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Diagnosis and management of undifferentiated fever in children

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Summary The incidence and likely causes of fever of unknown origin (FUO) have changed over the last few decades, largely because enhanced capabilities of laboratory testing and imaging have helped confirm earlier diagnoses. History and examination are still of paramount importance for cryptogenic infections. Adolescents who have persisting nonspecific complaints of fatigue sometimes are referred to Pediatric Infectious Diseases consultants for FUO because the problem began with an acute febrile illness or measured temperatures are misidentified as "fevers". A thorough history that reveals myriad symptoms when juxtaposed against normal findings on examination and simple laboratory testing can suggest a diagnosis of "fatigue of deconditioning". "Treatment" is forced return to school, and reconditioning. The management of patients with acute onset of fever without an obvious source or focus of infection is dependent on age. Infants under one month of age are at risk for serious and rapidly progressive bacterial and viral infections, and yet initially can have fever without other observable abnormalities. Urgent investigation and pre-emptive therapies usually are prudent. By two months of age, clinical judgment best guides management. Between one and two months of age, a decision to investigate or not depends on considerations of the height and duration of fever, the patient's observable behavior/interaction, knowledge of concurrent family illnesses, and likelihood of close observation and follow up. Children 6 months—36 months of age with acute onset of fever who appear well and have no observable focus of infection can be evaluated clinically, without laboratory investigation or antibiotic therapy, unless risk factors elevate the likelihood of urinary tract infection.

Unfocussed fever: Five cases, five approaches to diagnosis and management

Five cases are presented in which patients came to medical attention because of fever, yet had no clear cause after a detailed history, physical examination and simple laboratory testing. The reader is challenged to choose the most likely etiology or next step in management. The discussions are focussed to highlight evidence from recent medical literature.

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Case 1: Fever and back pain in a returned traveler

Box 1 shows the principal data for this case together with a question about the most likely diagnosis.

Chikungunya

Chikungunya virus is an alphavirus of the family *Togaviridae*, which is arthropod-borne, classically transmitted by *Aedes aegypti*. Gene mutations in the virus envelope in certain clades have permitted adaptation to a different mosquito vector, *Ae. albopictus*, and expansive transmissibility. For chikungunya virus, the important step to sustained mosquito—human—mosquito cycle appears to be related to human behavior driving vector adaptation, and vector adaptation driving virus adaptation.[1] In interepidemic periods, chikungunya is maintained in animals, and in epidemic periods humans are the reservoir and amplifying host. Chikungunya virus appears to have originated and evolved into distinct clades over centuries in Africa, with a pandemic involving parts of the Western hemisphere in the 1820s, and identification confirmed during a 1952 outbreak in southern Tanganyika (now Tanzania). From the 1960s to 1990s, sporadic outbreaks sometimes involving >100,000 people occurred due to distinct clades in Africa and Asia. Spread from a 2005 coastal Kenya epidemic to the islands of the Indian Ocean was the harbinger of worldwide distribution. In 2007, Italy had the first inter-tropical outbreak with indigenous transmission.

An outbreak beginning in late 2013 in the Caribbean led to >1.5 million clinical cases of chikungunya transmission documented by mid-2015, with spread to Latin America and travel-associated cases confirmed in most U.S. states. Indigenous transmission occurred in Florida, Puerto Rico and the U.S. Virgin Islands.[2] The Caribbean virus appears to be an Asia lineage, so far unadapted to *Ae. albopictus*.[3,4] *Ae. aegyptiacus*, however, is an aggressive daytime-biting mosquito and with high levels of human viremia, transmission to a naïve population occurs in rapid waves, typically affecting more than one-third of a population.[5]

The majority (72%—97%) of people infected with chikungunya virus develop symptomatic disease — high fever and bilateral, symmetrical and severe, debilitating arthralgia.[6] Acute symptoms abate over 7—10 days, but >50% of patients have relapsing or recurring polyarthralgia/arthritis or tenosynovitis that can persist for months to years.[7]

The patient's clinical diagnosis of chikungunya made in the Dominican Republic two months prior to admission likely was correct, considering epidemic disease there at the time. Recent progressive back pain and elevated sedimentation rate make postinfectious arthritis a consideration, however, isolated non-incapacitating back pain was not a perfect fit and made further considerations relevant.

Box 1. Case 1. 12-year-old Hispanic girl with fever and back pain.

History of presenting illness

- Progressive back pain over 1 month — flexion worse, supine & walking OK.
- 2 months previously, had fever and back pain for 2 weeks while in Dominican Republic. Dx of chikungunya made.

Examination findings

- 37 °C, BMI 29 (97th centile), vital signs normal. Lying supine without pain.
- No vertebral/paraspinal tenderness. Loss of normal lordotic curvature.
- Straight leg raising causes pain in lumbar spine.

Investigations

- Hb 12.4 g/dL, Hct 35.8%, WBC 9800 (49% neutrophils), Platelets 361,000.
- CRP 1.8 mg/dL, ESR 62 mm/h, protein 7.5 g/dL, albumin 3.7 g/dL.

Question 1. The most likely diagnosis is

A. Chikungunya
B. Another infectious disease
C. An oncologic diagnosis
D. A rheumatologic diagnosis
E. Nonspecific musculoskeletal pain

Fever of unknown origin

In a landmark publication by Petersdorf and Beeson in 1961,[8] fever of unknown origin (FUO) was codified for purposes of clinical approach to require temperature >38.3 °C (101 °F) documented on most days for >3 weeks, and no diagnosis after 1 week of hospitalization. In the 1990s, de-Kleijn et al.[9] modernized the definition by replacing stay in hospital with non-diagnostic computed tomography, if any localizing sign or symptom was present. The availability of improved diagnostic tests and imaging aided earlier diagnoses and led to dwindling cases of FUO and shuffling of etiologies. Durack and Street in 1991[10] grouped FUO by settings of occurrence, each having distinctive differential diagnoses: neutropenic host, nosocomial onset, HIV-associated, and classic (no clear predisposition). Horowitz[11] reviewed relative importance of categories of etiology reported in FUO studies, primarily in adults, from 1961 to 2007. Progressively over years, relative importance of infection fell from 36% to 16% and was replaced with "no diagnosis" rising from 9% to 51%, and "noninfectious inflammatory disease" exchanged place with "neoplasm" (each accounting for 22% and 7%, respectively in 2007). The fall in infectious etiologies likely reflects improving capability for earlier diagnosis rather than changes in disease incidence.

Studies of FUO in children are limited. Jacobs and Schutze in 1998[12] reported 146 children with fever for >2 weeks. Diagnoses were made in 58%, with infectious