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# Fever of Unknown Origin in an 11-Year-Old Girl

***Keith Herzog, MD***

## CASE PRESENTATION

### Initial Presentation and History

An 11-year-old previously healthy girl presented to an outpatient clinic with persistent fevers. The fever, accompanied by chills and headache, started 10 days prior to her clinic visit and persisted in the range of 101°F to 105°F (38.3°C–40.5°C) on a daily basis. The headache was nonfocal and was usually worse in the evening. She had no nausea, vomiting, or overt photophobia. The only other specific complaint was transient left knee and hip pain without swelling, redness, or limp. The patient had no eye complaints, rash, or swollen nodes as well as no symptoms of upper respiratory tract infection, no abdominal pain, and no change in stool patterns, including no hematochezia or melena. The only animal contact was a pet cat. She had not travelled recently and was not exposed to populations at high risk for tuberculosis.

Past medical history was unremarkable. She had received all appropriate vaccinations, including measles-mumps-rubella and varicella-zoster virus, without adverse reactions. Family history was negative for immunodeficiency (eg, HIV), rheumatologic diseases, and periodic fever syndromes.

### Physical Examination and Laboratory Studies

On physical examination, the patient's temperature was 96.8°F (36°C) (after acetaminophen), heart rate was 103 bpm, respiratory rate was 22 breaths/min, and blood pressure was 88/60 mm Hg. Height and weight were less than the fifth percentile, but previous records revealed that she had always tracked just below the fifth percentile. The patient's current weight represented a 6-lb loss over the preceding several weeks. She was quite thin but was generally well-appearing. Examination of the head, eyes, ears, nose, and throat was normal, including no external eye findings, papilledema, sinus tenderness, or oral ulcers. She had normal lymphoid tissue with no adenopathy. Lungs were clear, and cardiac examination revealed no murmur. The abdomen was soft with no hepatosplenomegaly, extremities were normal with no effusions or redness, and skin examination revealed no lesions.

Preliminary laboratory studies and computed tomography (CT) of the head and sinuses were ordered, and the patient was initially followed as an outpatient. Results of blood chemistries, including liver transaminases, were normal. Complete blood count (CBC) revealed a white blood cell count of $15.5 \times 10^3/\mu L$ with 74 neutrophils, 17 lymphocytes, and 8 monocytes; no atypical lymphocytes or blasts were seen. Additional laboratory results were as follows: hemoglobin level, 10.2 g/dL (normal, 11.2–16.5 g/dL); platelet count, $40.9 \times 10^3/\mu L$ (normal, $15–40 \times 10^3/\mu L$); erythrocyte sedimentation rate (ESR), 115 mm/hr (normal, 0–15 mm/hr); and C-reactive protein, 10 mg/dL (normal, 0–0.15 mg/dL). Urinalysis was normal, Epstein-Barr virus (EBV) titers were negative, HIV titer was negative, blood culture was negative, and tuberculin purified protein derivative (PPD) test was negative. Chest radiograph was normal, and CT of the head and sinuses was normal.

One week after the patient's initial presentation (17 days after the onset of fever), she continued to have persistent fevers and was admitted to the hospital for further evaluation.

- **What are the diagnostic considerations in a child with prolonged fever/fever of unknown origin (FUO)?**
- **What studies are appropriate in a child with FUO?**

## APPROACH TO EVALUATION OF FEVER OF UNKNOWN ORIGIN

Much of the descriptive literature on FUO involves

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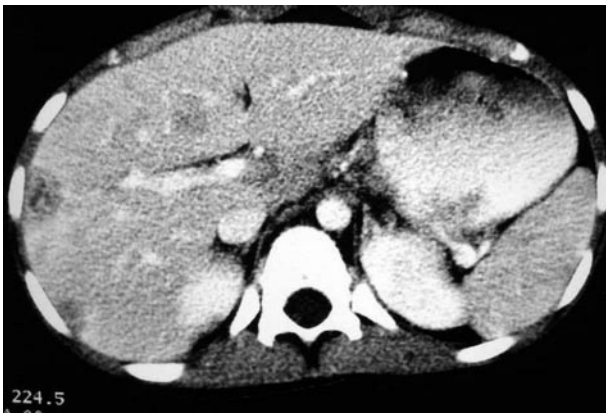


