

# Epidemiologic Features of Human Babesiosis in Wisconsin, 1996-2005

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## ABSTRACT

**Objective:** To characterize epidemiologic, clinical, and laboratory features of babesiosis occurring in Wisconsin residents.

**Design:** Conduct a review of all cases of babesiosis reported to the Wisconsin Division of Public Health with onsets during 1996-2005. For case patients with onsets during 2004, pertinent medical records were reviewed and patient interviews were performed.

**Interventions:** Increase awareness of the occurrence and recent trends and facilitate prompt, appropriate diagnosis and treatment of babesiosis. Increase awareness among clinicians of the Infectious Diseases Society of America guidelines for the management of babesiosis, Lyme disease, and human granulocytic anaplasmosis.

**Main Outcome Measures:** The study represents an analysis of data received through passive surveillance of a disease that is officially reportable to the Wisconsin Division of Public Health. Other than the description of the occurrence of babesiosis among Wisconsin residents, there were no planned outcome measures.

**Results:** Of the 32 cases of babesiosis reported to the DPH during the study interval, 23 (72%) occurred during 2004 and 2005. The majority of cases occurred in northwestern and west-central Wisconsin. At least 6 patients were co-infected with other tick-borne pathogens. Anemia, thrombocytopenia, and elevation of liver transaminase levels were the most notable laboratory abnormalities among case patients.

**Conclusions:** The apparent increased incidence in babesiosis among Wisconsin residents should impact clinicians' workups for acute febrile illness with known tick exposure, especially in northwest and west central Wisconsin. Babesiosis should now also be considered in patients diagnosed with Lyme disease who have marked constitutional symptoms, especially those with anemia or thrombocytopenia.

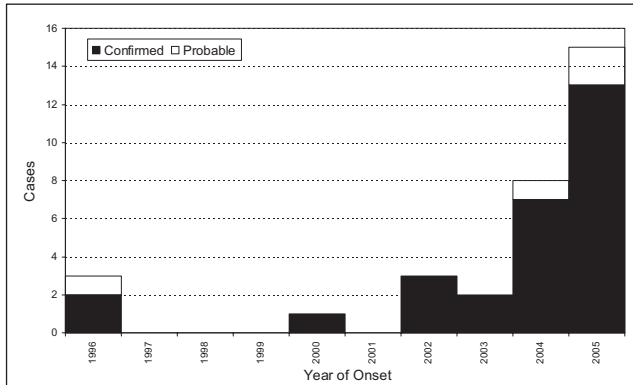
## INTRODUCTION

Human babesiosis can be a life-threatening illness with clinical manifestations that include fever, chills, myalgia, fatigue, hepatosplenomegaly, and hemolytic anemia. In the United States, the overwhelming majority of cases are caused by the intra-erythrocytic parasite *Babesia microti*.<sup>1-3</sup> The disease is typically more severe among individuals who are asplenic, immunocompromised, or elderly. The parasite is transmitted to humans by the *Ixodes scapularis* tick ("deer tick"), and its reservoir is the white-footed mouse, *Peromyscus leucopus*. Juvenile *I. scapularis* acquire *Babesia* when they feed on the mice during spring and summer. Subsequent feedings can transmit *Babesia* to new mammalian hosts.<sup>3,4</sup>

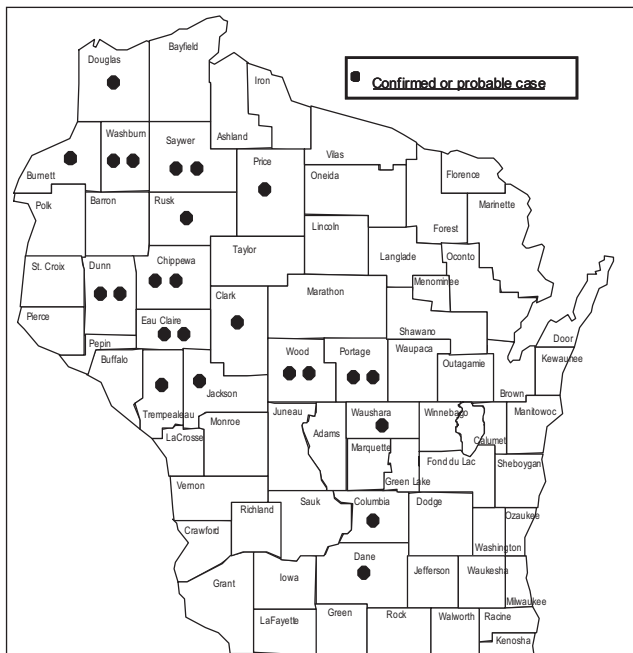
The first reported case of human babesiosis in the United States was acquired on Nantucket Island, Mass, in 1969.<sup>5</sup> Since then, babesiosis has become an increasingly prevalent disease in the northeastern United States, with most cases being acquired in Connecticut, Massachusetts, New York, and Rhode Island.<sup>6</sup> Endemic areas also exist in the upper Midwest; the first cases reported in the region occurred in Wisconsin in 1983.<sup>7</sup> Five additional Wisconsin cases were subsequently reported between 1987 and 1993.<sup>8</sup> During 1994-2003, reported occurrences of human babesiosis in Wisconsin remained sporadic despite statewide implementation of mandatory case reporting in 2001; however, the DPH received reports of 8 cases with onsets in 2004 and 15 cases with onsets in 2005. This report includes a comprehensive description of reported human babesiosis in Wisconsin from 1996 through 2005.

