

CHRONIC *BARTONELLA QUINTANA* BACTEREMIA IN HOMELESS PATIENTS

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ABSTRACT

Background Infection with *Bartonella quintana* can cause trench fever, endocarditis, bacillary angiomatosis, and peliosis. An outbreak of bacteremia due to *B. quintana* has been reported among homeless people in Seattle, and the seroprevalence is high among homeless people in both the United States and Europe. Body lice are known to be the vectors of *B. quintana*.

Methods We studied all the homeless people who presented in 1997 to the emergency departments of the University Hospital, Marseilles, France. Blood was collected for microimmunofluorescence testing for antibodies against *B. quintana* and for culture of the bacterium. Body lice were collected and analyzed by the polymerase chain reaction and sequencing of a portion of the citrate synthase gene of *B. quintana*.

Results In 10 of 71 homeless patients (14 percent), blood cultures were positive for *B. quintana*, and 21 of the patients (30 percent) had high titers of antibody against the organism. A total of 17 patients (24 percent) had evidence of recent infection (bacteremia or seroconversion). Tests of lice from 3 of the 15 patients from whom they were collected were positive for *B. quintana*. The homeless people with *B. quintana* bacteremia were more likely to have been exposed to lice ($P=0.002$), were more likely to have headaches ($P=0.03$) and severe leg pain ($P<0.001$), and had lower platelet counts ($P=0.006$) than the homeless people who were seronegative for *B. quintana* and did not have bacteremia; 8 of the 10 patients with bacteremia were afebrile. Five patients had chronic bacteremia, as indicated by positive blood cultures over a period of several weeks.

Conclusions In an outbreak of urban trench fever among homeless people in Marseilles, *B. quintana* infections were associated with body lice in patients with nonspecific symptoms or no symptoms. (N Engl J Med 1999;340:184-9.)

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TRENCH fever, the first reported clinical manifestation of infection with *Bartonella quintana*, was first recognized during World War I, when it is estimated to have affected more than 1 million people, with outbreaks reported in Russia and on the European fronts.¹ The disease was described as a five-day fever with clinical manifestations ranging from fever alone to serious illness with severe headaches and leg pain. Body lice were shown to be the vector, and improvements in hygienic con-

ditions have prevented large outbreaks since that time. New manifestations of infection with *B. quintana* were described in 1992 in patients with bacillary angiomatosis who were infected with the human immunodeficiency virus (HIV).² Since then, we and others have shown that the organism may also cause endocarditis with bacteremia.^{3,4} Homeless people and people with alcoholism are at risk for *B. quintana* infection. The reemergence of trench fever has been confirmed in Marseilles, France,⁵ in Seattle,⁶ in Baltimore (among injection-drug users),⁷ and in Burundi.⁸ However, the current clinical spectrum of the disease and the vector involved in urban trench fever have yet to be determined. After completing a two-year seroepidemiologic study in Marseilles, we investigated *B. quintana* infections and their relation to lice among homeless people who presented to the emergency department.

METHODS

Patients

From January 1 to December 31, 1997, we studied all the homeless people (people without a personal address) who presented to the emergency departments of the University Hospital in Marseilles. Informed consent was provided by all patients. On initial presentation they were given a full physical examination, and blood was collected for culture for *B. quintana* and serologic testing. An information form with clinical and epidemiologic data was completed, and lice, if present, were collected. Routine laboratory tests, including serologic tests for HIV, were performed. If their symptoms warranted hospitalization, patients could be admitted. Patients who were discharged and who returned to the emergency department were hospitalized if they were found to have bacteremia or to have positive results on serologic testing for *B. quintana*.

All the hospitalized patients were examined by one of us, and additional samples were collected for culture for *B. quintana* and serial serologic tests. Hospitalized patients were then treated with doxycycline at a dosage of 200 mg per day for 15 days, except in the case of Patient 9, who had high antibody titers and who was treated with doxycycline as well as gentamicin (3 mg per kilogram of body weight once per day) for 4 weeks. In patients with antibody titers greater than 1:400 (Patients 7, 9, and 11), transthoracic echocardiography was performed to determine whether endocarditis was present. Persons who were not homeless who presented to the emergency department were used as control subjects and were matched for sex, age (within four years), clinical presentation, and date of presentation (within one week) with the

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homeless patients. For serologic studies, an additional 250 serum samples were randomly obtained from healthy blood donors.

