (MO1) associated with the first reported case of babesiosis acquired in Missouri. MO1 is probably distinct from *B. divergens*, the two share morphologic, antigenic, and genetic characteristics. (Ann Intern Med. 124:643-50, 1996)

Ixodid (or hard-bodied) ticks, in particular *Ixodes dammini* (*Ixodes scapularis*) and *Ixodes ricinus*, are the vectors of the parasite. Ticks ingest Babesia while feeding, and the parasite multiplies within the tick's gut wall. The organisms then spread to the salivary glands; their inoculation into a vertebrate host by a tick larva, nymph, or adult completes the cycle of transmission. Asexual reproduction of Babesia within red blood cells produces two or four parasites

In the United States, the incidence of babesiosis is concentrated primarily in the Northeastern coastal areas, especially Cape Cod and the nearby coastal islands Nantucket, Martha's Vineyard, and Block Island. However, within the last decade an increasing number of cases are being reported in California, Washington, and Montana.

Taxonomic Issues.

Members of the genus Babesia, along with members of the genus Theileria, are called piroplasms because of the pear-shaped intraerythrocytic appearance of the dividing parasites. The two genera are distinguished on the basis of the presence or absence of a visible exoerythrocytic stage of parasite development. Classification of Babesia species is based mainly on morphologic features, particularly size, and host specificity.

The more than 100 species of Babesia are often categorized into two sizes--small (1.5 to 3 micro meter) and large (3 to 5 micro meter) intraerythrocytic variants. This classification system, however, has several shortcomings; parasites from different hosts are often similar or indistinguishable on the basis of only morphologic aspects, and the same parasite may have different microscopic appearances in different hosts. Furthermore, the generalization that Babesia species are strictly host specific, traditionally considered a clue for species designation, is no longer tenable since the discovery that *B. microti* infects not only various small terrestrial

mammals but also several subhuman primates and humans. *B. divergens*, another babesial parasite implicated in human disease, has similarly been found to infect rats and gerbils as well as its main bovine host.

Historical Perspective.

Intraerythrocytic piroplasms consistent with Babesia were first described by Babes in 1888 in his pursuit of the cause of febrile hemoglobinuria in cattle in Romania. The disease itself may have been described much earlier, however. The book of Exodus refers to a plague of murrain (hemoglobinuria) among cattle and other domestic animals. Possibly, this biblical reference was the first historical mention of babesial infection. The next historical reference to babesiosis, and the first possible description of human cases, was at the turn of the century.

More than 5 decades passed before Skrabalo and Deanovic identified definitively the first human case of babesiosis. A 33-year-old cattle farmer in Yugoslavia had febrile hemoglobinuria and intraerythrocytic organisms, which were presumed to be malarial, on peripheral blood smears. The clinical course in this patient who had undergone splenectomy was fatal, and a retrospective review of the blood smears confirmed the infection. Subsequent epidemiologic inquiry revealed that the cattle tended by the patient were infected with a bovine babesial species; possible tick vectors (*Dermacentor sylvarum* and *Ixodes ricinus*) were also identified. Since then, severe, often fatal cases of human babesiosis attributed to the bovine pathogen *B. divergens* have been reported in Europe.

EPIDEMIOLOGY

Since 1957, when the first human case of babesiosis was described in a Yugoslavian farmer who died of severe hemolytic anemia, sporadic cases have been reported with increasing frequency, especially along the northeastern coast of the United States. In the United States, infections have been reported from California, Washington State, and Georgia; the most endemic areas, however, are the islands off the coast of Massachusetts, including Nantucket and Martha's Vineyard, and eastern and south central Long Island, including Shelter Island and Fire Island in New York. Foci in Connecticut that overlap with Lyme disease, as well as in Wisconsin and Indiana, have been recorded. Sporadic cases have also been reported from France, Great Britain, Ireland, the Soviet Union, and Mexico. In the United States, with one possible exception, the murine species, *B. microti*, has been implicated. However, in the western United States those cases of babesiosis reported from California have been caused by a non-B microti species, whereas those cases reported from Washington State, although morphologically indistinguishable from *B. microti*, were shown to be antigenically and genotypically distinct from *B microti*. Most European and African cases have been caused by bovine and other nonmurine species of Babesia.

