Bartonella henselae as a Cause of Prolonged Fever and Fever of Unknown Origin in Children

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A prospective evaluation of 146 children with fever of unknown origin (FUO) and prolonged fever was performed from 1990 to 1996. FUO was defined as a documented daily temperature of ≥38°C for at least 14 days without diagnostic signs or symptoms. Prolonged fever was defined as fever for at least 14 days and no diagnosis at the time of referral for evaluation. An established diagnosis was made for 84 (57.5%) of 146 patients. The most common infectious disease diagnoses were Epstein-Barr virus infection (22 [15.1%] of 146), osteomyelitis (14 [9.6%] of 146), bartonellosis (7 [4.8%] of 146), and urinary tract infection (6 [4.1%] of 146). Three of seven patients with confirmed Bartonella henselae infection presented with FUO and no ultrasonographic findings compatible with hepatosplenic involvement; two patients presented with FUO and hepatosplenic involvement. The relatively common finding of acute bartonellosis in this population suggests that FUO and prolonged fever in children are other presentations of infection with B. henselae.

Fever of unknown origin (FUO) has had variable definitions in the medical literature. Petersdorf and Beeson [1] defined FUO in 1961 as fever persisting for >3 weeks, documented temperature of >101°F on several occasions, and an uncertain diagnosis after intensive study for at least 1 week. Subsequently, Dechovitz and Moffet [2] in 1968 defined FUO in children as fever lasting for >2 weeks for which no diagnosis could be made. Although several studies have demonstrated the differences in diagnostic criteria and categories between adults and children, infectious disease etiologies have predominated in confirmed cases [1–10]. Prolonged fever can manifest with a similar duration but will have clinical signs or symptoms that suggest a specific differential diagnosis [6].

New infectious disease etiologies have continuously been added to the list of causes of FUO in children. Epstein-Barr virus (EBV), Lyme disease, hepatitis viruses, and HIV are examples of new entities added in recent years [7, 9, 11]. This prospective evaluation from 1990 to 1996 continues to emphasize EBV, with and without clinical infectious mononucleosis, as a major contribution to FUO and prolonged fever in children. The other categories that differ from previous reported experiences of FUO in children include an increase in cases of osteomyelitis of the axial skeleton and infections due to different presentations of acute bartonellosis. Bartonella henselae infection manifesting as typical cat-scratch disease (CSD) has been described in children presenting with persistent or prolonged fever [12, 13]. Recently, Golden [14] described two children with “atypical CSD” (hepatosplenic CSD) who were febrile for 2.5 and 3 weeks, respectively. Since patients with hepatosplenic CSD can present with persistent fever [14,15], this entity has been considered for inclusion in the differential diagnosis of prolonged fever in children.

To date, those patients for whom CSD has been diagnosed and who have presented with FUO or prolonged fever have had hepatosplenic involvement. We describe seven children with the presentation of FUO or prolonged fever in whom infection with B. henselae was confirmed serologically. Two children presented with signs and symptoms consistent with typical CSD, and two children presented with hepatosplenic involvement; however, three children presented with FUO and no clinical or radiographic manifestations of typical or hepatosplenic CSD. Bartonellosis should be considered in the initial evaluation of FUO and prolonged fever in children with specific epidemiological exposures, especially to kittens and/or cats.

Methods

Since 1990, a prospective database of all children for whom FUO and prolonged fever have been diagnosed has been collected to assess the continued evolution of infectious disease diagnoses. The definition of FUO for this study included documented and recorded daily temperature of ≥38°C (core temperature) for at least 14 days and no diagnostic signs or symptoms of an obvious clinical disease. A diagnosis of prolonged fever required the same temperature criteria plus no diagnosis at the time of referral for evaluation and no previous diagnosis or clinically apparent features of a congenital or acquired immunodeficiency. Patients were classified as having prolonged fever instead of FUO if the subsequent evaluation was indicative of a clinical disease presentation that suggested a specific diagnosis (i.e., regional lymphadenitis plus associated cat exposure – CSD).
A focused approach utilizing an institutional protocol for evaluation of children with FUO and prolonged fever was employed as described previously [7]. The initial evaluation was carried out in either an inpatient or outpatient setting and usually included determination of complete blood cell count, erythrocyte sedimentation rate (ESR), and hepatic enzyme levels; chest roentgenography; urinalysis and urine culture; blood culture; tuberculin skin test; and obtaining acute-phase serum samples for future use. The most common assay performed was EBV serology because of the finding of EBV infection as the most likely infectious disease diagnosis in a previous study from our institution [7].

