Fever of unknown origin in children: a systematic review

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Background: There are no previous systematic reviews of published pediatric case series describing the etiology of fever of unknown origin (FUO). The purpose of collecting these data is to determine the etiologies for children with FUO in both developing and developed countries.

Methods: The database Ovid Medline R (1950 to August 2009 week 4) and Ovid Embase (1980 to 2010 week 2) were used to conduct the search. Studies in any language were included if they provided the diagnosis in a series of 10 or more children with FUO. The diagnosis of each child at the time of publication of the study was recorded.

Results: There were 18 studies that met the inclusion criteria, describing 1638 children. The diagnosis at the time of publication was malignancy for 93 children (6%), collagen vascular disease for 150 (9%), miscellaneous non-infectious conditions for 179 (11%), infection for 832 (51%), and no diagnosis for 384 (23%). There were 491 bacterial infections (59% of all infections) with common diagnoses being brucellosis, tuberculosis, and typhoid fever in developing countries, osteomyelitis, tuberculosis, and Bartonellosis in developed countries, and urinary tract infections in both. For children with no diagnosis after investigations, most had fever that ultimately resolved with no sequelae.

Conclusions: About half of FUOs in published case series are ultimately shown to be due to infections with collagen vascular disease and malignancy also being common diagnoses. However, there is such a wide variety of possibilities that investigations should primarily be driven by the clinical story.

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Introduction

Fever of unknown origin (FUO) was firstly described in 1961 and defined as well-documented fever of at least 3 weeks duration with no apparent source after 1 week of investigations. It is now generally accepted that unexplained fever that persists longer than 1 week in a child warrants preliminary investigations as fever from viral infections generally resolves within that time frame. Therefore, most recent case series of pediatric FUO require persistence of fever for only 1 or 2 weeks with negative preliminary investigations, and the investigations required varied by study.

This study summarized the literatures on pediatric FUO to determine the relative incidence of different etiologies, expecting that etiology will vary by geographical location related to the economy of the region, the presence of vectors of infection, and the availability of diagnostic tests.

Methods

Search methods for identification of studies

The database Ovid Medline R (1950 to August 2009 week 4) and Ovid Embase (1980 to 2010 week 2) were used to conduct the search. Key words and phrases used to refine the search included "fever of unknown origin" and "pyrexia of unknown origin", limited to children 0 to 18 years. The search was then further limited to include clinical trials, meta-analysis, epidemiologic studies, evaluation studies, validation studies, review articles, retrospective and prospective studies. All abstracts were then reviewed.

Study characteristics

Studies were included if they provided the diagnosis in a series of 10 or more inpatients or outpatients of less than 18 years of age evaluated for FUO persisting...
for a minimum of one week duration. Because one of the goals of the study was to look at the incidence in different geographic areas, no language restriction was applied. Studies were excluded if they included only acute FUO (fever for less than one week) or focused only on long-term follow-up of children with unexplained FUO.

Data extraction
Data were recorded on the demographics and diagnosis at the time of publication for enrolled children. The data were separated for studies from advanced economies (developed countries) versus emerging or developing economies (developing countries) using International Monetary Fund classification from 2008 (Imf-advanced-un-least-developed-2008.svg).

Data analysis
This was purely a descriptive study so it was not possible to report study quality or risk of bias. The etiologies of fever were classified into the following groups: a) infectious diseases, b) malignancy, c) collagen vascular disease (CVD), d) miscellaneous diseases including hemophagocytic lymphohistiocytosis, inflammatory bowel disease, and any other conditions with a proven etiology, and e) no etiology established at the time of publication. Infectious diseases where classified as bacterial, fungal, parasitic, or as infectious syndromes with no specified pathogen.

Results
The search revealed 643 abstracts of which 18 studies met the inclusion criteria (13 in English, 2 in French, 2 in Spanish and 1 in Polish). Six other studies were included as they included children up to 21 years of age, the duration of fever was less than 1 week in some children, or there were less than 10 patients in the study, or the study was limited to children with unexplained FUO following a full evaluation. Only the latter two studies provided data on a long-term follow-up of children with FUO. One study looked at children referred to a rheumatology clinic with a mean follow-up of 5 years: 32 of 37 children had resolution of their fever with no diagnosis, 3 had persistent periodic fever, and 2 had a diagnosis of Crohn's disease. Another study from Chicago reported follow-up of 19 children for a mean of 3.5 years after assessment: 16 had resolution of their fever with no established etiology, 2 were eventually diagnosed with juvenile idiopathic arthritis, and 1 had recurrent intussusception that may be due to the initial fever.

The 18 included studies published from 1968 to 2008 consisted of 8 studies (all more than a decade old) from only 3 developed countries (Germany, USA and Spain) and 10 studies from developing countries (Table 1). The number of children in each case series varied from 10 to 221 (median 89.5) for a total of 1638 children (770 males; 628 females; 240 unknown). Definitions of FUO varied widely. The values for the definition of fever varied from minimum 37.5 degrees Celsius to minimum 38.9 degrees Celsius. The duration of fever ranged from 1 week to 3 weeks with the majority of the papers requiring a minimum of 2 to 3 weeks duration. In terms of the site of investigation, 1316 children were inpatients during at least part of their investigation, 209 were outpatients and for 113 it was not specified.

The total number of patients with a diagnosis of malignancy was 93 (6%), of which 41 had leukemia, 16 had lymphoma, 23 had other types of malignancy including neuroblastoma, Wilms tumour, and myelodysplastic syndrome, and 13 had an unspecified malignancy. The number of patients with a diagnosis of collagen vascular disease was 150 (9%), of which 90 had juvenile idiopathic arthritis, 22 had systemic lupus erythematositis, 27 had some other forms of CVD and 11 patients had an unspecified type of CVD. One hundred and seventy-nine patients had a miscellaneous non-infectious etiology for their fever (11%) with nonspecified autoimmune disease and inflammatory bowel disease predominating in developing countries and Kawasaki disease in developed countries.

Infection was by far the most commonly identified etiology of FUO in all studies. In total, 832 patients (51%) had a final diagnosis of infection with bacterial infections followed by infectious syndromes being the most common etiologies. There were 491 bacterial infections (59% of all infections) with common diagnoses of brucellosis, tuberculosis, and typhoid fever in developing countries, osteomyelitis, tuberculosis, and Bartonellosis in developed countries, and urinary tract infections in both (Table 3). There were 58 patients with viral infections (7% of all infections) with Epstein-Barr virus (EBV) accounting for over half of cases. Another 193 patients (23% of those with infections) had infectious syndromes associated with pneumonia accounting for fully one-quarter of these in developing countries. Fungal infection was diagnosed in only 3 of the 832 patients, but 86 had parasitic infections (10%), predominantly leishmaniasis in developing countries.