Human infection usually occurs from late spring to early fall, when many nymphs are questing and when humans enter the tick-infested habitat. Evidence of transovarial transmission in *B microti*, as there is in other species of *Babesia*, has been reported occasionally.

Seroepidemiologic studies carried out on residents of Nantucket and Shelter Islands have shown a 4% to 7% seroconversion. Similar results were obtained in studies on residents of a rural area along the Gulf Coast of Mexico that was a known focus of babesiosis of domestic animals. These studies imply that asymptomatic human infection seems to be common. In some of these symptom-free people, low numbers of circulating parasites have been found and have been a source of transfusion babesiosis. Despite the widespread prevalence of asymptomatic infection, clinical disease has not been reported from people immunodepressed during a course of corticosteroid or cyclophosphamide therapy. Patients with acquired immunodeficiency syndrome (AIDS), however, are apparently unable to control their infection naturally or after usual treatment and must be maintained on antibiotic therapy indefinitely.

Transfusions are another source of babesiosis. In several transfusion-associated cases, no parasites were detected in blood donors, but serologic testing of their blood for *Babesia* gave positive results.

Epidemiologic Features of Babesiosis in the United States.

Although babesiosis is commonly thought to be limited in its distribution to the northeastern United States and the Upper Midwest, the first case of zoonotic babesiosis in the United States was, in fact, described in a California patient. A 46-year-old male amateur photographer had undergone a splenectomy 2 years earlier because of hereditary spherocytosis. He had presumably contracted the infection after hiking in coastal parklands north of San Francisco. He was treated with chloroquine for 3 weeks for a presumptive malarial infection and had a benign clinical course. Although the identity of the causative organism was not confirmed, an intraerythrocytic ``Maltese cross"-shaped parasite was described. More than a decade later, Bredt and associates described a similar-appearing organism in a California patient who had undergone splenectomy; this patient's infection was resistant to chloroquine but was responsive to quinine and pyrimethamine. The patient's serum failed to react by complement fixation or indirect immunofluorescence study with any known Babesia species, but it was presumed on morphologic grounds that the patient was infected with *B. equi*. Most likely, both patients from California were infected with a newly characterized Babesia-like piroplasm that may be endemic to certain areas of the United States (see subsequent discussion). During the 1970s, babesiosis gained increased attention because of reports of ``Nantucket fever" among residents of the islands off the coast of New England.

In contrast to the cases reported in California and in Europe, the infections in the Northeast commonly occurred in patients with normal spleens and were attributed to *B. microti*. Subsequent investigations of the transmission cycle of this infection led to the discovery of high infection rates for *B. microti* in field mice (*Microtus pennsylvanicus*) and white-footed mice (*Peromyscus leucopus*) on Nantucket Island in Massachusetts. The tick vector was also identified in these studies; Spielman found that two species of ticks were present on P. leucopus from Nantucket. The predominant species closely resembled *I. scapularis* (later named *I. dammini*); *D. variabilis* was found occasionally. The greatest number of immature types of ticks (larvae and nymphs) were found during spring and early summer. All but 1 of the hamsters (10 of 11) on which the Ixodes ticks had fed became infected with *B. microti*. These studies, in

conjunction with the finding of a relative paucity of other ticks on the island, implicated the Ixodes tick as a vector in the transmission of *B. microti.*

The number of reported cases of *B. microti* infection likely underestimates the actual incidence of infection in certain parts of the United States, presumably because the disease in most persons is mild or self-limiting (or both). Serosurveys have helped to estimate the prevalence of infection in the Northeast. A 1977 serosurvey of patients undergoing routine diagnostic studies in hospitals for unrelated reasons revealed varying seroprevalence rates (defined as a titer of 1:64 or more) for *B. microti*, depending on the geographic location. Of the samples from 150 patients in a Martha's Vineyard hospital and from 100 patients in a Cape Cod hospital, none were positive, whereas samples from 2% of asymptomatic patients (11 of 555) in a Nantucket Island hospital and 7.5% of symptomatic patients (10 of 133) with a history of tick bite and fever were positive. In another study, seropositivity was found with a prevalence of 4.4% (6 of 136) in early summer and 6.9% (7 of 102) in early fall, with a variable change in paired sera. A seroepidemiologic study of the prevalence of infection in children revealed a seroprevalence as high as 11.5% (6 of 52). **Error! Bookmark not defined.**

