Persistent and Relapsing Babesiosis in Immunocompromised Patients

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Background. Human babesiosis is a tickborne malaria-like illness that generally resolves without complication after administration of atovaquone and azithromycin or clindamycin and quinine. Although patients experiencing babesiosis that is unresponsive to standard antimicrobial therapy have been described, the pathogenesis, clinical course, and optimal treatment regimen of such cases remain uncertain.

Methods. We compared the immunologic status, clinical course, and treatment of 14 case patients who experienced morbidity or death after persistence of Babesia microti infection, despite repeated courses of antibabesial treatment, with those of 46 control subjects whose infection resolved after a single course of standard therapy. This retrospective case-control study was performed in southern New England, New York, and Wisconsin.

Results. All case patients were immunosuppressed at the time of acute babesiosis, compared with <10% of the control subjects. Most case patients experienced B cell lymphoma and were asplenic or had received rituximab before babesial illness. The case patients were more likely than control subjects to experience complications, and 3 died. Resolution of persistent infection occurred in 11 patients after 2–10 courses of therapy, including administration of a final antimicrobial regimen for at least 2 weeks after Babesia were no longer seen on blood smear.

Conclusions. Immunocompromised people who are infected by B. microti are at risk of persistent relapsing illness. Such patients generally require antibabesial treatment for ≥6 weeks to achieve cure, including 2 weeks after parasites are no longer detected on blood smear.

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a Deceased.

Human babesiosis is a zoonotic malaria-like illness that usually resolves 1–2 weeks after administration of a single course of atovaquone and azithromycin or clindamycin and quinine [1, 2]. Babesiosis is caused by intraerythrocytic protozoa that reproduce by budding and generate as many as 4 merozoites that allow progression of the infection by invading other erythrocytes. Extracellular forms are observed in heavily parasitized cases [3, 4]. Clearance of parasites is dependent on both the innate and adaptive branches of the immune system. Although asymptomatic parasitemia may persist...
persistent or relapsed illness despite antibabesial therapy with those of patients whose acute illness was cured after a single course of therapy. In particular, we employed a case-control strategy to determine whether the presence of identifiable immunosuppressive conditions correlated with disease outcome and to determine the optimal therapy to achieve cure.

METHODS

Case patients and control subjects. The group of case patients consisted of people who did not clear acute Babesia microti infection, as evidenced by the persistent presence of parasites on blood smear, symptoms, and anemia for >1 month after administration of a single course of standard antibabesial therapy of atovaquone and azithromycin or clindamycin and quinine for 7–10 days. The group of control subjects consisted of patients who also experienced B. microti infection but whose blood smear cleared and symptoms resolved within 1 month after a single course of such standard therapy.

Study protocol. We reviewed clinical and laboratory information on 14 case patients and 189 control subjects who experienced babesiosis during the period 1991–2005. Case patients were directly referred to 1 of the authors (P.J.K.), whereas the control subjects were enrolled in a longitudinal study of tickborne infection [12]. As part of that study, participating physicians attempted to enroll any patient experiencing an illness suggestive of babesiosis that occurred during the months of May through September from 1991 to 2005, among residents living in areas in southern New England where B. microti is endemic. Study physicians followed a study protocol that included obtaining a written informed consent, completing a history, and performing a physical examination. They recorded comorbid condition(s), clinical course, and antibabesial therapy for these patients. They obtained another medical history at least once within the month following the diagnosis of babesiosis and then repeatedly until the patient became asymptomatic. In some cases, a sample of blood was obtained during the