**Figure 1.** Computed tomography scan of the abdomen of the case patient demonstrating multiple focal lesions throughout the liver.

adult patients and dates to 1961, when Petersdorf and Beeson[1] described 100 patients with FUO, defined as fever greater than 38.3°C on "several" occasions over a 3-week period with no diagnosis established after 1 week of inpatient evaluation. In this case series, a diagnosis was eventually established in 93% of patients, with infectious diseases accounting for the largest percentage (36%) followed by neoplasms (19%) and collagen diseases (13%). Subsequent adult case series[2–5] employed a similar definition of FUO but assigned different diagnostic categories for noninfectious, nononcologic processes, including collagen vascular diseases,[3] multisystem diseases,[4] or noninfectious inflammatory diseases.[5] Although there was variation in the percentage of patients who remained undiagnosed, infectious diseases, including occult abscesses, urinary tract infections, endocarditis, and tuberculosis, consistently dominated established diagnoses. Other diagnoses included malignancies (hematologic disorders, solid tumors) or collagen vascular diseases/noninfectious inflammatory diseases, such as rheumatic fever (early studies), systemic lupus erythematosus, temporal arteritis, inflammatory bowel disease, and sarcoidosis.

In most of the aforementioned studies, the diagnostic approach to FUO varied. A prospective study by de Kleijn et al[5,6] employed a standardized approach to assessment and diagnostic evaluation of FUO. Features that were likely to predict a diagnosis were continuous fever (versus intermittent or recurrent), increased ESR, and low hemoglobin level. Nonspecific screening tests, such as electrolytes or liver enzymes, were not helpful in establishing a diagnosis. However, tests directed by history and physical examination, specifically CBC, chest radiograph, and abdominal ultrasound, helped lead to a diagnosis. Blood chemistries, including liver transaminases, occasionally led indirectly to diagnoses but were just as often misleading.

Studies of FUO in children have had similar findings, with some modest but important differences. Although final diagnoses were established less frequently (42%–67%), infectious diseases, including EBV infection, urinary tract infection, osteomyelitis, cat-scratch disease (CSD), and enterovirus infections, predominated to an even greater degree.[7,8] When compared with adults, autoimmune diseases were significantly less frequent in children (6%–8%), and malignancies were unusual (2%). Studies often employed early in the diagnostic evaluation included CBC, ESR, blood culture, urinalysis and urine culture, PPD test, EBV titers, viral assays (antigen detection and/or culture), and chest radiography. Even in the absence of abdominal symptoms, abdominal ultrasound or CT may be useful in revealing occult abscesses or, more rarely, tumors; however, other radiologic tests (eg, bone scan, gallium scan) used for screening are of little value. Most authors emphasize a thorough history and physical examination supplemented by basic laboratory studies to look for clinical clues. Further investigation should be guided by these clinical clues, although it may take weeks (or months) for a diagnosis to become clinically apparent.

**Key Point**

Infectious diseases are the most frequently established diagnoses in children with FUO. Fastidious history and physical examination are essential in eliciting clues to the diagnosis.

## CASE PATIENT: HOSPITAL COURSE

As part of the patient's hospital evaluation, abdominal ultrasound and CT scans were performed. The CT scan revealed multiple focal lesions with low attenuation throughout the liver (**Figure 1**). Administration of intravenous contrast resulted in peripheral enhancement of the lesions, suggesting multiple abscesses (**Figure 2**).

- **What organisms cause multiple hepatic abscesses in children?**

Multiple hepatic abscesses suggest a hematogenous source of infection. Because the liver is supplied/perfused by both the portal venous system and the hepatic artery, infection may originate from the gut (eg, perforated appendix) or systemic circulation (eg, endocarditis).[9] In the former, enteric bacilli predominate as pathogens. In the latter, *Staphylococcus aureus* is the primary pathogen, with or without immunocompromising conditions (eg, chronic granulomatous disease).[9] CSD (*Bartonella henselae*) can also involve the

liver and/or spleen.[10,11] In developing countries, amebiasis must be considered.