The number of reported transfusion-acquired infections indicates the existence of an asymptomatic carrier state, which may become an increasing hazard to the blood supply. The risk factors for the donors have included exposure to endemic areas and being a recipient of blood transfusions. The time that the blood was stored varied from 5 to 35 days; even frozen-thawed blood has been implicated. In a survey of 779 blood donors in Cape Cod, seropositivity ranged from 3.3% (4 of 120) to 4.9% (7 of 142), depending on the time of year, and these findings were not significantly different from those in 148 blood donors tested in metropolitan Boston, an apparently nonendemic area, where a seroprevalence rate of 4.7% was found. Patients receiving erythrocyte transfusions are at highest risk, although transfusion of platelets may also have an associated risk because of the presence of erythrocytes or cosedimented parasites in the platelet concentrates. In the recipients, the incubation period varied from 17 days to 8 weeks, and the donor may or may not have been symptomatic. Infection after transfusion of plasma has not been reported. Hilton *et al* studied the seroprevalence and seroconversion for tick-borne diseases in a high-risk population in the northeast United States. This 1-year seroconversion study of patients residing in New York state who were at high risk for tick-borne diseases showed that of the 671 participants, antibodies to *B. microti* were seen in 7 participants (1%), including one asymptomatic seroconversion during the year of observation. There was evidence of possible dual infection in 5 patients. (Am J Med. 106(4):404-9, 1999)

PATHOGENESIS

After an infectious tick bite, the organisms invade red blood cells and a trophozoite differentiates, replicating asexually by budding with the formation of two to four merozoites. A second type of undifferentiated trophozoite is also formed that does not replicate but enlarges and differentiates into gametocyte-like forms similar to that seen in *Plasmodium* species.

Merozoites eventually disrupt infected erythrocytes and reinvade other red blood cells. These events cause a hemolytic anemia that, when severe, can bring about hemoglobinuria, renal insufficiency, or renal failure.

Although symptomatic infection with *B microti* is seen regularly in otherwise immunocompetent people, the most severe cases have been recorded from patients splenectomized for a variety of reasons, including trauma.

Splenectomized animals have more severe infections than those with intact spleens, and they often die with an extraordinarily high parasitemia. In animal experiments, after recovery from a *B microti* infection, splenectomy often provokes a severe and fatal relapse.

If untreated, clinically symptomatic *B microti* infections in immunocompetent patients are usually self-limited; it has been shown that both humoral and cell-mediated immune mechanisms influence the outcome of the infection. Experimental studies have demonstrated that without T-helper cells, specific humoral immunity cannot be established, and the animals die. Similarly, athymic nude mice have been shown to have severe and fatal infections. Several studies have documented that, in patients with acute babesiosis, in vitro lymphocyte mitogenic responses were profoundly depressed; on recovery, these T-cell changes returned to normal. It is not clear whether the age of the host influences the severity of a *Babesia* infection, except at the extremes of life, when these patients are probably immunocompromised.

CLINICAL FEATURES

After a recognized tick bite, the incubation period varies from 5 to 33 days, whereas after an infected blood transfusion, the incubation period has been 6 to 9 weeks.

As frequently found in malaria, splenomegaly is often evident but lymphadenopathy is not. A mild to severe hemolytic anemia and a normal to slightly depressed leukocyte count are usually found.

The clinical spectrum of the US cases ranges from asymptomatic to rapidly progressive and fatal, with increasing disease severity among elderly people.

From a clinical perspective, babesiosis in New England has varied substantially from that described in Europe. To date, most of the European patients described did not have a spleen, and their clinical courses have been fatal in all except two patients from France. In all the cases, the organisms identified were of bovine origin; *B. divergens* was implicated in virtually all the cases except one. In light of the difficulty of speciation of the parasite, the causative agent in that one case, *B. bovis*, could easily have been misclassified. In contrast, the numerous North American cases have occurred mainly in people with apparently normal spleens, with the exception of the majority of those confirmed in the western United States.