All microbiological, virological, and serological studies were individualized on the basis of the initial history of present illness, contact and exposure history, season, physical examination, initial laboratory studies, and radiographic evaluation. All patients were followed up with the use of a temperature and symptom diary by the parents. Temperatures (rectal, oral, or axillary) were taken three times daily with a written numerical record and site of determination record and on any occasion when the parent thought that the child appeared febrile or symptomatic. Signs and symptoms were included in a narrative corresponding to the body temperature and time of day. During hospitalization, temperatures taken by a registered nurse were recorded (to include site of determination) at least once per 8-hour shift.

On the basis of findings of a previous study in our institution [7], an abdominal ultrasound examination was performed on all children with FUO or prolonged fever and abdominal signs or symptoms, an elevated ESR, or elevated hepatic enzyme levels. All patients with serological evidence of acute infection with \textit{B. henselae} underwent an abdominal ultrasound examination.

\textbf{Infectious disease diagnoses.} Urinary tract infections, cytomegalovirus or enterovirus infections, and blastomyocytosis were confirmed microbiologically. In cases of osteomyelitis, positive cultures of blood, bone aspirates, joint fluid, or biopsy specimens were considered diagnostic. All other cases of osteomyelitis were confirmed in patients with compatible signs and symptoms for whom a bone scan, CT, MRI, or a combination of these images was positive. EBV infection, bartonellosis, HIV infection, tularemia, and ehrlichiosis were diagnosed serologically by using commercial assays and definitions. EBV serology included an IgM antibody to viral capsid antigen (VCA) (indirect fluorescent antibody test: positive titer, >1:10; Gull Laboratories, Salt Lake City). Acute EBV infection was diagnosed when there was a positive titer of IgM antibody to VCA or a fourfold rise in titers of IgG antibody to VCA (indirect fluorescent antibody test: positive titer, >1:320; Grandbio, Temecula, CA).

Evidence of HIV infection was diagnosed for a patient older than 15 months of age when HIV type 1/HIV type 2 serology (EIA, Abbott Laboratories, Abbott Park, IL) was positive. Tularemia was diagnosed with a positive slide and tube agglutination titer (titer in acute-phase serum of $\geq 1:160$ or fourfold rise in titer; Difco Laboratories, Detroit). Acute ehrlichiosis was diagnosed with a positive titer in acute-phase serum of antibody to \textit{Ehrlichia chaffeensis} or the human granulocytic ehrlichia agent (indirect fluorescent antibody test: positive titer of $\geq 1:64$ or fourfold rise in titer; Mayo Medical Laboratories, Rochester, MN). \textit{B. henselae} serology was performed by indirect immunofluorescence assay (reference negative titer: IgM, <1:20; IgG, <1:64; Microbiology Reference Laboratory, Cypress, CA). A positive titer included $>1:20$ for IgM or a fourfold rise in titer of IgG. These assays have been shown to have a sensitivity of 84%–100% and a specificity of 96%–100% [16, 17].

\section*{Case Reports}

\subsection*{Case 1}

A 45-month-old girl presented with a 16-day history of fever (daily temperature, $\geq 38^\circ$C). Her illness began with fever, listlessness, and anorexia. On day 2 of illness, she was taken to her local pediatrician, and pharyngitis was diagnosed without laboratory testing. Therapy with a 10-day course of oral penicillin was started without resolution of symptoms. Her listlessness and anorexia continued, but no specific signs or symptoms were apparent. She denied any history of abdominal pain, headache, myalgias, nausea, vomiting, diarrhea, nasal congestion, or rash. She had a history of exposure to ticks, cats, and kittens.

At the time of physical examination, she was afebrile and had a relatively normal level of activity. The remainder of the examination was nonfocal and unremarkable. A PPD skin test was performed and, at 48 hours, showed no induration. Her EBV serology revealed no evidence of recent or past infection. Her tularemia and ehrlichiosis serologies were negative. Her serology for \textit{B. henselae} revealed the following titers: IgG, 1:1,024; IgM, 1:80. An abdominal ultrasound examination with visualization of the liver and spleen was unremarkable. Following her diagnosis of \textit{B. henselae} infection, a return clinic visit revealed that her fever had abated 7 days after the initial evaluation. No therapy was given, and she had no evidence of complications.

\subsection*{Case 2}

A 13-year-old girl was referred to our institution following a 22-day history of daily temperatures of $>38^\circ$C. Her history included fever, intermittent myalgias, headache, and anorexia. She was treated with antipyretics for control of fever and symptoms. Over the ensuing 5 days, her daily fevers continued, and she returned to her primary care physician. She was given a 10-day course of oral cefprozil for treatment of an uncertain diagnosis but returned 6 days later with continued fever and worsening myalgias, headache, and anorexia. On the 22nd day of fever, she was referred for evaluation.