**Key Point**

Few screening tests lead directly to a diagnosis in patients with FUO, but abdominal ultrasound or CT may be helpful as the evaluation progresses, particularly in delineating occult abscesses.

## CASE PATIENT: CONTINUED MANAGEMENT

After the patient's abdominal CT scan, a liver biopsy was performed under ultrasound guidance without complications. Pathologic evaluatioin of a specimen from 1 lesion revealed focal necrosis with infiltration by mononuclear and polymorphonuclear inflammatory cells. Tissue stains for bacteria and mycobacteria were negative, as was a Warthin-Starry silver stain (for *B. henselae*). Cultures were negative for bacteria, fungus, and acid-fast bacilli. There was no suggestion of malignancy.

Shortly after the liver biopsy, serum studies that were ordered as an outpatient became available. Because the patient reported having a cat, serologic testing for *B. henselae* antibody had been ordered, which ultimately revealed an IgG titer greater than 1:1024.

The diagnosis of CSD could not be corroborated by classic histopathology. However, given the patient's exposure history, the compatible clinical scenario, strong serologic support, and no evidence of a more serious systemic disease (eg, malignancy), empiric therapy with intravenous gentamicin was begun. The patient's fever started to resolve before therapy was initiated, and after 3 days of treatment, the C-reactive protein level began to decrease. She was discharged on hospital day 3 with orders to continue trimethoprim-sulfamethoxazole and rifampin orally for 3 weeks. On 3-week follow-up, the patient had gained weight, remained afebrile, and was clinically well. Follow-up magnetic resonance imaging revealed complete resolution of the hepatic lesions.

**Key Point**

Exposure history is critical in the evaluation of a patient with FUO.

- **What are the common and unusual manifestations of CSD?**
- **What is the appropriate treatment for CSD?**

## CAT-SCRATCH DISEASE

### Etiology

CSD is caused by the gram-negative bacillus *B.* (formerly *Rochalimaea*) *henselae.* Cats, especially kittens (age < 1 yr), are the primary reservoir for the organism, with asymptomatic bacteremia found in up to 40% of young cats. Human inoculation is achieved through a bite or scratch (fleas may convey cat-to-cat transmission); therefore, contact with a cat (90%) and a history of bite or scratch (50%–80%) is expected when considering a diagnosis of CSD. The initial lesion is an inflammatory papule at the site of inoculation, arising in 1 to 2 weeks and lasting 1 to 4 weeks.

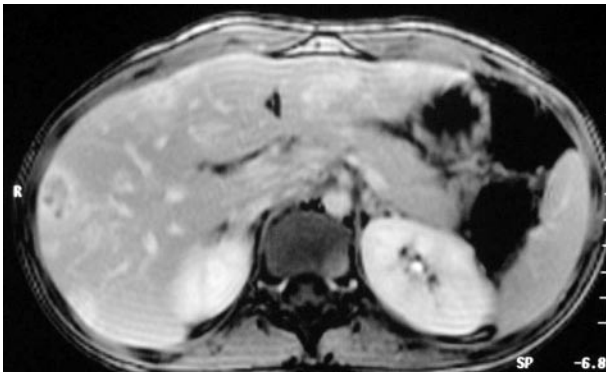


**Figure 2.** Computed tomography scan of the abdomen of the case patient after administration of intravenous contrast demonstrating peripheral enhancement of focal lesions in the liver.

### Clinical Presentation and Evaluation

The most common clinical presentation of CSD is regional lymphadenopathy (most frequently axillary lymphadenopathy followed by cervical and inguinal lymphadenopathy). CSD is the most common cause of subacute lymphadenitis in the United States.[12] In contrast to patients with acute bacterial (*S. aureus* or group A streptococcus) adenitis, cat-scratch adenitis progresses over several days to weeks, and there is usually a paucity of systemic symptoms (a minority have fever). Although up to 30% of infected nodes may drain spontaneously, most resolve over several weeks without antimicrobial therapy.