The clinical onset of the illness begins 1-4 weeks after the tick bite; however, the majority of patients do not recall recent tick exposure. Symptoms include persistent or undulating high fevers, chills, diaphoresis, weakness, fatigue, anorexia, and headache. Later in the course of the illness depending on the degree of intravascular hemolysis , the patient may develop jaundice and dark urine. Physical exam may include hepatomegaly and splenomegaly, or evidence of shock and DIC such as hypotension, petichiae, or ecchymoses. Whereas rash is

the hallmark in other tick-bourne illnesses such as Rocky Mountain Spotted Fever and Lyme disease, it is uncommon in babesiosis. Signs of CNS involvement may include headache, photophobia, neck and back stiffness, altered sensorium, and emotional lability.

Babesiosis is usually a self-limited flu-like illness in most hosts. However, patients with babesiosis who seek medical attention usually do so after one week of symptoms and likely include those with more fulminant disease. A recent retrospective analysis of 139 patients hospitalized with a diagnosis of babesiosis in New York state from 1982-1993 shows a mortality rate of 6.5%. In addition to severe hemolytic anemia, the most common complication was congestive heart failure (10.9%) and acute respiratory distress syndrome (8.0%). Factors associated with more severe disease include advanced age, previous splenectomy, and immunodefficient states including AIDS.Even after clindamycin and quinine have been administered, infection may continue for more than two months. Silent infection, of course, may recrudesce spontaneously or after splenectomy or immunosuppression. Fatal cases have also been reported in the geographically distinct areas of Rhode Island, Georgia California, Wisconsin and Missouri.

In light of the fact that the clinical spectrum of babesial infection varies from asymptomatic to severe, babesiosis might be viewed as two distinct diseases: (1) a potentially life-threatening hemolytic disease in persons predisposed to severe infection because of advanced age, asplenia, or immune suppression and (2) an occult disease process with few known sequelae. Virtually all the cases described to date have been in persons with severe, acute hemolysis or are prolonged cases that are refractory to therapy. In all these cases, the presence of characteristic organisms on peripheral blood smears was confirmed. Thus, little is known about the course of subclinical infection, during which the numbers of circulating parasites are likely to be much lower than in clinically apparent cases. More recent studies that use the PCR to monitor the acute and chronic parasitemic phases of the infection will likely lead to a better understanding of less severe cases (see subsequent discussion).

Of the clinically apparent cases of babesiosis reported to date, the ages of patients vary from neonate to 86 years; most patients are in their fifth or sixth decade of life. The youngest reported patient with babesiosis was a 4-week-old infant who was examined because of fever and hemolytic anemia; transmission of infection was thought to be transplacental. In adults, the incubation period varies from 1 to 6 weeks, although it can be as long as 3 months. The initial complaints--malaise, fatigue, low-grade fever or shaking chills, headache, generalized musculoskeletal problems, emotional lability, nausea, emesis, and weight loss--are usually nonspecific. The patient may have jaundice, depending on the acuteness of the hemolysis. Palpable lymphadenopathy is usually absent, but hepatomegaly and splenomegaly may be present. Temperatures may be as high as 40°C. No consistent dermatologic manifestation of babesiosis has been verified, but concurrent infection with *B. burgdorferi* may be manifested by the presence of erythema chronicum migrans. In light of the nonspecific manifestation of babesiosis, a history of outdoor activity, even if it involves an area not yet known to be endemic, should be sought in the appropriate clinical setting. A history of tick bite is not consistently obtained, but in most cases a history of travel to an endemic area is noted.

In severe cases, hemolytic anemia and brownish urine suggestive of hemoglobinuria are often present. The hemolysis is predominantly intravascular, as reflected by a decreased serum

haptoglobin level. The mechanism of the hemolysis, whether immune or nonimmune, is currently unknown, although a Coombs test result may be positive. The reticulocyte count is usually increased, a reflection of a brisk bone marrow response; however, if the hemoglobinuria has been chronic with a resultant loss of iron in the urine or a deficiency of folic acid, the count may not be increased. Peripheral blood smears will show a regenerative picture with parasitemia that varies from undetectable to levels as high as 85%, depending on the severity. The duration of the parasitemia detectable on peripheral smears varies from 3 weeks to 12 weeks; the longest reported duration of smear positivity as detected by light microscopy was 7 months (in a patient with no spleen) and by PCR was 25 months in a patient with an apparently normal spleen. The erythrocyte sedimentation rate may be increased. No specific erythrocyte antigens predispose to infection with Babesia. Hemocytophagia has been described on bone marrow examination. Complications include the respiratory distress syndrome, and one report described pancarditis due to coinfection with B. burgdorferi.

