Risk factors for hospitalization, severe infection, and prolonged disease in patients with babesiosis in the upper Midwest.

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Abstract

Background: Babesiosis is an emerging parasitic tick-borne disease. Severity of infection can range from asymptomatic to fatal and, though many infections are self-limited or cured with a short course of antibiotics, some patients have prolonged illness despite antimicrobial therapy. Early prognostic indicators to guide clinical decisions and antimicrobial prescribing are needed.

Methods: A retrospective chart review of patients diagnosed with babesiosis by PCR or smear from 1999-2015 at Marshfield Clinic Health System in northern Wisconsin was completed. Univariate and multivariate analyses were completed and relative risk ratios (RR) with 95% confidence intervals were determined for symptoms, laboratory studies, clinical outcomes, and treatment associated with hospitalization, severe infections, and prolonged disease.

Results: 128 cases of babesiosis were detected. 81(63%) patients were hospitalized, 26(20%) had severe infection, and 11(8.6%) required >14 days of antibiotics. There were no fatalities. Coinfection with Lyme disease, erhlichiosis, or anaplasmosis reduced risk of hospitalization (RR 0.73 CI 0.53-0.99, p=0.03) and did not change risk for severe infection (RR 1.08 CI 0.53-2.18, p=0.84) or prolonged disease (RR1.3 CI 0.66-2.58, p=0.45). Initiation of antibiotic treatment for babesiosis was delayed in patients without coinfection (23.3 vs 17.3 days, p<0.01). Asplenia, nausea or vomiting, diarrhea, urinary changes and total bilirubin >1.9 were associated with need for hospitalization, severe infection, and persistent disease (all p ≤ 0.03). Age >75 years (RR 1.44 CI 1.14-1.82, p=0.01) and underlying cardiac disease (RR1.40 CI 1.09-1.41, p=0.01) were associated with hospitalization. Treatment delay of greater than 7 days after symptom onset increased risk for severe infection (RR2.35 CI 1.01-5.48, p=0.03).

Conclusions: Babesiosis can result in serious and persistent infection. Delays in diagnosis and start of treatment significantly increase risk for severe disease. Clinical and laboratory findings are useful in identifying patients who may require hospitalization, develop severe infection, or require prolonged courses of antibiotics. Contrary to previous studies coinfection with other tick- borne pathogens reduced risk for hospitalization, possibly from earlier recognition of disease.

Background

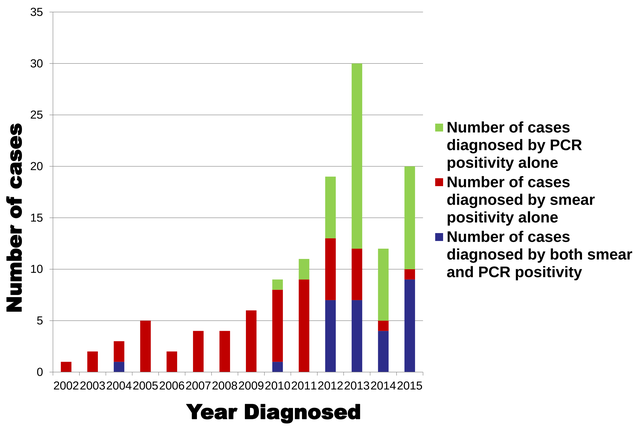
- Babesiosis, primarily caused by *B.microti* in the United States, is an emerging parasitic tick-borne disease.
- The primary vector for the parasite is the deer tick, *Ixodes scapularis*. In the United States, 95% of cases occur in 7 states in Northeast and upper Midwest: Connecticut, Massachusetts, Minnesota, New Jersey, New York, Rhode Island, and Wisconsin.
- Severity of *Babesia* infections ranges from asymptomatic to severe and are sometimes fatal.
- Some patients have prolonged illness despite antimicrobial therapy.
- Early prognostic indicators to guide clinical decisions and prescription of antimicrobial therapy are needed to prevent patients from developing serious complications with *Babesia* infection and determine which patients may require extended treatment.