Collection of Specimens and Isolation Procedures

Blood-culture bottles (Bactec Plus, Becton Dickinson Diagnostic Instrument Systems, Sparks, Md.) were used. If no bacterial growth was detected after 7 days, 1 ml of inoculated blood-culture broth was plated onto sheep-blood agar plates (Columbia, Biomérieux, Marcy l'Etoile, France) and incubated for 45 days before the culture was deemed negative.⁹

Identification of Isolates

The polymerase chain reaction (PCR) was performed with the extracted DNA from agar-grown *B. quintana* (QIAmp Tissue Kit, Qiagen, Hilden, Germany) and primers CS 443¹⁰ and CS 979 (TGCATGATTTTGCACGTGG), which permit the amplification of a citrate synthase (*gltA*) gene fragment (unpublished data). Sequencing of the PCR product was carried out with the Ampli-Cycle sequencing kit (Perkin Elmer, Foster City, Calif) and fluorescein-labeled forms of the above primers. Molecular detection of *B. quintana* from lice was performed as reported elsewhere.⁸

Serologic Testing

Serum samples were tested for IgM and IgG by indirect immunofluorescence assay. *B. quintana* Oklahoma, a reference strain (provided by D.F. Welch, University of Oklahoma, Oklahoma City), *B. henselae* Houston (American Type Culture Collection 49882), and *B. henselae* serotype Marseilles¹¹ were used as described previously.¹² Seroconversion was considered to have occurred if a high titer (greater than 1:100) was observed in a previously seronegative patient.

RESULTS

Blood Cultures

A total of 186 blood samples, from 71 homeless people who presented 120 times at emergency departments and of whom 46 were hospitalized, were cultured. Most of the blood cultures (112, or 60.2 percent) were prepared and tested between October 1 and December 31, 1997 (Table 1); 36 cultures from 10 patients were positive for *B. quintana*, and 5 of these 10 patients had chronic bacteremia (Table 2). In the case of Patient 4, 11 of 19 blood cultures were positive over a one-month period; in the case of Patient 6, 5 of 8 blood cultures were positive over a two-week period; in the case of Patient 7, 2 of 7 blood cultures were positive over a five-week period; in that of Patient 8, 4 of 7 blood cultures were positive over a five-week period; and in that of Patient 9, 7 of 10 blood cultures were positive over a six-week period. The mean length of time required for isolation of the pathogen in culture was 24 days (range, 5 to 42 days), but 2 of the 36 positive cultures were identified by the automated blood-culture system in less than 7 days. None of the cultures of blood samples from the 31 control subjects were positive (P<0.02). No other important organisms were recovered from blood culture.

Serologic Testing

Of the 134 serum samples tested from the 71 homeless patients, 34 samples from 21 patients (30

TABLE 1. HOMELESS PEOPLE WHO PRESENTED TO EMERGENCY DEPARTMENTS IN MARSEILLES IN 1997 AND THE RESULTS OF BLOOD CULTURES AND SEROLOGIC TESTS.

MONTH	NO. OF PRESENTATIONS	BLOOD CULTURES		SEROLOGIC TESTS	
		NO. PERFORMED	NO. POSITIVE	NO. PERFORMED	NO. POSITIVE
January	5	10	1	7	0
February	2	4	2	2	1
March	1	2	0	1	0
April	10	11	0	10	1
May	1	1	1	1	0
June	8	16	1	10	3
July	4	19	10	7	0
August	6	6	0	6	1
September	3	5	0	3	1
October	9	16	2	9	2
November	29	36	3	36	10
December	42	60	16	42	15
Total	120	186	36	134	34

percent) had positive results on immunofluorescence assay for *B. quintana*, 3 had positive results for *B. henselae* Houston, and none had positive results for *B. henselae* Marseilles. The three patients with positive results for *B. henselae* were those with *B. quintana* antibody titers of up to 1:400. In 10 patients (14 percent), 4 of whom had positive blood cultures, seroconversion was demonstrated. Altogether, 17 homeless patients had evidence of acute infection (bacteremia or seroconversion) during the year. The 31 control patients (P<0.001 for the comparison with homeless patients) and the 250 blood donors had negative titers (<1:100) of antibodies to *B. quintana*. All the homeless patients and all the control patients were seronegative for HIV.