RESULTS

Immune status of study population. Study subjects included 14 case patients whose standard antibabesial therapy failed and 46 control patients who cleared babesial infection after a single course of atovaquone and azithromycin or clindamycin and quinine. All but 3 of the study subjects lived in southern New England; 2 subjects acquired their infection in southern New York, and 1 acquired it in Wisconsin. The age and sex distributions were similar among case patients and control subjects; median ages were 60 and 66 years, and male subjects comprised 64% and 61% of the subject groups, respectively. All of the case patients had evidence of immune suppression at the time of babesial illness, compared with only 7% of control subjects (P < .001). Most case patients experienced B cell lymphoma and were asplenic and/or received immunosuppressive medication within 18 months of the onset of babesial illness (table 1). The 1 HIV-infected subject met the case definition for AIDS, with
Table 1. Clinical characteristics of case patients and control subjects with preexisting immunosuppressive conditions who experienced babesiosis.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, years</th>
<th>Sex</th>
<th>Preexisting condition</th>
<th>Asplenia</th>
<th>Immunosuppressive therapy administered before and after the diagnosis of babesiosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case patient 1</td>
<td>53</td>
<td>Female</td>
<td>B cell lymphoma (diffuse, large cell)</td>
<td>Yes</td>
<td>Rituximab (18 months before), decadron (18 months before until 2 months after), and hydrocortisone (3 months after)</td>
</tr>
<tr>
<td>Case patient 2</td>
<td>82</td>
<td>Female</td>
<td>B cell lymphoma (non-Hodgkin)</td>
<td>Yes</td>
<td>Rituximab and CHOP (33 months before)</td>
</tr>
<tr>
<td>Case patient 3</td>
<td>86</td>
<td>Female</td>
<td>B cell lymphoma (follicular, grade 2)</td>
<td>No</td>
<td>Rituximab and CHOP (4 months before)</td>
</tr>
<tr>
<td>Case patient 4</td>
<td>61</td>
<td>Male</td>
<td>B cell lymphoma (follicular, grade 2)</td>
<td>No</td>
<td>Rituximab (1 week before until 2 weeks after)</td>
</tr>
<tr>
<td>Case patient 5</td>
<td>52</td>
<td>Male</td>
<td>B cell lymphoma (follicular, grade 1)</td>
<td>Yes</td>
<td>Prednisone (1 week after)</td>
</tr>
<tr>
<td>Case patient 6</td>
<td>41</td>
<td>Male</td>
<td>B cell lymphoma (chronic lymphocytic leukemia)</td>
<td>No</td>
<td>Rituximab (12 and 6 months before) and prednisone (2 months before)</td>
</tr>
<tr>
<td>Case patient 7</td>
<td>71</td>
<td>Male</td>
<td>B cell lymphoma (chronic lymphocytic leukemia and colon cancer)</td>
<td>Yes</td>
<td>Rituximab (5 months before) and prednisone (5 months before)</td>
</tr>
<tr>
<td>Case patient 8</td>
<td>67</td>
<td>Male</td>
<td>Brain tumor</td>
<td>Yes</td>
<td>Irinotecan (3 months before)</td>
</tr>
<tr>
<td>Case patient 9</td>
<td>59</td>
<td>Male</td>
<td>Gastric stromal tumor</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Case patient 10</td>
<td>40</td>
<td>Female</td>
<td>Carcinoma of colon</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Case patient 11</td>
<td>72</td>
<td>Male</td>
<td>HIV infection (AIDS)</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Case patient 12</td>
<td>49</td>
<td>Male</td>
<td>Evan syndrome</td>
<td>Yes</td>
<td>Rituximab (1 month before) and prednisone (7 months before until 5 months after)</td>
</tr>
<tr>
<td>Case patient 13</td>
<td>84</td>
<td>Male</td>
<td>Hereditary spherocytosis</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Control subject 1</td>
<td>73</td>
<td>Female</td>
<td>None</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Control subject 2</td>
<td>51</td>
<td>Male</td>
<td>None</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Control subject 3</td>
<td>66</td>
<td>Male</td>
<td>Multiple myeloma</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

**NOTE.** Case patients 8 and 14 were described elsewhere [10, 11]. CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone. 