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**Figure 1.** Reported confirmed and probable cases of babesiosis (n=32), Wisconsin, 1996-2005.



**Figure 2.** Reported confirmed and probable cases of babesiosis (n=32) among Wisconsin residents by county of most likely exposure, 1996-2005. Exclusions include 1 case that was transfusion-acquired, 2 that were non-Wisconsin exposures and 5 for which county of exposure could not be determined.

## METHODS

Babesiosis became an officially reportable disease in Wisconsin in 2001. Previously, the Wisconsin Division of Public Health (DPH) received voluntary case reports of babesiosis and follow-up investigations were not standardized. Since 2001, suspect or confirmed cases of babesiosis are reported by clinicians to local health departments and the DPH using the DPH Acute and Communicable Disease Case Report Form 4151. Results of positive *Babesia* tests in Wisconsin residents are sent from reference laboratories directly to the DPH. Local

health department officials complete a standardized babesiosis case report form for each case and submit it to the DPH. Information on this form includes patient demographics, epidemiologic history including likely county of tick exposure, clinical signs and symptoms, diagnostic modality, basic laboratory findings, and outcome data if available.

Data were evaluated for all reported cases of babesiosis among Wisconsin residents reported from 1996-2005. For those cases reported in years other than 2004, medical records were not obtained, although DPH surveillance records and, in some cases, data abstracted during prior telephone interviews were reviewed. The county of most likely exposure was deduced based on case-patient histories of reported exposures to ticks or tick habitat during the 90 days prior to illness onset.

For the 8 cases that occurred in 2004, pertinent medical records were requested and reviewed. An additional standardized patient questionnaire was developed, which included more detailed questions regarding illness time course, signs and symptoms, past medical history, exposure history, travel and activity history, diagnosis, specific therapy received, and time to clinical recovery. Telephone interviews using this questionnaire were then conducted with the 2004 case patients or their spouses when case patients could not be interviewed.

The Wisconsin babesiosis case definition was used for classification. A confirmed case of babesiosis for surveillance purposes was defined as a clinically compatible illness with *Babesia* parasites visualized on peripheral blood smear. A probable case was defined as a compatible clinical illness without competing diagnoses and either of the following: *Babesia* immuno-fluorescence antibody (IFA)  $\geq 1:256$ , or positive polymerase chain reaction (PCR) assay for *B. microti*.

## RESULTS

### All Cases During 1996-2005

During January 1, 1996 through December 31, 2005, 32 cases of babesiosis met the surveillance case definition (28 confirmed, 4 probable) and were reported to the DPH. Notably, 23 of these case patients had illness onsets during 2004 and 2005 (Figure 1).

Among case patients, 21 (66%) were male, 21 (66%) were hospitalized, and 1 (3%) died. Case patients' ages ranged from 28 to 90 years with a mean age of 64.5 years. Comorbid conditions included asplenia (5), diabetes mellitus (2), cancer (2), and HIV infection (1). Evidence of co-infections occurred with both *Borrelia burgdorferi* (5 patients) and *Anaplasma phagocytophi-*

*lum* (formerly called the human granulocytic ehrlichiosis agent, 1 patient).

All cases were presumed to be tick-borne with the exception of 1 case that was blood transfusion related. The infected donor was asymptomatic and was therefore not included among the case patients. Among the tick-borne cases, 2 were likely acquired in Minnesota, 5 were acquired in Wisconsin but the county of acquisition was not known, and 24 had a known county of probable acquisition in Wisconsin; the majority of infections were acquired in the northwest and west-central counties of Wisconsin (Figure 2).