Krause PJ *et al*. studied whether patients coinfected with Lyme disease and babesiosis in sites where both diseases are zoonotic. They conducted a community-based, yearly serosurvey and clinic-based cohort study. The study was conducted at an island community in Rhode Island and 2 Connecticut medical clinics from 1990 to 1994. Of 1156 serosurvey subjects, 97 (8.4%) were seroreactive against Lyme disease spirochete antigen, of whom 14 (14%) also were seroreactive against babesial antigen. Of 240 patients diagnosed with Lyme disease, 26 (11%) were coinfected with babesiosis. Coinfected patients experienced fatigue ($P = .002$), headache ($P < .001$), sweats ($P < .001$), chills ($P = .03$), anorexia ($P = .04$), emotional lability ($P = .02$), nausea ($P = .004$), conjunctivitis ($P = .04$), and splenomegaly ($P = .01$) more frequently than those with Lyme disease alone. Thirteen (50%) of 26 coinfected patients were symptomatic for 3 months or longer compared with 7 (4%) of the 184 patients with Lyme disease alone from whom follow-up data were available ($P < .001$). Patients coinfected with Lyme disease experienced more symptoms and a more persistent episode of illness than did those ($n = 10$) experiencing babesial infection alone. Circulating spirochetal DNA was detected more than 3 times as often in coinfected patients as in those with Lyme disease alone ($P = .06$). The authors concluded that approximately 10% of patients with Lyme disease in southern New England are coinfected with babesiosis in sites where both diseases are zoonotic. The number of symptoms and duration of illness in patients with concurrent Lyme disease and babesiosis are greater than in patients with either infection alone. In areas where both Lyme disease and babesiosis have been reported, the possibility of concomitant babesial infection should be considered when moderate to severe Lyme disease has been diagnosed. (JAMA. 275(21):1657-60, 1996)

White DJ, et al. reviewed the clinical data and prognostic factors among 139 hospitalized cases in New York State, between 1982 and 1993. Nine patients (6.5%) died, 35 (25.2%) were admitted to the intensive care unit, and 35 (25.2%) required hospitalization for more than 14 days. Mean age at first hospitalization was 62.5 years. Sixty-two percent were male, and 91% resided in Suffolk County, Long Island. The most common symptoms were fatigue/malaise/weakness (91%), fever (91%), shaking chills (77%), and diaphoresis (69%). Past medical records showed that 52% of patients had a history of chronic disease; 12% had a history of Lyme disease; 12% had undergone a splenectomy; and 2% had undergone a blood

transfusion. There was a 12- to 14-day delay between onset of symptoms and initiation of appropriate antibiotic treatment. Univariate analyses showed alkaline phosphatase levels greater than 125 U/L, white blood cell counts greater than 5 x 10(9)/L, history of cardiac abnormality, history of splenectomy, presence of heart murmur, and parasitemia values of 0.04 or higher to be significantly associated with disease severity.

Multiple logistic regression analyses indicated that male sex, alkaline phosphatase values greater than 125 U/L, and white blood cell counts greater than 5 x 10(9)/L remained strong predictors of severe outcome. (Arch Intern Med. 158:2149-54, 1998)

DIAGNOSIS

A Wright- or Giemsa-stained peripheral blood smear is most commonly used to demonstrate the presence of intraerythrocytic parasites; however, in many cases a high index of suspicion is necessary because the level of parasitemia may be low. Factors that influence the sensitivity of this procedure include the experience of the observer and the time needed to analyze the smear. Although the ring variants may be confused with the malarial parasite *Plasmodium falciparum*, the absence of hemozoin should alert the observer to the possibility of Babesia. Of note, during the early stages of infection by the malarial parasite, no pigment formation may be present. Rarely, tetrads of merozoites may be visible. The typical morphologic picture in conjunction with epidemiologic information will assist in determining a diagnosis. The diagnosis can be overlooked if one relies solely on autoanalyzers, the smear may not reveal the parasite; however, the PCR may be strongly positive, an outcome consistent with persistence of the organism.