Table 2. Severity and outcome of illness of study population.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Preexisting condition</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case patient 1</td>
<td>B cell lymphoma (diffuse, large cell)</td>
<td>Rituximab (18 months before), decadron (18 months before until 2 months after), and hydrocortisone (3 months after)</td>
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<td>B cell lymphoma (non-Hodgkin)</td>
<td>Rituximab and CHOP (33 months before)</td>
<td>Successful</td>
</tr>
<tr>
<td>Case patient 3</td>
<td>B cell lymphoma (follicular, grade 2)</td>
<td>Rituximab and CHOP (4 months before)</td>
<td>Successful</td>
</tr>
<tr>
<td>Case patient 4</td>
<td>B cell lymphoma (follicular, grade 2)</td>
<td>Rituximab (1 week before until 2 weeks after)</td>
<td>Successful</td>
</tr>
<tr>
<td>Case patient 5</td>
<td>B cell lymphoma (follicular, grade 1)</td>
<td>Prednisone (1 week after)</td>
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</tr>
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<td>Successful</td>
</tr>
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<td>B cell lymphoma (chronic lymphocytic leukemia and colon cancer)</td>
<td>Rituximab (5 months before) and prednisone (5 months before)</td>
<td>Successful</td>
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<tr>
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<tr>
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<td>Evan syndrome</td>
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<td>Successful</td>
</tr>
<tr>
<td>Case patient 13</td>
<td>Hereditary spherocytosis</td>
<td>None</td>
<td>Successful</td>
</tr>
<tr>
<td>Control subject 1</td>
<td>None</td>
<td>None</td>
<td>Successful</td>
</tr>
<tr>
<td>Control subject 2</td>
<td>None</td>
<td>None</td>
<td>Successful</td>
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<tr>
<td>Control subject 3</td>
<td>Multiple myeloma</td>
<td>None</td>
<td>Successful</td>
</tr>
</tbody>
</table>

**NOTE.** Case patients 8 and 14 were described elsewhere [10, 11]. CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone. 

A CD4 cell count of 28 cells/μL at the time of acute babesiosis. None of the control subjects had both an immunosuppressive illness and asplenia, and none received immunosuppressive medication. Patients who do not respond to a course of standard antibabesial therapy are likely to have medical conditions that severely impair immune function.

**Severity and outcome of illness of study population.** We examined whether case patients who experienced persistent or relapsed babesiosis despite standard antibabesial therapy experienced more severe acute illness than did control subjects who cleared infection after standard therapy. Peak parasite load, the number of babesiosis-related hospital admissions, the frequency of complications, and fatal outcome were greater among case patients than among control individuals (table 2). The parasite load decreased in all but 1 case patient after an initial course of standard antibabesial therapy, but each case patient subsequently experienced persistent or increased parasitemia accompanied by continued or worsening symptoms and anemia. One subject had no improvement in parasitemia and had a deteriorating clinical course during initial therapy that required an additional 2 months of therapy for cure. People who are immunosuppressed and who do not respond to initial antibabesial therapy are more likely to experience severe illness and to have a worse outcome than are subjects who respond to standard therapy.