Detection of *B. quintana* in Lice

Lice from 15 homeless patients were tested. In none of the lice samples were inhibitors of the PCR present. *B. quintana* DNA was detected in lice from three homeless patients, of whom two (Patients 6 and 10) had bacteremia and one (Patient 11) was seropositive but negative on blood culture. No DNA amplification was observed in uninfected control lice.

Patients

Clinical observations in 10 patients with bacteremia are summarized in Table 3. To determine risk factors, patients were grouped according to the data collected (Table 4). Group A consisted of homeless patients with bacteremia; group B consisted of patients without bacteremia but with high titers of anti-

TABLE 2. RESULTS OF LABORATORY TESTS IN PATIENTS WITH EVIDENCE OF *B. QUINTANA* INFECTION.*

PATIENT No.	SEX	AGE (YR)	BLOOD-CULTURE RESULTS (DATE)†	ANTIBODY TITERS (DATE)‡		AMPLIFICATION OF BODY-LICE <i>gItA</i>
				FIRST SAMPLE	LAST SAMPLE	
1	M	54	+ (1/06)	<1:100	<1:100	ND
2	M	34	+ (10/29)	<1:100	ND	–
3	M	21	+ (2/10)	<1:100	<1:100	ND
4	M	42	+ (6/17, 7/17)	<1:100	<1:100	ND
5	M	52	+ (5/16)	<1:100	<1:100	ND
6	M	44	+ (12/2, 12/17)	<1:100	<1:100	+
7	M	55	+ (11/12, 12/16)	<1:100 (8/29)	1:400 (11/19)	ND
8	M	41	+ (11/7, 12/16)	<1:100 (11/12)	1:100 (12/10)	ND
9	M	45	+ (11/10, 12/29)	<1:100 (11/13)	1:1600 (12/14)	ND
10	M	55	+ (12/23)	<1:100 (1/7)	1:100 (12/23)	+
11	F	36	–	1:400 (12/1)	1:400 (12/7)	+
12	M	59	–	<1:100 (10/22)	1:200 (11/15)	ND
13	M	63	–	<1:100 (1/5)	1:200 (11/25)	ND
14	M	55	–	<1:100 (1/6)	1:200 (6/24)	ND
15	M	40	–	<1:100 (1/3)	1:200 (9/4)	ND
16	M	38	–	<1:100 (11/22)	1:100 (12/20)	ND
17	M	62	–	<1:100 (4/1)	1:200 (12/29)	–

*ND denotes not done. All dates are in 1997.

†Dates for blood culture are the dates of the first and last positive results. In Patients 1, 2, 3, 5, and 10, only one blood culture was tested.

‡Dates are not provided for Patients 1 through 6 because no seroconversion occurred.

body against *B. quintana*; group C combined groups A and B and consisted of patients who had been exposed to *B. quintana*, as shown by the presence of bacteremia or reactive antibodies to *B. quintana*; and group D consisted of homeless people without bacteremia who were seronegative for antibody against *B. quintana*. Among the 71 homeless people studied, blood cultures were positive for *B. quintana* in 10 patients (14 percent). These patients with bacteremia (group A) were more likely to have leg pain ($P < 0.001$), headaches ($P < 0.03$), thrombocytopenia (platelet count, $< 150,000$ per cubic millimeter) ($P = 0.006$), and were more frequently infested with body lice ($P < 0.002$) than homeless people who were seronegative for *B. quintana* (group D). Comparison of patients with bacteremia (group A) and patients with only positive serologic results (group B) demonstrated that leg pain ($P = 0.01$) and thrombocytopenia ($P = 0.017$) were more prevalent in patients with bacteremia. Only one patient described the typical pain in the shin. For homeless people, the risk of exposure to *B. quintana* (i.e., of being in group C) is associated with the presence of body lice ($P = 0.002$).