At the time of presentation, she was febrile (temperature to 39.2°C) with complaints of myalgias, headache, and anorexia. She denied photophobia but described a frontal to bitemporal
Table 1. Diagnosis by category of FUO and prolonged fever in 146 children from 1990 to 1996.

<table>
<thead>
<tr>
<th>Category</th>
<th>No. (%) of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established diagnosis</td>
<td>84 (57.5)</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>64 (43.8)</td>
</tr>
<tr>
<td>Autoimmune disorder</td>
<td>11 (7.5)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Other*</td>
<td>5 (3.4)</td>
</tr>
</tbody>
</table>

NOTE. FUO = fever of unknown origin.
* Drug-induced FUO (3 patients), sarcoid FUO (1), and mercury poisoning FUO (1).

Table 2. Infectious disease etiologies in 64 children with FUO and prolonged fever from 1990 to 1996.

<table>
<thead>
<tr>
<th>Infectious disease</th>
<th>FUO</th>
<th>Prolonged fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr virus infection</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>12*</td>
<td>2*</td>
</tr>
<tr>
<td>Bartonellosis</td>
<td>5†</td>
<td>2†</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Enterovirus infection</td>
<td>1</td>
<td>1†</td>
</tr>
<tr>
<td>Cytomegalovirus infection</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>HIV infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tularemia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ehrlichiosis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>16</td>
</tr>
</tbody>
</table>

NOTE. CSD = cat-scratch disease; FUO = fever of unknown origin.
* Intervertebral disk space/vertebral body osteomyelitis (8 patients), pelvic osteomyelitis (3), vertebral body osteomyelitis (2), and pyogenic sacroiliitis/ pelvic osteomyelitis (1).
† Two patients with CSD, two patients with hepatosplenic CSD, and three patients with acute bartonellosis.
‡ One patient for whom hypogammaglobulinemia was diagnosed.
patients. The two children with prolonged fever for whom an immunodeficiency was subsequently diagnosed (HIV infection and hypogammaglobulinemia, respectively) had no previous workup or evaluation for recurrent infections. All of the cases of osteomyelitis were identified in the axial skeleton (table 2). Although two patients had localizing signs and symptoms with prolonged fever, 12 presented with FUO.

Infection due to *B. henselae* was the third most common infectious disease diagnosis and accounted for 10.4% of cases of FUO, 5.9% of confirmed diagnoses, and 7.8% of infectious disease cases. The cases of bartonellosis are described in table 3. The signs and symptoms were relatively nondescript and did not confirm a diagnosis in five of seven cases. In two cases, the presence of prolonged fever with regional lymphadenitis, fever, and cat and kitten exposure led to the presumptive diagnosis of CSD. For two patients who presented with abdominal pain, abdominal ultrasound examination revealed multiple hypoechogenic lesions in the liver and spleen that were compatible with hepatosplenic CSD. In the remaining three patients, no evidence of regional lymphadenitis or lymphadenopathy, abdominal complaints, or localizing signs could be found; these three patients had unremarkable abdominal ultrasound examinations, as did the two patients with typical CSD.

The mean duration of fever following evaluation ± SD for six patients was 9.0 ± 4.98 days (range, 2–18 days); the mean total duration of fever ± SD was 27.83 ± 4.99 days (range, 23–33 days). Three of the seven patients received antibiotic therapy, but no significant differences in outcomes were noted for this limited number of patients. All patients recovered without complications.

### Discussion

A prospective database evaluating children with prolonged fever and FUO over 6 years is presented to emphasize the impact of bartonellosis in these patient groups in Arkansas. In 1992, Gartner [8] reviewed six series of cases of FUO in children and found that 44.6% of 446 children in these series had an infectious disease etiology. Infectious disease diagnoses prominent in these series included urinary tract infections, skeletal and CNS infections, brucellosis, tuberculosis, abscesses, tularemia, infections due to enteric bacteria (*Yersinia* and *Salmonella*), EBV infection, congenital syphilis, and HIV infection. In comparison, we did not diagnose cases of abscesses, tuberculosis, brucellosis, congenital syphilis, or infections due to enteric bacteria. Our study continues to emphasize skeletal infections, urinary tract infection, and epidemiologically based infections (tularemia, ehrlichiosis, and blastomycosis) as common diagnoses for children with FUO. The significant rate of EBV infections in these patients has continued in the two studies from our institution.