**Antibabesial therapy for case patients.** We determined the type and duration of antibabesial therapy that was most effective in clearing parasitemia and symptoms among our case patients. Although multiple courses of antibabesial drug therapy were used, no single drug combination was uniformly effective in achieving cure (table 3). In contrast, the duration of therapy was associated with successful outcome. Drug combinations that resulted in cure were administered for a minimum of 6 weeks in all but 1 case (n = 11; median duration, 14 weeks; range, 1.5–100 weeks). Similar antimicrobial combinations that failed to permanently clear parasitemia were administered for a shorter duration (n = 49; median duration, 1.5 weeks; range, 0.25–22 weeks; P<.001). Antibabesial therapy was discontinued on 16 occasions when no parasites were observed on blood smear. Relapse occurred in 5 cases, at 3, 5, 6, and 7 weeks and at 3 months after cessation of therapy. In these instances, antibiotic treatment was discontinued after the apparent clearance of parasites (1, 1, 6, 8, and 13 days). In contrast, apparent cure of infection occurred in 11 cases when antibiotic treatment was discontinued after 2 weeks after parasites were no longer detected on blood
smear (median duration, 6 weeks; range, 2–100 weeks; OR not defined; 95% CI, 8.03–∞; P < .001). These subjects have remained asymptomatic without parasitemia for a median of 13 months (range, 4–79 months) after antibiotic treatment was discontinued. Antibabesial therapy was discontinued on 14 other occasions because the parasite frequency decreased to <1%. Relapse of infection occurred in all these cases. Because only 3 case patients received exchange transfusion early in the course of infection, we could not evaluate the efficacy of this mode of therapy on outcome in our case patients. Cure of immunocompromised patients whose initial antibabesial therapy fails generally is associated with the use of antibabesial treatment for ≥6 weeks, including 2 weeks after parasites are no longer detected on blood smear.

**DISCUSSION**

Asymptomatic babesial infection may persist for months or years in previously healthy patients, especially if the infection is not diagnosed and promptly treated [5]. These patients usually clear infection with or without antibabesial therapy. They may transmit babesia when they donate blood, and such transmission is an uncommon but well-recognized complication of the infection [13–16]. We now report a series of immunocompromised patients who experienced persistent and relapsing symptomatic babesiosis despite the use of standard antibabesial therapy. Previous individual case reports of a neonate, 2 patients experiencing malignancy, and several patients with AIDS have shown that the duration of “cure” after completion of antibabesial therapy in some immunocompromised hosts is uncertain [4, 6–11, 16]. Two of our case patients experienced persistent infection despite a year of intermittent antibabesial therapy, and 1 patient experienced recrudescence 3 months after parasites were no longer detected on blood smear. *Plasmodium ovale* or *Plasmodium vivax* malaria may recrudesce years after completion of therapy that does not include primaquine, because of hypnozoites in the liver. Although plasmodia are related intraerythrocytic Apicomplexa protozoa, no such extraerythrocytic stage has been described for babesia. Certain immunocompromised hosts who travel or reside in areas where babesiosis is endemic may develop persistent symptomatic babesiosis that is unresponsive to standard antimicrobial therapy.

We attempted to characterize immunologic deficits that result in persistent symptomatic babesiosis. Most of our study patients experienced B cell lymphoid malignancies, and most were treated with rituximab-containing regimens, including all 3 subjects who died. Rituximab depletes CD20+ B cells, including the majority of the B cell lineage, before plasma cell differentiation [17]. The rituximab-depleted cell population includes naive B cells, the same cells that would be responsible for antibody production in response to a new babesial infection.

Because plasma cells generally are differentiated cells from B cells that have been stimulated by antigen in the past, it is reasonable to expect that most people do not have antibabesial plasma cells before initial infection. Thus, rituximab-treated patients would be left with little or no antibabesial B cell activity. Rituximab has been associated with fatal reactivation of viral and fungal infections and a recent case of chronic relapsing babesiosis in a patient with lymphocyte predominant Hodgkin disease [8, 18–20]. After completion of treatment, rituximab remains detectable in serum for 3–6 months. B cell counts begin to increase at ∼6 months and generally return to normal by 12–18 months. All but 1 of our rituximab-treated case patients received the drug within 18 months after the onset of babesial illness. Approximately three-fourths of our case patients also were asplenic; the spleen is an important site for B cell activation. Previous studies have not identified persistent relapsing babesiosis in asplenic patients, although asplenia is a well-recognized cause of severe and sometimes fatal babesial infection [21, 22]. A meaningful comparison of antibabesial antibody concentrations and avidity between case and control subjects was not possible, but babesial antibody could not be detected in 1 of our case patients who died. All these data support the importance of B cell function in eradicating babesial parasites.