To evaluate the prevalence of nonspecific clinical signs associated with homelessness, we compared all the homeless patients (group E in Table 4) to a control group of patients who were not homeless (group

F), and to homeless patients without evidence of exposure to *B. quintana* (group D). Common among the homeless people (group E) were headaches, leg pain, body lice, alcoholism, and the absence of Achilles reflexes, and those among them who were hospitalized for leg pain were more likely to be infected with *B. quintana*. Acute bacteremic trench fever among the homeless patients was associated with the presence of body lice, headaches, and thrombocytopenia, but not fever. Fever was also not significantly associated with the presence of antibodies against *B. quintana*. No cardiac vegetations were observed in the patients who underwent echocardiography (Patients 7, 9, and 11), and none of those patients have been hospitalized since for endocarditis.

DISCUSSION

The various species of bartonella share common characteristics, such as the ability to cause chronic infections, especially bacteremia, in their natural hosts^{13,14} and close association with their hosts' cells, especially erythrocytes.^{15,16} To date, humans are the only known hosts of *B. quintana*,¹⁷ but in our study we found relatively few overt manifestations of *B. quintana* infection in homeless people. The bacteremia was chronic in five of our patients, however, indicating that the infection can be chronic in humans, as is the case with *B. henselae* infection in cats.

CHRONIC BARTONELLA QUINTANA BACTEREMIA IN HOMELESS PATIENTS

TABLE 3. CLINICAL PRESENTATION OF 10 HOMELESS PEOPLE WITH CULTURES POSITIVE FOR *B. QUINTANA*.

CHARACTERISTIC	PATIENT No.									
	1	2	3	4	5	6	7	8	9	10
Sex	M	M	M	M	M	M	M	M	M	M
Age (yr)	54	34	21	42	52	44	55	41	45	55
Geographic origin	North Africa	Eastern Europe	North Africa	Western Europe	North Africa	Western Europe	Western Europe	North Africa	Western Europe	Eastern Europe
Reason for hospitalization	Confusion	Hypothermia	Tonsillitis	Fall in the street	Tibial pain	Head trauma	Pneumonia	Leg pain	Leg pain	Erysipelas
Clinical finding										
Alcoholism	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Leg pain	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Confusion	Yes	No	No	No	No	No	No	No	No	No
Fever	No	Yes	Yes	No	No	Yes	No	No	No	Yes
Loss of Achilles reflexes	Yes	No	Yes	Yes	Yes	No	Yes	No	No	No
Pruritic lesions	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Body lice	No	No	Yes	Yes	No	No	No	No	No	Yes
Myalgia	No	No	Yes	No	No	No	No	No	No	No
Sweats	No	No	No	Yes	No	Yes	No	No	No	No