Methods

- Patients were identified by query of the Marshfield Clinic Health System (MCHS) electronic health records (EHR) for ICD 9 or ICD 10 code and by query of Marshfield Labs database for positive babesiosis blood smear or nucleic acid testing (NAT) from 1999 to 2015.
- Patients were included if blood smear or NAT was positive for babesiosis and clinical information was available in EHR.
- Patients with serologic evidence only of babesiosis were not included.
- Outcome measures included mortality, need for hospitalization, severe infection, or need for >14 days of antimicrobial therapy. Patients were defined as having severe infection if they required ICU care, intubation, had shock, ARDS, or required exchange transfusion.
- Categorical data were compared by using the χ2 or Fisher exact test. Continuous variables were compared by using univariate and multivariate analyses including the Wilcoxon rank–sum test. Means were compared by using the t test. Significance was defined as a P value of <0.05 and relative risks (RR) with 95% confidence intervals were determined.

Results

Epidemiologic Data:



- 81% of patients were diagnosed between July-September
- Co-infection was present in 41 (37%) of patients, of which 87% had Lyme disease, and 17% had anaplasmosis.
- Most patients, 85 (67%), were male with a mean age of 64.9 (19-94.7) years.

Table 1: Risk factors for hospitalization, severe infection, and length of therapy >14 days in patients with babesiosis.