The laboratory tests requested for the case patients varied considerably, but the following laboratory abnormalities were reported with sufficient frequency to warrant mention: anemia, 19 of 23 cases (84%); thrombocytopenia, 24 of 26 cases (92%); and leukopenia 5 of 18 cases (28%) (Table 1). Other laboratory test results (liver and renal function, and inflammatory markers) and detailed information on clinical signs and symptoms were not available except for the 2004 cases.

#### 2004 Cases

**Case Patient Profiles:** Illnesses described in 8 reports of suspected babesiosis in 2004 met the case definition; 7 cases were confirmed and 1 was a probable case. Three reported illnesses did not fulfill the case criteria; 1 patient with a compatible clinical illness complicated by autoimmune hemolytic anemia recovered with steroids and anti-babesia therapy, and the other 2 patients had compatible clinical illness but insufficient antibody titers (1:128) to meet the case definition. The age, gender, and co-infections of the 2004 case patients are summarized in Table 1. Comorbidities of the patients included prior splenectomy (1), diabetes mellitus (1), and heart disease (3). None had received chemotherapy, chronic steroid treatment, or transfused blood products. Seven patients were hospitalized (mean 7 days, range 4-14 days), and 1 patient died.

**Clinical Manifestations and Laboratory Abnormalities:** Signs and symptoms of illness included fatigue (all 8 case patients), fever and chills (7), abdominal pain (4), myalgias (3), sweats (3), nausea (3), cough (3), headache (1), vomiting (1), jaundice (1), and dark urine (1). Laboratory abnormalities of the 2004 case patients are summarized in Table 1.

**Treatment, Morbidity, and Mortality:** All 8 patients received combination therapy; 5 were prescribed atovaquone with azithromycin, and 3 initially received quinine and clindamycin. The latter regimen was not

**Table 1.** Demographic and Laboratory Findings of Reported Babesiosis, Wisconsin, 1996-2005

Characteristic	1996-2005 Cases* No. (%)	2004 Cases† No. (%)
Male	21 (66)	7 (88)
Mean Age	64.6 years	71 years
(Range)	(28-90 years)	(53-88 years)
Hospitalized	21 (66)	7 (88)
Deaths	1 (3)	1 (13)
<b>Co-infection</b>		
<i>Borrelia burgdorferi</i>	5 (16)	3 (38)
<i>Anaplasma phagocytophilia</i>	1 (3)	0 (0)
<b>Laboratory Findings</b>		
Anemia	19/23 (84)	7/8 (88)
Mean (Range)	NA	26.1% (14-35)
Thrombocytopenia	24/26 (92)	8/8 (100)
Mean (Range)		81,000/ $\mu$ L (31,000-112,000)
Leukopenia	5/18 (28)	1/8 (13)
Leukocytosis	NA	1/8 (13)
ESR elevated	NA	5/5 (100)
Mean (Range)		89 mm/hr (45-140)
CRP elevated	NA	4/4 (100)
Mean (Range)		18.5 mg/dL (9.7-23.3)
Transaminases (AST, ALT) elevated	NA	6/7 (86)
Total bilirubin or alkaline phosphatase elevated	NA	5/7 (71)
Acute kidney injury	NA	3/8 (38)

\* n=32

† n=8

Anemia=HCT <35%, or, if that value was not available, Hgb <12 g/dL; Thrombocytopenia=platelets <150,000/ $\mu$ L; Liver function test elevation=ALT, AST, total bilirubin, and/or alkaline phosphatase elevation above the upper limit of normal (ULN) for the testing laboratory; Leukocytosis=WBC >11 x 10<sup>3</sup>/ $\mu$ L; Leukopenia=WBC <3.5 x 10<sup>3</sup>/ $\mu$ L; Acute kidney injury=Creatinine (Cr) >1.5 times the patients' baseline value or, if unavailable, Cr >1.5 mg/dL; Erythrocyte sedimentation rates (ESR) and C-reactive protein (CRP) elevations=greater than ULN for the testing laboratory; NA=Not available.

tolerated in 1 case patient, whose therapy was subsequently switched to atovaquone and azithromycin. In addition, 5 case patients received packed red blood cell transfusions; however, none required dialysis or exchange transfusions. One patient underwent bone marrow biopsy for diagnostic purposes. Among survivors, mean time to convalescence was 4 weeks (range 2 to 10 weeks). The primary cause of death listed on the death certificate of the case patient who died was severe congestive heart failure from ischemic cardiomyopathy. This patient had developed severe babesiosis that was

diagnosed shortly prior to death. An autopsy was not performed.