Serologic evaluation with the indirect immunofluorescent antibody test with use of *B. microti* antigen is available in a few laboratories. The cutoff titer for determination of a positive result varies with the particular laboratory protocol used, but in most laboratories titers of more than 1:64 are considered consistent with *B. microti* infection. Tenfold to 20-fold higher titers can be observed in the acute setting, with a gradual decline over weeks to months. The correlation between the level of the titer and the severity of symptoms is poor. Persistence of a low titer of antibody and even an increase have been described, but whether a recurrent parasitemia exists in association with the increase in antibody is unknown.

The serologic test is fairly specific; cross-reactivity with Babesia of other species and with malarial organisms has been described at low dilutions. Animal inoculation studies can be performed with golden hamsters to isolate the parasite and confirm the diagnosis. In cases that are difficult to diagnose on the basis of smears, the parasitemia is usually evident in 2 to 4 weeks.

With the evolution of more sensitive PCR-based techniques, molecular diagnosis and monitoring of babesial infections have become possible. Detection of B. microti by PCR was first described in 1992. More recent studies, in which PCR was used prospectively for diagnosing suspected cases in the northeastern United States, have shown that, in comparison to direct smear examination and hamster inoculation, PCR is more sensitive and equally specific for the diagnosis of acute cases. PCR-based methods may also be indicated for monitoring of the infection. In the previously mentioned study, 7 of 21 persons harbored detectable B. microti DNA in their blood for 6 months or longer; in one person, B. microti DNA persisted up to 25 months. Persistence of B. microti DNA was often associated with prolonged symptoms of severe fatigue, anorexia, or intermittent fevers. Clindamycin and quinine treatment of 17 persons with acute hemolysis was associated with good clinical outcomes (mild postinfectious sequelae) and a brief duration of PCR positivity, despite the greater severity of the initial manifestations. These studies suggest that early recognition and treatment of babesiosis, for which the only clinical manifestation may be ``summer flu," may be important not only for preventing long-term sequelae but also for protecting the blood supply from asymptomatic carriers who may become blood donors.

Coinfection With Other Tick-Transmitted Agents.

As previously indicated, coinfection with B. burgdorferi and B. microti may be relatively common in endemic areas of the northeastern and upper midwestern United States. Recently, another tick-transmitted bacterial zoonosis, human granulocytic ehrlichiosis (HGE), was described in patients from Minnesota. Subsequently, HGE cases have been recognized in Wisconsin, Connecticut, New York, Maryland, Florida, and Arkansas; serologic evidence of human exposure in northern California and Europe has been noted. The clinical manifestation of patients with granulocytic ehrlichiosis is similar to that described for the other known zoonotic Ehrlichia species, *Ehrlichia chaffeensis*. Typically, patients have a nonspecific febrile illness, usually with no rash. Laboratory findings often include leukopenia, thrombocytopenia, and increases in serum hepatic enzyme activities. The spectrum of illness ranges from asymptomatic to fatal. To date, four deaths have been attributed to infection with HGE.

OPTIMAL MANAGEMENT

Since the mid-1980s, clindamycin plus quinine has been regarded as the standard therapy for this infection on the basis of numerous clinical observations and experimental hamster studies. Clindamycin, 1200 mg intravenously every 12 hours for 7 days, combined with quinine, 650 mg orally every 8 hours for 7 days, has been used successfully to treat in adults. The pediatric dose is clindamycin, 20 to 40 mg/kg/d in three doses for 7 days, and quinine, 2.5 mg/kg/d in three doses for 7 days. However, there have been anecdotal reports and unpublished observations that in some immunocompromised and human immunodeficiency virus-infected patients, babesiosis has been difficult to treat with the standard therapy, and other modalities such as exchange transfusion have been required. In these patients, it was unclear whether this was because of relapse, persistence, or emergence of resistance. AIDS patients initially respond to the recommended therapy but usually experience relapse after it is discontinued. They usually become refractory to further repeated treatment with quinine and clindamycin.

The fortuitous discovery of the currently recommended regimen for human babesiosis was made during the management of a patient with presumed transfusion-acquired malarial infection. The patient was initially treated with chloroquine; however, because of lack of response, treatment was changed to quinine and clindamycin, and the patient experienced defervescence. The correct diagnosis was made early during the course of treatment and was later confirmed with serologic studies. Subsequent studies in animals have verified the value of this combined regimen; thus, this is the recommended treatment for patients with babesiosis, although occasional reports have described failure with this regimen. More recently, success with a combination of pentamidine and cotrimoxazole was reported, but because of the previously mentioned side effects with pentamidine, this regimen is not recommended. Erythrocyte exchange transfusion has been used in seriously ill patients who do not respond to pharmacologic intervention.