Other organ involvement in CSD is well described, including encephalopathy, hepatic and/or splenic involvement, osteomyelitis, and ophthalmic involvement. Encephalopathy is perhaps the most enigmatic manifestation; it is uncommon (≤ 2% of CSD cases) but often dramatic in onset. These patients often present with seizures, including status epilepticus,[13] and they may progress to coma that may be brief or last days. During the subacute or recovery phase, combative behavior is frequently observed. Cerebrospinal fluid findings may be normal or may demonstrate a mild mononuclear pleocytosis with slightly increased protein. Neuroimaging is often normal but may show

a variety of disseminated or focal lesions. Electroencephalogram usually shows diffuse slowing. Despite the dramatic presentation, complete recovery is common. In rare cases, direct central nervous system invasion by *B. henselae* has been suspected by molecular or antibody testing of cerebrospinal fluid, but because the pathophysiology of CSD in general is thought to involve immune-mediated mechanisms or vasculitis, antimicrobial therapy may not be necessary.

Also far less common than adenitis, hepatosplenic CSD accounts for 7% of hospitalizations for CSD[14] and may present a diagnostic dilemma. Patients often present with FUO[8] and abdominal pain.[15] Common nonspecific symptoms include headache and extremity and back pain. The majority of patients will have a history of contact with a cat (or kitten), but lymphadenopathy or an inflammatory papule[10] as well as hepatomegaly and/or splenomegaly may be absent. Because there may be a paucity of definitive clinical findings despite a careful physical examination, exposure history and clinical suspicion based on knowledge of CSD are critical. Liver transaminase levels are usually normal, CBC occasionally reveals an increased white blood cell count, and ESR is almost universally elevated, often markedly so (> 100 mm/hr). Abdominal ultrasound and/or CT are important diagnostic tests, revealing multiple lesions in the liver and/or spleen (the multifocal nature suggests hematogenous seeding). Biopsy of lesions in the liver may be considered to rule out more serious pathology (eg, malignancy). Classic histopathology reveals necrotizing granulomas, stellate abscesses, and identification of the organism by Warthin-Starry silver stain. However, absence of "classic" granulomas or demonstrable organisms is not unusual and does not eliminate the possibility of CSD. Diagnosis can be supported or confirmed by serology for *B. henselae*; titers of 1:64 or greater are considered positive.

**Key Point**

Systemic CSD should be considered in the differential diagnosis of a child with FUO. Histopathology and serology are useful diagnostic tools for CSD.

### Treatment

The majority of patients with CSD, especially those with adenitis, will improve without antimicrobial therapy. Infrequently, nodal excision (not incision and drainage) may be necessary. The bacillus is sensitive to a broad range of antibiotics in vitro, but few have been demonstrated to have clinical efficacy. A retrospective analysis of 268 patients with CSD suggests that gentamicin, ciprofloxacin, trimethoprim-sulfamethoxazole, and rifampin may be effective.[16] Several authors recommend that the best outcome is achieved with regimens that include rifampin.[10,16] A randomized, placebo-controlled study of 5-day treatment with azithromycin in patients with adenitis demonstrated a more rapid decrease in node volume (as measured by ultrasound) over the first month following initiation of therapy.[17] Beyond 30 days, there was no difference between treated patients and controls, underscoring the high spontaneous resolution rate. At best, therapy with any of the above antibiotics may hasten resolution of clinical symptoms. Therapy for atypical disease, as in hepatosplenic disease, has not been carefully studied; however, 2 to 3 weeks of antibiotic therapy is often undertaken.

**Key Point**

Many patients with CSD do not require treatment. Although there are few controlled trials evaluating the effectiveness of antibiotic therapy in CSD, regimens that include rifampin are often recommended if treatment is warranted.

## SUMMARY

Careful history-taking is essential when investigating the cause of FUO. In the majority of cases, FUO in children has an infectious etiology, including CSD. CSD is caused by *B. henselae*, and humans can acquire the disease through contact with a cat. The most common manifestation of CSD is lymphadenopathy, and CSD can be confirmed by serology. In most cases, the infection will resolve without treatment. If the patient has evidence of hepatosplenic CSD, antibiotic therapy is often initiated; however, further study is needed to determine which antibiotics are most effective. **HP**

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