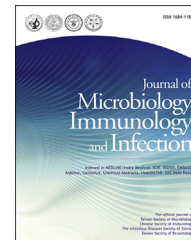




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ORIGINAL ARTICLE

# Clinical analysis of fever of unknown origin in children: A 10-year experience in a northern Taiwan medical center



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## KEYWORDS

Fever of unknown origin;  
FUO;  
Children;  
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**Background:** Fever of unknown origin (FUO) was first described in 1961 as fever  $>38.3^{\circ}\text{C}$  for at least 3 weeks with no apparent source after 1 week of investigations in the hospital. Infectious disease comprises the majority of cases (40–60%). There is no related research on FUO in children in Taiwan. The aim of this study is to determine the etiologies of FUO in children in Taiwan and to evaluate the relationship between the diagnosis and patient's demography and laboratory data.

**Methods:** Children under 18 years old with fever  $>38.3^{\circ}\text{C}$  for  $>2$  weeks without apparent source after preliminary investigations at Taipei Veterans General Hospital during 2002–2012 were included. Fever duration, symptoms and signs, laboratory examinations, and final diagnosis were recorded. The distribution of etiologies and age, fever duration, laboratory examinations, and associated symptoms and signs were analyzed.

**Results:** A total of 126 children were enrolled; 60 were girls and 66 were boys. The mean age was 6.7 years old. Infection accounted for 27.0% of cases, followed by undiagnosed cases (23.8%), miscellaneous etiologies (19.8%), malignancies (16.6%), and autoimmune disorders (12.7%). Epstein-Barr virus (EBV) and cytomegalovirus (CMV) were the most commonly found pathogens for infectious disease, and Kawasaki disease (KD) was the top cause of miscellaneous diagnosis.

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*Conclusions:* Infectious disease remains the most common etiology. Careful history taking and physical examination are most crucial for making the diagnosis. Conservative treatment may be enough for most children with FUO, except for those suffering from malignancies.

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## Introduction

Fever of unknown origin (FUO) is defined as a well-documented fever with a body temperature  $>38.3^{\circ}\text{C}$  ( $101^{\circ}\text{F}$ ) for at least 3 weeks without any apparent source after 1 week of investigation in a hospital.<sup>1</sup> It is generally accepted that a fever for  $>1$  week in a child warrants further investigation, since most viral febrile episodes subside within 1 week. A fever that continues beyond 5–7 days, or one that occurs on and off, usually prompts parents to seek medical advice. For this reason, the inclusion criteria in recent systematic reviews on pediatric FUO are pediatric patients with a fever persisting for 1–2 weeks with negative preliminary investigations, or without a diagnosis after three outpatient visits.<sup>2</sup> These criteria are more acceptable to most primary care physicians.

The incidence of FUO ranges from 0.5% to 3% in all hospitalized children,<sup>3</sup> with the proportion of those diagnosed varying from study to study. Overall, an infectious illness is the most common cause of FUO in children (40–60%), followed by autoimmune disease (10–20%), malignancies (5–10%), and miscellaneous conditions (5–10%),<sup>2,5</sup> with 10–20% of cases being undiagnosed.<sup>2,4</sup> The number of undiagnosed cases is increasing, which may be due to improvements in diagnostic techniques so that illnesses which were previously thought to be among the causes are now diagnosed earlier before the onset of the FUO.<sup>6</sup>

The diagnosis of a prolonged fever in children requires extensive history taking, thorough physical examination, and a series of complementary laboratory examinations. A delay in ordering appropriate surveys and a failure to interpret the findings may lead to the actual underlying cause being missed, potentially resulting in a life-threatening condition. As there are currently no published studies describing the causes and distribution of FUO in children in Taiwan, the present study aimed to determine the etiologies of FUO among children in Taiwan, and compare the findings to previous research to elucidate the indicators of life-threatening conditions.

## Materials and methods

This retrospective study analyzed the medical records of children aged  $<18$  years old with a fever of  $>38.3^{\circ}\text{C}$  for longer than 2 weeks without an apparent source after preliminary investigations at Taipei Veterans General Hospital from January 2000 to December 2012. The Institutional Review Board of Taipei Veterans General Hospital approved the study protocol (VGHIRB No. 2013-05-026B).

Children with a definitive diagnosis at the time of referral, any previously known congenital or acquired immunosuppressive deficiency, or malignancies were

excluded. Data on age, sex, duration of fever, history of illness, physical examination findings, basic laboratory investigations such as white blood cell (WBC), differential, and platelet count, levels of hemoglobin, C-reactive protein (CRP), and ferritin, urinalysis, and urine and blood cultures were obtained. Further serum examinations including complement component 3 (C3), complement component 4 (C4), double-stranded deoxyribonucleic acid (dsDNA), antinuclear antibody (ANA), and virology studies were retrieved based on individual situations. Imaging studies such as chest X-ray, abdominal sonography, and computed tomography, and invasive procedures such as lumbar puncture and bone marrow aspiration were also recorded.

We made the diagnosis of cytomegalovirus (CMV), Epstein-Barr virus (EBV), and mycoplasma infection based on the clinical presentations using positive viral serologic tests; that is, positive CMV immunoglobulin (Ig) M antibody (Ab) and/or positive urine CMV culture, positive EBV-viral capsid antigen (EBV-VCA) IgM Ab with a four-fold increase of IgG titer in paired sera, and positive mycoplasma IgM Ab. Children presenting with injected tonsils, productive cough, and rhinorrhea were grouped into upper respiratory infection. The definition of central nervous system infection was based on clinical manifestations such as headache, neck stiffness, and fever, with cerebrospinal fluid (CSF) pleocytosis and low CSF sugar level. Urinary tract infection was diagnosed using positive urine cultures. Summer fever and central fever were diagnosed using clinical presentation and exclusion. Patients who had prolonged fever especially during midnight or early morning, along with some institutional symptoms such as anorexia, sleeplessness, and gastrointestinal illness, which resolved while staying in an air-conditioned room, were diagnosed as having summer fever. Central fever indicated the absence of a documented infection in the febrile patients with neurologic disease, such as brain tumor or traumatic injury. It resulted from the dysfunction of the regulatory center at the hypothalamus.

The definitive diagnosis, if any, and prognosis were documented according to the discharge notes and outpatient department records. After reviewing all of these data, the patients were categorized as having fever due to infectious disease, autoimmune disease, malignancy, or a miscellaneous condition. If the cause of fever was not identified, the case was classified as being undiagnosed.

Statistical analysis was performed using the Chi-square test (goodness-of-fit) with SPSS software (SPSS Inc., Chicago, IL, USA).

## Results

One hundred and twenty-six children suffering from a prolonged fever of  $>14$  days without an initial definite

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