Earlier studies on FUO have included cases of infectious mononucleosis, but the representation of EBV-proven disease was minor in an era before specific serology [3, 4, 6]. Although age differences existed for a “viral syndrome” etiology in children younger than 6 years of age (13 of 34) compared with older children (four of 18), infectious mononucleosis was diagnosed for a single older patient [4]. In our study, only six of 22 patients had a distinct presentation of infectious mononucleosis. Of these six patients, only one was younger than 6 years of age. In contrast, 10 of 16 patients with FUO, EBV infection, and a presentation not suggestive of infectious mononucleosis were younger than 6 years of age.

These earlier studies included children with osteomyelitis, but most studies represented single cases or patients with chronic osteomyelitis [3, 4, 6]. Osteomyelitis of the axial skeleton with a presentation of FUO was diagnosed for 9.6% of patients in this series, compared with a single patient with osteomyelitis in the 1985–1990 study [7]. The other obvious difference between the earlier studies and this database is the absence of upper respiratory tract infections. Earlier studies had sinusitis, tracheobronchitis, chronic pharyngitis, tonsillitis, peritonsillar abscess, and pneumonia as common diagnoses. Disease due to enteric bacteria, subacute bacterial endocarditis, and tuberculosis are well-established causes of FUO, but these diagnoses were not identified in our study. Although patients with each of these infections were seen during this study period, none presented with the criteria of FUO or prolonged fever that were used in this study.

*B. henselae* infection manifesting as FUO or prolonged fever was the cause of 4.8% of the total cases, 8.3% of the confirmed diagnoses, and 10.9% of the infectious disease diagnoses in our study. In 1977, Lohr and Hendley [6] described 54 children with FUO and a diverse pattern of fevers that included intermittent, intermittent, and relapsing fever over a 3-week period in the outpatient setting or for 1 week on the inpatient service. Of the 18 patients with an infectious disease etiology, one patient with CSD was described. In a subset of 23 patients with CSD and prolonged or recurrent severe bacterial infections, Margileth and colleagues [12] described prolonged morbidity...
that included fever, malaise, fatigue, myalgia, arthralgia, skin eruptions, weight loss, and splenomegaly. Of 18 patients for whom detailed information was available, nine (50%) had a temperature of ≥38.0°C for at least 14 days. Therefore, fever for >14 days has been described in cases of typical CSD and atypical CSD with abdominal pain, hepatomegaly, and/or splenomegaly [14, 18, 19].

With the availability of serological tests for B. henselae [20], the ability to culture the organism [21], PCR techniques to detect the organism, and molecular studies to classify the organism, a variety of clinical descriptions have been reported [22]. Although infections were serologically confirmed, culture and/or PCR analysis was unavailable in this study. Four clinical syndromes have been described, including bacillary angiomatosis, bacillary peliosis hepatitis, relapsing fever with bacteremia, and CSD. Hepatosplenic CSD was described in 1985 [23]. Four additional cases in children with FUO (fever for >4 weeks in each case), abdominal pain, and regional lymphadenopathy (axillary, epitrochlear, and cervical) were reported in 1988 [18]. Although both of our patients with FUO and hepatosplenic CSD had abdominal pain, only one had lymphadenopathy. Neither patient had regional lymphadenopathy.

Typical or atypical CSD and bartonellosis without hepatosplenic involvement should be added to the differential diagnosis of FUO in children, especially for those with a history of significant cat or kitten exposure. With new information regarding fleas as a vector for transmission of organisms to cats [24], the possibility of arthropod transmission of infection awaits further investigation. This prospective study did not address questions related to specific antibiotic therapy. Controlled trials are needed to determine the type of therapy and antibiotics that are effective as treatment of CSD, atypical CSD, hepatosplenic CSD, or FUO (with or without bacteremia). A new presentation of bartonellosis has been described, and it will probably not be the last. In an era of expanding serological assays and molecular microbiology, it is not surprising that infectious causes were diagnosed for a higher percentage of children with FUO.

Although our data represent patients with FUO and prolonged fever in the same study, the overall rate and breakdown of the infectious disease etiologies support some important considerations. The patients seen in this study were referred to an infectious disease specialist for evaluation. In the current era of medical care, these issues are important but will become more of a standard practice in coming years. The infectious disease specialist should use these data to promote referral of this patient group. New diagnostic tests and the discovery of new human pathogens make for an interesting era for basic scientists and clinicians. The translational research efforts in the area of molecular microbiology may continue to reduce the number of undiagnosed causes of FUO and prolonged fever in children.

References