B. microti infections in patients with intact spleens are generally self-limiting without treatment. Treatment with the combination of quinine sulfate (650 mg of salt orally, three times daily) and clindamycin (600 mg orally, three times daily; or 1.2 g parenterally, twice daily) for 7 to 10 days is effective in some cases but may not eliminate parasites. The pediatric dose is 20 to 40 mg/kg per day for quinine sulfate and 25 mg/kg per day for clindamycin, both in three doses given over 7 to 10 days.

Before the discovery of this effective regimen, treatment of the first reported case of babesiosis in the United States was with chloroquine for what was presumed to be a malarial infection.

Krause PJ *et al*. compared the duration of parasitemia in people who had received specific antibabesial therapy with that in silently infected people who had not been treated. Forty-six babesia-infected subjects were identified from 1991 through 1996 in a prospective, community-based study designed to detect episodes of illness and of seroconversion among the residents of southeastern Connecticut and Block Island, Rhode Island. Subjects with acute babesial illness were monitored every 3 months for up to 27 months by means of thin blood smears, *Bab. microti* polymerase-chain-reaction assays, serologic tests, and questionnaires. Babesial DNA persisted in the blood for a mean of 82 days in 24 infected subjects without specific symptoms who received no specific therapy. Babesial DNA persisted for 16 days in 22 acutely ill subjects who received clindamycin and quinine therapy (P=0.03), of whom 9 had side effects from the treatment. Among the subjects who did not receive specific therapy, symptoms of babesiosis persisted for a mean of 114 days in five subjects with babesial DNA present for 3 or more months and for only 15 days in seven others in whom the DNA was detectable for less than 3 months (P<0.05); one subject had recrudescent disease after two years. The authors concluded that when left untreated, silent babesial infection may persist for months or even years. Although treatment with clindamycin and quinine reduces the duration of parasitemia, infection may still persist and recrudesce and side effects are common. Improved treatments are needed. (N Engl J Med. 339(3):160-5, 1998)

Experimental babesiosis in hamsters was shown to be unaffected by chloroquine, as well as by sulfadiazine, primaquine, or metronidazole in combination with pyrimethamine. Minocycline and tetracycline, when used at high and toxic doses, had some effect in reducing parasitemia; at usual therapeutic levels, however, tetracycline had no effect. Pentamidine isethionate (Pentam 300), 4 mg/kg/d for 14 days by deep muscle injection, has had limited success when used to treat human *B microti* infection, lowering but not eliminating the parasitemia. Recrudescence occurred after completion of therapy. Significant side effects included the development of renal insufficiency, severe pain at the injection site, and formation of large sterile abscesses.

Several other drugs have been tried, including tetracycline, primaquine phosphate, sulfadiazine, and pyrimethamine; results have varied. Pentamidine has been used and has proved to be moderately effective in diminishing symptoms and decreasing parasitemia. Of interest, animal studies with pentamidine failed to show any benefit. The use of pentamidine in an experimental hamster model of infection showed that parasites were isolated as late as 5 weeks after initiation of therapy. Patients treated with intramuscular injections of pentamidine

experienced a substantial degree of discomfort. Diminazene aceturate, an antitrypanosomal drug, has been used but has produced severe neurologic side effects.

Atovaquone suspension (750 mg twice daily) plus azithromycin (500 to 1000 mg/d) may be effective when quinine and clindamycin fail. Symptoms may persist for months with or without treatment, although there are no permanent sequelae. More severe infections with high-level *B. microti* parasitemia in asplenic patients have been successfully treated with exchange transfusions in addition to quinine and clindamycin

In asplenic patients and those infected with *Babesia bovis* or *Babesia divergens,* symptoms are often too severe to temporize. Bovine babesiosis usually is severe with a fulminant downhill course and must be treated aggressively if the patient is to survive. Several patients who were placed on renal dialysis and transfused have survived. Diminazene aceturate (Berenil), an aromatic diamidine that is an effective babesiacide in animals, was unsuccessful in a fatal case of *B divergens* infection. More recently, however, a human case of *B divergens* infection was treated successfully with trimethoprim-sulfamethoxazole and pentamidine.