Table 2. Severity of infection among case patients and control subjects.

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Case patients (n = 14)</th>
<th>Control subjects (n = 46)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak parasitemia, median % (range)</td>
<td>8 (1.8–75)</td>
<td>2.5 (0.5–10)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Antibiotic courses, median no. (range)</td>
<td>4 (2–10)</td>
<td>1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. (%) admitted to the hospital</td>
<td>12 (86)</td>
<td>21 (46)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Hospital admissions per person, median no. (range)</td>
<td>1.5 (0–4)</td>
<td>1 (0–1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Therapy duration, median weeks (range)</td>
<td>13 (4–102)</td>
<td>1 (0.5–1.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. (%) of complications</td>
<td>8 (57)</td>
<td>2 (4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hematologic</td>
<td>6 (43)</td>
<td>0 (0)</td>
<td>…</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>6 (43)</td>
<td>2 (4)</td>
<td>…</td>
</tr>
<tr>
<td>Kidney</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>…</td>
</tr>
<tr>
<td>No. (%) of fatal infections</td>
<td>3 (21)</td>
<td>0 (0)</td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>
Table 3. Antibabesial therapy and outcome among patients who did not respond to standard therapy.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Antiparasitic drugs (weeks of therapy)</th>
<th>Duration of therapy, weeks</th>
<th>Time since cure, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AAz (2), none (5), AAz (1)→ACDQ (0.5)→AAzCQ (2.5)</td>
<td>6</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>CQ (0.5)→AAz (1.5), none (7), AAz (1.5)</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>AAz (1), none (4), CQ (2.5)→AAz (3)→AAzC (1)→ACP (2)→CQ (3), none (3), CQ (2)→AAz (1)→PeT (1)→ACD (21)</td>
<td>42</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>CQ (3), none (6), AAz (3), none (12), CQ (14)</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>AAz (1), none (11), AAz (4)→CQ (6), none (7), CQ (6)→AAz (16)</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>AAz (1.5), none (3), AAz (12)→AAzD (6)</td>
<td>20</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>AAz (1.5), none (7), AAz (22), none (5), AAz (12)→ACD (2)→ACD artemisinin (4)→AD artemisinin (11)</td>
<td>52</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>CQ (2), none (1.5), CQ (10), none (4), AAz (1)→CQ (2)</td>
<td>15</td>
<td>Died</td>
</tr>
<tr>
<td>9</td>
<td>CDQ (1)→AAzD (3)→ACD (6)</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>CQ (0.5)→AAz (1.5)→AAz (8)</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>11</td>
<td>AAzD (1)→AAz (1)→CQ (0.5)→ACD (10)</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>AAz (1.5), none (6), CQ (1.5)→AC (0.5)→AAzC (88)</td>
<td>102</td>
<td>25</td>
</tr>
<tr>
<td>13</td>
<td>AAz (4.5), none (12), CQ (1)</td>
<td>6</td>
<td>Died</td>
</tr>
<tr>
<td>14</td>
<td>AAz (2), none (12), CQ (0.25)→AAz (7)→AAzP (0.5), none (1), AAzCP (5)→AAzPQ (3), none (3), AAzCQ (1)→ACP (2), none (2), AAzC (8)→AAz (14)</td>
<td>43</td>
<td>12</td>
</tr>
</tbody>
</table>

**NOTE.** Drug combinations shown with dashes were consecutively administered. Drug combinations in bold type are considered curative, because of resolution of parasitemia and symptoms during their administration. For patient 12, a very prolonged course of antibiotic therapy was prescribed because of previous success with such prolonged therapy in patients with HIV [6]. A, atovaquone; Az, azithromycin; C, clindamycin; D, doxycycline; P, proguanil; Pe, pentamidine; Q, quinine; T, trimethoprim-sulfamethoxazole.