TABLE 4. EPIDEMIOLOGIC, CLINICAL, AND LABORATORY INFORMATION FOR 71 HOMELESS AND 31 CONTROL PATIENTS.*

VARIABLE	GROUP A (N=10)	GROUP B (N=16)	GROUP C (N=26)	GROUP D (N=45)	GROUP E (N=71)	GROUP F (N=31)	P VALUE†			
							A vs. B	A vs. D	C vs. D	E vs. F
Mean age (yr)	45.5	52.6	47.9	46.8	53.3	57.8				
Hospitalization	9/10	11/16	20/26	26/45	47/71	31/31	NS	NS	NS	NS
Temperature, >38°C	4/10	3/16	6/26	10/45	17/71	14/31	NS	NS	NS	NS
Leg pain	9/10	6/16	15/17	8/45	24/62	1/31	0.01	<0.001	<0.001	<0.001
Lack of Achilles reflexes	5/10	4/11	8/20	8/45	17/65	0/31	NS	0.045	NS	<0.001
Headache	4/10	3/16	7/26	4/45	12/71	2/31	NS	0.03	0.048	<0.001
Lice or scratching‡	9/10	11/16	19/26	16/45	36/71	2/31	NS	0.002	0.002	<0.001
Alcoholism	9/10	16/16	24/26	43/45	68/71	4/28	NS	NS	NS	<0.001
Male sex	9/10	15/16	24/26	44/45	69/71	31/31	NS	NS	NS	NS
Sweats	2/10	0/16	2/26	6/45	8/71	2/29	NS	NS	NS	NS
Rash	0/10	0/16	0/26	2/45	2/71	0/31	NS	NS	NS	NS
White-cell count, >5000/mm ³	2/10	5/16	6/25	6/36	13/62	11/31	NS	NS	NS	NS
γ-Glutamyltransferase, >60 U/liter	4/10	6/16	9/25	12/36	22/62	12/31	NS	NS	NS	NS
Aspartate aminotransferase, >50 U/liter or alanine aminotransferase, >60 U/liter	5/10	5/16	9/25	7/37	16/62	13/31	NS	NS	NS	NS
Creatinine, >125 μmol/liter (>1.4 mg/dl)	0/10	1/16	1/25	1/36	2/62	0/31	NS	NS	NS	NS
Platelet count, <150,000/mm ³	6/10	2/16	8/25	5/36	13/62	3/31	0.017	0.006	NS	NS
Hospitalization for leg pain	5/10	0/16	5/26	0/45	5/71	0/31	0.004	<0.001	0.005	NS
Lice with <i>B. quintana</i> DNA	2/3	1/2	3/5	0/10	3/15	0/0	NS	0.04	0.02	NS
Bacteremia	10/10	0/16	10/26	0/45	10/71	0/31	NS	NS	NS	0.02
Titer of antibody against <i>B. quintana</i> , ≥1:100	4/10	16/16	20/26	0/45	20/71	0/31	NS	NS	NS	0.001
Seroconversion	4/10	6/16	10/26	0/45	10/71	0/31	NS	NS	NS	0.02

*Values other than those for age are numbers of patients with the characteristic and of all patients with data available in the group. Group A consisted of homeless patients with blood cultures positive for *B. quintana*, group B homeless patients with blood cultures negative for *B. quintana* but positive serologic tests, group C the patients in groups A and B considered together, group D homeless patients with blood cultures negative for *B. quintana* and negative serologic tests, group E the patients in groups C and D considered together, and group F control patients. For some variables, denominators are less than the total number of patients in the group because not all the patients were tested. NS denotes not significant.

†P values were determined by Fisher's exact test.

‡Scratching was considered indirect evidence of the presence of lice.

Primary isolation of bartonella from the blood of infected patients, which can be accomplished by a variety of techniques,^{3,4,18-21} is difficult, and it may take up to 45 days before colonies become apparent. In our study, an automated blood-culture system proved to be highly effective, enabling us to isolate *B. quintana* from 10 of 71 homeless patients. Seropositivity for *B. quintana* was clearly associated with homelessness: 21 of 71 homeless patients (30 percent) had titers of antibody to *B. quintana* greater than 1:100, whereas none of the 31 control patients or 250 blood donors were seropositive. Seroconversion was observed in 10 of 21 of the homeless patients, and of these 10 patients, 4 had a blood culture that was positive for the bacterium. The seroprevalence of 30 percent is much higher than the 16 percent seroprevalence we reported previously⁵ and confirms the existence of an outbreak in Marseilles.

The detection of *B. quintana* in lice from patients with bacteremia strongly suggests that body lice play a part in the infection of humans, as they did in trench fever under wartime conditions.²² *B. quintana* infections in lice are thought to evolve over periods as long as a year,¹ so infestation of humans with infected lice cannot be considered indicative of transmission of infection. Nevertheless, the persistence of bacteremia, as in Patients 4, 6, 7, 8, and 9 in our study, probably facilitates the transmission of *B. quintana* to other lice. In experimental infection, lice may become infected while feeding on patients with bacteremia up to 76 days after the onset of disease.²³ The use of techniques based on the PCR to detect pathogens in arthropod vectors has become common,²⁴ and we have used this approach to demonstrate the presence of *Rickettsia prowazekii* and *B. quintana* in lice from patients with fever during an outbreak of epidemic typhus in Burundi.⁸ The PCR is rapid and is indicative of active infection, yielding positive results in 3 of 5 lice from recently or currently infected patients as compared with 0 of 10 lice from uninfected patients ($P < 0.02$).