Red blood cell or whole-blood exchange transfusion has been used with apparent success in several ill patients who had high parasitemias (40% to 60%).

Experimental animal studies suggest that azithromycin and quinine may be effective alternatives for *B microti* infections. Animal and human studies have suggested that the combination of atovaquone and azithromycin is effective in immunocompromised patients who have become resistant to the quinine-clindamycin regimen.

The current recommended treatment for babesiosis is a 7-10 day course of clindamycin and quinine. Clindamycin can be given orally or intravenously 600mg tid, and the quinine orally 650mg tid. In areas endemic for Lyme disease and ehrlichiosis it may be advisable to add doxycycline 100mg bid by mouth until serologic confirmation has been made. Exchange transfusion may be necessary in patients with a high level of parasitemia and severe intravascular hemolysis.

Wittner *et al*. used the hamster model to determined the efficacy of atovaquone alone as well as atovaquone plus azithromycin for the treatment of experimental babesiosis. Atovaquone (100 mg/kg/day) and atovaquone (100 mg/kg/day) with azithromycin (150 mg/kg/day) were effective agents for the treatment of experimental babesiosis in hamsters. When atovaquone was used as monotherapy recrudescences occurred. Organisms obtained from recrudescent animals, when inoculated into uninfected animals, proved to be unresponsive to atovaquone therapy, suggesting the emergence of drug resistance. Resistant organisms did not emerge in hamsters treated with the combination of atovaquone and azithromycin. Atovaquone should be considered in the therapeutic regimen of patients with babesiosis who have either failed standard therapy or have become intolerant to such therapy (Am J Trop Med Hyg 1996;55:219-22).

PREVENTION

Babesiosis in humans is an emerging zoonotic disease with an apparently increasing incidence. As with many emerging infectious diseases, the apparent increase in the number of cases is explained by an increase in both incidence and awareness of the disease. Prevention of babesiosis is similar to that for prevention of Lyme disease. Simple measures include avoidance of outdoor activity in known endemic areas, minimization of exposure to tick-infested areas, and a thorough examination of the skin for the presence of ticks after being outdoors. The use of tick repellents before potential outdoor activity is also effective. With better understanding of the life cycle of the parasite and vector, a biologic approach could be explored.

Prevention of babesiosis involves avoiding endemic regions during the peak transmission months of May through September. This may be relevant for asplenic or immunocompromised individuals for whom babesiosis can be a devastating illness. Insect repellant is advised during outdoor activities, especially in wooded or grassy areas. Early removal of ticks is important because the tick must remain attached for at least 24 hours before the transmission of *B. microti* occurs. Therefore daily self-examination is recommended for those who engage in outdoor activities in endemic areas. Pets must also be examined for ticks because they may carry ticks into the home. Specific chemoprophylaxis is not available.

Those who are immunocompromised, especially splenectomized patients, should avoid tick-infested areas. Because normal, immunocompetent people may acquire symptomatic and sometimes severe disease, they also should be wary when entering these areas. Because *I scapularis* (= *dammini*) is small and often feeds undetected for long periods (ie, 48 hours), patients should carefully inspect themselves and their pets daily and remove ticks completely. Gentle traction with a forceps applied close to the capitulum (head) usually suffices to remove the entire tick. If the tick is deeply entrenched in the skin, mineral oil or even a hot needle can be applied and usually causes the tick to relax its hold. In tick-infested areas, repellents should be used on clothes, especially on the lower parts of trousers. It is advisable to wear long-sleeved garments, and shirts should be tucked under the belt. One of the most effective tick repellents is *N*,*N*-diethyl-*m*-toluamide, or DEET. It is commercially available in concentrations up to 100%. Care should be taken in its use because 10% to 15% of each application can be recovered in urine. Serious toxic and allergic reactions have been reported in those people who have used it frequently or in high concentrations. In young children, toxic encephalopathy has occurred. Use of nonabsorbable, long-acting formulations such as Ultrathon or DEET-Plus should obviate many of these adverse reactions.

People from known endemic areas should be screened for asymptomatic infection before being accepted as blood donors.

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