(N=128)	Hospitalization				Severe Infection				Length of Therapy >14 Days			
	Yes (81)	No (47)	RR (95%CI)	p-value	Yes (26)	No (102)	RR (95%CI)	p-value	Yes (26)	No (96)	RR (95%CI)	p-value
Age >75 years	25	5	**1.44 (1.14 - 1.82)**	**0.01**	7	23	1.67 (0.54 - 2.50)	0.69	7	22	1.22 (0.57 - 2.63)	0.61
Male	54	31	0.99 (0.75 - 1.31)	0.93	18	67	0.88 (0.42 - 1.86)	0.73	16	67	1.33 (0.67 - 2.66)	0.42
Comorbidities	70	29	**0.54 (0.33 - 0.87)**	**0.001**	22	77	0.62 (0.23 - 1.66)	0.32	24	71	**0.29 (0.07 - 1.16)**	**0.05**
Cardiac	39	12	**1.40 (1.09 - 1.81)**	**0.01**	11	40	1.11 (0.55 - 2.21)	0.77	9	38	0.84 (0.41 - 1.74)	0.64
Asplenia	14	0	**1.70 (1.46 - 1.98)**	**<0.01**	7	7	**3.00 (1.54 - 5.84)**	**<0.01**	12	2	**6.61(3.88 - 11.27)**	**<0.01**
Autoimmune	10	1	**1.50 (1.18 - 1.90)**	**0.05**	5	6	**2.53 (1.19 - 5.38)**	**0.04**	6	4	**3.36 (1.77 - 6.39)**	**<0.01**
Any Co-infection	24	23	**0.73 (0.53 - 0.99)**	**0.03**	10	37	1.08 (0.53 - 2.18)	0.84	11	33	1.30 (0.66 - 2.58)	0.45
Signs & Symptoms												
Fever	73	32	**0.50 (0.28 - 0.89)**	**<0.01**	22	83	0.83 (0.32 - 2.18)	1.0	22	78	0.83 (0.32 - 2.16)	0.78
Fatigue	74	35	**1.84 (1.01 - 3.37)**	**0.01**	26	83	**0.76 (0.69 - 0.85)**	**0.01**	24	80	2.08 (0.54 - 8.04)	0.36
Chills	56	24	**1.34 (0.99 - 1.83)**	**0.04**	17	63	1.13 (0.55 - 2.34)	0.73	16	61	0.94 (0.46 - 1.88)	0.85
Myalgia or Arthralgia	46	39	**0.66 (0.52 - 0.85)**	**<0.01**	14	71	0.59 (0.30 - 1.16)	0.13	11	71	**0.36 (0.18 - 0.71)**	**<0.01**
Nausea or Vomiting	35	8	**1.50 (1.18 - 1.92)**	**<0.01**	15	28	**2.70 (1.38 - 5.35)**	**<0.01**	13	26	**2.13 (1.09 - 4.15)**	**0.03**
Lightheaded or Dizzy	33	5	**1.63 (1.29 - 2.05)**	**<0.01**	10	28	1.48 (0.74- 2.96)	0.28	9	24	1.43 (0.71 - 2.88)	0.33
Diarrhea	19	1	**1.65 (1.38 - 2.00)**	**<0.01**	10	10	**3.37 (1.80 - 6.34)**	**<0.01**	8	11	**2.41 (1.23 - 4.73)**	**0.02**
Rash	11	15	**0.62 (0.39 - 0.98)**	**0.01**	6	20	1.18 (0.53 - 2.63)	0.69	4	22	0.67 (0.25 - 1.78)	0.41
History of Tick Bite	25	28	**0.63 (0.46 - 0.86)**	**<0.01**	7	46	0.52 (0.24 - 1.15)	0.99	6	45	**0.42 (0.18 - 0.97)**	**0.03**
Parasitemia >10% (n)	8 (28)	0 (2)	1.10 (0.96 - 1.26)	1.0	7	1	**2.14 (1.21 - 3.77)**	**0.04**	6	2	2.25 (1.09 - 4.65)	0.09
WBC x 10^3/µL (n)	(75)	(38)			(24)	(89)			(24)	(83)		
<5.0	32	15	1.04 (0.80 - 1.36)	0.74	4	43	**0.28 (0.10 - 0.77)**	**<0.01**	4	40	**0.29 (0.11 - 0.78)**	**<0.01**
>10.0	7	1	1.35 (1.00 - 1.82)	0.19	4	4	**2.14 (1.21 - 3.77)**	**0.04**	5	3	**3.26 (1.66 - 6.38)**	**<0.01**
Hb <12.0 g/dL (n)	45 (76)	9 (37)	**1.59 (1.21 - 2.08)**	**<0.01**	14 (25)	40 (88)	1.39 (0.69 - 2.79)	0.35	15 (26)	34 (81)	1.61 (0.83 - 3.18)	0.16
Platelets x 10^3/µL (n)	(74)	(39)			(26)	(87)			(24)	(83)		
<50	25	13	1.00 (0.76 - 1.34)	0.96	12	26	1.69 (0.87 - 3.29)	0.12	9	27	1.18 (0.57 - 2.44)	0.65
50-100	34	7	**1.49 (1.16 - 1.91)**	**<0.01**	8	33	0.78 (0.37 - 1.63)	0.51	7	33	0.69 (0.31 - 1.52)	0.34
100-150	7	5	0.88 (0.53 - 1.45)	0.58	2	10	0.70 (0.19 - 2.61)	0.58	4	6	1.94 (0.83 - 4.56)	0.16
>150	8	13	**0.53 (0.30 - 0.93)**	**<0.01**	4	17	0.80 (0.31 - 2.07)	0.63	4	16	0.87 (0.33 - 2.27)	0.77
Na <135 mmol/L(n)	50 (73)	11(32)	**1.57 (1.15 - 2.13)**	**<0.01**	18 (24)	43 (81)	2.16 (0.94 - 5.01)	0.06	15 (24)	43 (75)	1.18 (0.57 - 2.43)	0.65
Creatinine >1.2 mg/dL (n)	23 (72)	4 (32)	**1.34 (1.06 -1.69)**	**0.04**	10 (24)	17 (80)	**2.04 (1.03 - 4.03)**	**0.04**	9 (24)	17 (74)	1.66 (0.83 - 3.33)	0.16
ALT >54 U/L (n)	2 (69)	5 (29)	**0.39 (0.12 - 1.26)**	**0.01**	1 (23)	6 (75)	0.59 (0.09 - 3.76)	0.55	1 (24)	5 (69)	0.63 (0.10 - 3.90)	1.0
AST >40 U/L (n)	52 (69)	19(32)	1.29 (0.92 - 1.82)	0.10	17 (23)	54 (78)	1.20 (0.52 - 2.74)	0.67	20 (24)	46 (72)	2.27 (0.85 - 6.07)	0.08
ALP >147 units/L (n)	11(65)	7 (30)	0.87 (0.59 - 1.29)	0.57	4 (22)	14 (73)	0.95 (0.37 - 2.47)	1.0	6 (24)	10 (66)	1.54 (0.73 - 3.26)	0.35
Total Bilirubin >1.9 mg/dL (n)	21 (65)	2 (30)	**1.49 (1.19 - 1.87)**	**0.01**	14 (23)	9 (72)	**4.87 (2.43 - 9.74)**	**<0.01**	12 (24)	10 (66)	**3.09 (1.63 - 5.86)**	**<0.01**
Albumin <3.4 g/dL (n)	51(66)	11(30)	**1.86 (1.26 - 2.77)**	**<0.01**	18 (23)	44 (73)	1.97 (0.80 - 4.85)	0.14	20 (24)	39 (67)	**2.71 (1.01 - 7.25)**	**0.04**
CRP >3.0 mg/dL (n)	30 (32)	5 (8)	**2.14 (0.73 - 6.32)**	**0.05**	12 (12)	23 (28)	0.66 (0.52 - 0.83)	0.30	13 (14)	22 (94)	1.86 (0.31 - 11.29)	0.64