Informative case descriptions of 2 selected Wisconsin babesiosis patients can be found in an appendix to the on-line version of this article ([www.wisconsinmedicalsociety.org/\\_WMS/publications/wmj/\\_files/pdf/KazmierczakAppendix.pdf](http://www.wisconsinmedicalsociety.org/_WMS/publications/wmj/_files/pdf/KazmierczakAppendix.pdf)).

## DISCUSSION

The first confirmed cases of babesiosis acquired in Wisconsin occurred in Washburn County in 1983.<sup>7</sup> From 1983 to 2001 there were 10 reported cases. Since 2001, cases have been reported annually and there has been a recent dramatic increase in occurrence. We believe this likely represents a real increase in the incidence of this disease in Wisconsin. However, contributing explanations likely include increased awareness of babesiosis among health care professionals, more accessible and reliable diagnostic testing, and the initiation of mandatory reporting of babesiosis in Wisconsin in 2001.

*Ixodes scapularis* is the tick vector for babesiosis, Lyme disease, and anaplasmosis. In Wisconsin, the number of reported cases of both Lyme disease and anaplasmosis is increasing. In 2001 there were 648 reported cases of Lyme disease and 19 cases of anaplasmosis, whereas in 2005 reported cases had increased to 1441 and 155, respectively (Wisconsin Division of Public Health, unpublished data). The highest rates of reported Lyme disease and anaplasmosis occur in the northwest and west-central counties of Wisconsin, a distribution similar to that of reported babesiosis. Thus, it is not surprising to note an accompanying increase in babesiosis cases occurring in those same areas.

Co-infections with any combination of these 3 tick-borne agents are common in parts of the country where geographic distribution overlaps. A study in southern New England found that among 192 patients with an acute illness suspected to be tick-borne in nature, 75 (39%) were co-infected, the majority with *B. microti* and *B. burgdorferi*.<sup>9</sup> In Wisconsin, the presence of concomitant infection with tick-borne agents is not as well defined. In a study of patients from both Wisconsin and Minnesota, sera from 13 of 116 patients (9%) diagnosed with Lyme disease, babesiosis, or anaplasmosis demonstrated serologic evidence of co-infection.<sup>10</sup> In this current 10-year case series of babesiosis, 6 co-infections (19%) were reported. This finding supports the recently published Infectious Diseases Society of America (IDSA) guidelines on Lyme disease, anaplas-

mosis, and babesiosis, which advise testing of Lyme disease patients for babesiosis and/or anaplasmosis if the patient has more severe systemic symptoms, signs, or laboratory abnormalities than would be expected from Lyme disease alone.<sup>11</sup>

The typical laboratory profile of babesiosis includes hemolytic anemia, thrombocytopenia, elevated liver tests, and, in severe cases, acute renal failure. In our 10-year series, anemia and thrombocytopenia were present in the overwhelming majority of case patients. On the other hand, leukopenia, a finding common in anaplasmosis,<sup>12</sup> was reported in only 28% of our babesiosis case patients. We also found CRP and ESR levels to be extremely high in the few patients who had these tests performed.

Prompt diagnosis of babesiosis is important because rapidly active and minimally toxic treatment is available. A randomized-controlled trial has shown the combination of azithromycin and atovaquone to be similarly effective and better tolerated for patients with mild to moderate disease as compared to a combination regimen of clindamycin and quinine, the former standard of care.<sup>13</sup> The findings of that trial are incorporated into the new IDSA guidelines, which recommend the combination of azithromycin with atovaquone for first line therapy in acute babesiosis with the exception of continued preferential use of clindamycin with quinine for severe cases.<sup>11</sup> In the 2004 Wisconsin cases, the atovaquone and azithromycin combination was used often and with good results.

A retrospective case series of 139 consecutive hospitalized patients in New York State found that common severe complications of babesiosis included congestive heart failure (11%), acute respiratory distress syndrome (8%), and shock or myocardial infarction (4%).<sup>14</sup> In previously published case series, mortality in the setting of acute babesiosis has been approximately 5%.<sup>15,16</sup> The single Wisconsin case fatality is consistent with this reported mortality rate.

## CONCLUSION

With the apparent increasing incidence of babesiosis in Wisconsin, clinicians should increase their index of suspicion for this disease and include acute babesiosis in the initial differential diagnosis for an acute febrile illness in the setting of possible tick exposure. Early recognition is vital, because prompt diagnosis and treatment can be life saving, particularly in elderly, asplenic, or otherwise immunocompromised patients in whom this infection is a significant cause of morbidity and mortality.

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