Currently, our understanding of the epidemiology of *B. quintana* infections is limited, although the occurrence of the disease is strongly associated with poor living conditions. In a previous study, we showed that the incidence of endocarditis due to *B. quintana* is significantly associated with homelessness and alcoholism.¹⁸ Koehler et al.² showed that there was a significant association between the incidence of bacillary angiomatosis due to *B. quintana* and the presence of lice and homelessness. Jackson et al.⁶ found that 20 percent of homeless people in Seattle had positive serologic tests for *B. quintana*. Similarly, Comer et al.⁷ found that 33 percent of people in Baltimore who abused intravenous drugs had antibodies to bartonella. Of 104 people who worked with lice in a laboratory, trench fever developed in

90, and of 14 apparently healthy people, chronic bacteremia and low antibody titers developed in 5.²⁵

In early reports of trench fever, the outstanding features of typical cases were the sudden onset of marked headaches, general body pain, polymorphonucleosis, and spiking, relapsing fevers.^{26,27} In contrast to these observations, which were supported by the findings of Spach et al.³ in Seattle, there was no significant association in our patients between febrile reactions and acute bacteremic trench fever or recent infection. In experimental infections in human volunteers, the incubation period of trench fever was two to nine weeks²³ and the clinical manifestations were extremely variable, ranging from low-grade fever to typical, severe trench fever.

Our study has shown, however, that the absence of fever does not preclude the possibility of infection with *B. quintana*. Only 2 of 10 of our patients with bacteremia had fever (temperature above 38°C) when blood cultures were performed, and in all these patients the febrile reaction may have had other causes, mainly tonsillitis and erysipelas. However, homeless people in Marseilles can present with typical manifestations of trench fever,²⁸ suggesting that the disease may have two main clinical presentations. The first is an acute form characterized by high-grade fever, leg pain, granulocytosis, and a rapid antibody response, whereas the second is chronic, without fever, and is characterized by prolonged bacteremia and delayed antibody responses.

A chronic form of trench fever was described in early reports of *B. quintana* infections. In an experimental model in which three volunteers were inoculated with *B. quintana*, two of the subjects had no febrile reaction, seroconversion occurred in only one, and all three had chronic bacteremia lasting 38 to 76 days.²³ Kostrzewski reported the isolation of *B. quintana* from the blood of people who had had trench fever up to eight years previously.²⁵ He studied a group of 39 patients who had chronic bacteremia, 10 of whom had no clinical signs of infection and, surprisingly, as in our study, 1 of whom had tonsillitis.

The natural history of *B. quintana* infection could be described tentatively as follows. The bacteria are transmitted to people after infestation by infected body lice. After inoculation with *B. quintana*, acute trench fever develops in some patients,^{26,28} who also may have moderate titers of antibody to *B. quintana*. Other patients have a chronic infection, with clinical signs including chronic lymphadenopathy,^{20,29} and if the immune system is compromised, especially in patients infected with HIV, bacillary angiomatosis characterized by subcutaneous and lytic bone lesions without peliosis hepatis may develop.³⁰ As previously observed in the United States³ and also as observed in our study, homeless people are at risk for chronic bacteremia associated with a paucity of clinical signs and, in particular, an absence of fever.

In the chronic forms of the disease, no antibody responses can be detected, and the detection of low antibody titers seems to indicate recovery. High antibody titers in chronically infected people could be associated with the presence of endocarditis.^{4,18}

We believe that *B. quintana* infections are far more prevalent than is currently recognized. The potential for outbreaks of other louse-borne infections, such as epidemic typhus and relapsing fever, cannot be ignored, and active surveillance programs should be encouraged.

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