Broader immunosuppression appears necessary for persistent babesial illness, however. Animal models have suggested the importance of both cellular and humoral immunity in clearing babesial infection [23–26]. Furthermore, our data and those of others [6–11] suggest that an array of immunosuppressive diseases are associated with persistent relapsing babesiosis and that additional immunosuppression—from asplenia or chemotherapeutic agents or both—usually are associated with this condition. Physicians caring for significantly immune-impaired patients who develop babesiosis should be aware of their increased risk of developing persistent relapsing disease and should discontinue immunosuppressive therapy until the infection has resolved.

Selection of case patients and control subjects may introduce selection bias and thus compromise the validity of a case-control study [27]. Although control subjects were recruited from our longitudinal tickborne diseases study, most case patients were referred to 1 of us (P.J.K.) for assistance with case management. The strong association that we observed between a subset of case patients with hematologic malignancies and the risk of developing persistent babesiosis might partially have been explained by selection bias, if referral of cases had been influenced by the presence or absence of such hematologic conditions. Persistent relapsing babesiosis appears to be unusual in the general population, however, and physicians in the longitudinal study referred all cases meeting the case definition, regardless of underlying medical condition. Finally, the episodes of recrudescent babesiosis in our case patients occurred either before or after the babesial transmission season and thus were unlikely to represent reinfection.

We attempted to identify a management strategy that would permanently eradicate persistent *B. microti* infection in people who do not respond to a single course of standard antibabesial therapy. Because of the difficulty encountered in clearing infection, our case patients received a series of antimicrobial drugs. Although no systematic therapeutic approach was used, the type of antibiotic regimen did not appear to influence outcome. In contrast, the duration of antibiotic therapy appeared to be associated with cure. Eradication of disease occurred only when antibabesial therapy was administered for ≥2 weeks after parasites were no longer detected on thin blood smear and, generally, for ≥6 weeks. Relapse of infection always occurred when antibiotic treatment was discontinued before parasites were no longer visible on blood smear, even if <1% of erythrocytes were infected. These data suggest that antimicrobial resistance was not a factor in the failure of antibabesial therapy. There are no reports of babesial resistance to atovaquone and azithromycin or clindamycin and quinine, although drug resistance is well described for *Plasmodium* species [28]. Antibiocists may serve to restrain parasite growth until a sufficient antibabesial immune response develops, especially with im-
mune recovery following cessation of immunosuppressive medication.

The incidence and geographic distribution of human babesiosis has markedly expanded since the first report of Babesia divergens infection in a Yugoslavian farmer 50 years ago [12, 29, 30]. Five other Babesia species have been found subsequently to infect humans, including B. microti, Babesia duncani (formerly known as “WA-1”), EU-1, MO-1, and TW-1 [8, 31–35]. B. microti, a species that perpetuates in mice, is the most frequent cause of human babesiosis and the source of an increasing number of human infections in the northeastern and northern midwestern United States, Asia, and Europe [12, 29, 36, 37]. The increasing incidence and geographic dispersion of human babesiosis, coupled with a growing number of immunocompromised people who live or travel in areas where babesiosis is endemic, emphasize the need for a better understanding and management of complicated babesial infection.

We conclude that immunocompromised patients who experience babesiosis and whose initial antimalarial therapy fails may experience a prolonged and relapsing course of disease, accompanied by severe complications. Patients with conditions that significantly impair immune function and who travel or reside in areas endemic for babesiosis should be advised to minimize their risk of tick exposure. Those who experience babesiosis and whose initial course of standard antimalarial therapy fails should be re-treated for ≥2 weeks beyond the time when no parasites are observed on blood smear. Most of these patients will require antimalarial antibiotics for ≥6 weeks. These patients should be monitored for ≥3 months after apparent cure, and blood smears should be examined for intraerythrocytic parasites if the patients develop symptoms that are suggestive of babesiosis.

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