Summary Statistics

Table 2: Clinical signs and symptoms of patients with Babesiosis

Signs & Symptoms	N=128 n (%)
Fatigue	109 (85.2)
Fever	105 (82.0)
Myalgia/Arthralgia	85 (66.4)
Chills	80 (62.5)
Nausea/Vomiting	43 (33.6)
Cough/SOB	43 (33.6)
Anorexia	42(32.8)
Headache	40 (31.2)
Night sweats	39 (30.5)
Lightheadedness/Dizziness	38 (29.7)
Rash	26 (20.3)
Abdominal Pain	21(16.4)
Diarrhea	20 (15.6)
Hepatosplenomegaly	6 (4.7)

Table 3: Laboratory findings of patients with Babesiosis

Laboratory Data	Median (Min - Max)
Highest % Parasitemia	2.65 (0.03-31.10)
Highest titer	1: 512 (1: 16 – 1:1024)
Platelet at diagnosis (x10^3)	68 (3 - 703)
Lowest Platelet (x10^3)	56 (3 - 703)
Lowest HCT	30 (16 - 46)
Highest WBC (10^3/uL)	7.1 (2 - 25)
CRP at diagnosis (mg/dL)	10.25 (0.5 – 45.3)
ESR at diagnosis (mm/hr)	40 (7 – 117)
Procalcitonin at diagnosis (ng/mL)	1.72 (0.16 – 46.48)
Sodium at diagnosis (mmol/L)	134 (120 – 145)
Peak Creatinine (mg/dL)	1.1 (0.58 – 7.6)
Peak Alk Phos (U/L)	101 (49 – 344)
Peak ALT (U/L)	62.5 (10 – 540)
Peak AST (U/L)	75 (13 – 998)
Peak Bili (mg/dL)	1.4 (0.3 – 24.3)
Peak LDH (U/L)	587 (207 – 3500)

Table 4: Treatment and outcome data for patients with Babesiosis

Treatment and Outcomes	N=128 n (%)
Hospitalized	81 (63.3)
Severe infection	26 (20.3)
Length of therapy >14 Days	26 (20.3)
Time from symptom onset to start of treatment (median, days)	10 (0 - 721)
Duration of treatment (median, days)	9 (0 – 730)
Type of treatment received	
Clindamycin	31 (24.2)
Quinine	29 (22.7)
Atovaquone	108 (84.4)
Azithromycin	112 (87.5)

Conclusions

- About 80% of babesiosis cases occurred between the months of July and September.
- The patients with age greater than 75 years were more at risk for hospitalization, though there was no increased risk for either severe infection or need for longer duration of therapy with age >75 years.
- Contrary to the general belief, relative risk of hospitalization is significantly less in patients with co-infection with other tick-borne illnesses.
- Among patients with comorbidities, the patients with prior cardiac problems, asplenia and autoimmune problems were at increased risk for hospitalization.
- The patients with asplenia and autoimmune conditions are at increased risk of having severe infection and needed longer duration of therapy. Immunocompromised patients also required longer duration of therapies.
- Nausea/vomiting and diarrhea were predictive of increased risk for hospitalization, severe infection as well as longer duration of therapies.
- Various laboratory findings associated with increased risk for hospitalization were Hb <12 gm/dl, sodium <135 mmol/L, creatinine >1.2 mg/dl, ALT > 54 U/L, total bilirubin >1.9 mg/dL, albumin <3.4 g/dL and CRP >3.0 mg/dL.
- Sodium <135 mmol/L, creatinine >1.2 mg/dL and total bilirubin >1.9 mg/dL were the only laboratory findings associated with severe infection.
- Longer durations of therapies were required in patients with elevated AST, total bilirubin and low albumin levels.
- Parasitemia >10% is associated both with increased risk of severe infection as well as need for longer duration of treatment.
- Elevated total bilirubin >1.9 mg/dL was the only lab finding predictive of increased risk for hospitalization, severe infection as well as need for longer duration of treatment.

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