

CONTAGIOUS COMMENTS

Department of Epidemiology

Series on the Top 5 Questions Regarding Pediatric Infectious Diseases

Topic # 1: Chronic Fatigue Syndrome

Mary Glodé, M.D.

Does Chronic Fatigue Syndrome (CFS) occur in children?

Chronic Fatigue Syndrome is a serious, debilitating and frustrating condition experienced by thousands of adolescents in the U.S. Our ID group diagnoses approximately 40 cases of CFS per year. Most cases occur in previously healthy, high achieving adolescent females. There is no official case definition for children. The case definition used in adults includes two criteria:

1. Severe, chronic fatigue of six months or longer, with other known medical conditions excluded by clinical diagnosis: and
2. Concurrently have four or more of the following symptoms: short term memory or concentration impairment, sore throat, tender lymph nodes, muscle or joint pain without redness or swelling, headaches of a new type, unrefreshing sleep, and post-exertional malaise lasting more than 24 hours.

We generally do not wait six months to diagnose CFS in adolescents since school absenteeism is a common feature of this illness and early intervention by the PCP may help avoid the academic and school consequences of prolonged school absence.

What are the important questions to ask when obtaining the history?

CFS is a clinical diagnosis and therefore a diagnosis of exclusion. It is essential that a very complete history be obtained. A complete review of systems is particularly important. The syndrome often begins abruptly with an acute mono-like illness followed by prolonged convalescence with multiple complaints of excessive fatigue, generalized weakness and often headache or muscle aches. The working diagnosis often includes "chronic mono or chronic Lyme." By the time we evaluate these children, they are almost always unable to attend school and are being home schooled or tutored. They often have very disturbed sleep cycles and excessive sleep. The history should include recent travel, animal exposure, foreign visitors, prior significant infections, details of any fevers, signs or symptoms of depression, family history of rheumatologic disease, oncologic disease, thyroid disease, and psychiatric disease. The adolescent should be interviewed privately at some point regarding any issues of sexual activity, drug use, abuse, or depression. Fever (temps more than 38.3) is **NOT** a feature of CFS and a daily fever diary with the temperature measured at the same time each evening should be recommended and reviewed if the family reports fever.

What diseases should I consider in the differential diagnosis?

You should think about diseases that may present with non-specific signs and symptoms in adolescent females. Collage vascular diseases, including lupus, autoimmune hepatitis and inflammatory bowel disease present in this age group. If headache is a prominent symptom, brain tumor should be considered. Chronic infectious diseases that might present with months of symptoms include TB, fungal disease, HIV, endocarditis or Lyme arthritis. Oncologic diseases in this age group would include leukemia and lymphoma. Metabolic diseases to think about include hypothyroidism and Addison's disease.

What about the Physical Exam?

The physical exam should be normal. Mouth ulcers, rash, or evidence of arthritis should prompt consideration of Lupus. Lymphadenopathy should raise concern for lymphoma, and an abnormal neurologic exam might suggest a brain tumor. A flat affect should suggest depression or bipolar disease. Significant weight loss could suggest anorexia nervosa or cancer.

What lab tests should I order?

Screening tests that we believe are helpful include a CBC, ESR, CRP, complete metabolic panel, LFTs, TSH, UA, EBV titres, HIV antibody, PPD and a chest X-ray. Other labs or imaging should be prompted by the history or physical exam. We would not test for Lyme disease unless there was a history of travel to a Lyme endemic area and probable tick exposure.

Shouldn't children with CFS be seen by a specialist?

A working diagnosis of CFS can and should be made by the PCP. Parents and patients should be told that all providers will keep an open mind and pursue other diagnoses if new signs or symptoms develop. The PCP has the best relationship with the child and family and is in the best position to diagnose and begin treatment for CFS.

What is the best treatment for CFS?

The best therapy for CFS is cognitive behavior therapy. The child should be seen weekly by the PCP and a plan should be created and modified each week. Initially the plan should focus on gradually restoring a normal wake, sleep cycle. Gradual increases in general activity should be specifically outlined, understanding that the first few days after the prescribed increase will result in more exhaustion transiently. Depression often

accompanies CFS, but families are often reluctant to seek help from a mental health professional. The PCP should assist families in identifying a mental health provider and all 3 groups (patient/family, PCP and mental health provider) should communicate with each other regularly. Patients should be told of the excellent prognosis for children with CFS. The goal of therapy is to gradually increase activity levels at home and school until the child is back to their baseline state. This will often take several weeks to accomplish. Close communication by the PCP and family with the school is also essential.



What is the prognosis for adolescents with CFS?

Adolescents with CFS have a better prognosis than CFS in older adults. Most children are asymptomatic or significantly improved within 1-2 years after diagnosis.

References:

- Marshall, GS: Report of a workshop on the epidemiology, natural history, and pathogenesis of chronic fatigue syndrome in adolescents. *J Pediatr* 1999 134(4): 395-405.
- Prins, JB, van der Meer, JWM, Bleijenberg, G. Chronic Fatigue Syndrome, *Lancet* Jan 2006; 367: 346-355.

Topic #2: Approach to the Child with Prolonged Fever

Mark J. Abzug, MD

What is considered a prolonged fever?

Prolonged fever, or Fever of Unknown Origin (FUO), is generally defined as a fever that persists beyond 14 days, which distinguishes it from common, self-resolving (often viral) illnesses which may include fever that lasts a week or longer, but generally not as long as two weeks.

What are common causes of an FUO?

Many different diseases may present as an FUO, including:

- *Infections* - urinary tract, upper respiratory tract, bone and joint, central nervous system, endocarditis
- *Autoimmune diseases* - juvenile rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosum, inflammatory bowel disease
- *Malignancies* -leukemia, lymphoma, neuroblastoma
- *Miscellaneous* - factitious fever, drug fever, etc.

A significant percentage of cases self-resolve over a period of weeks to months without ever coming to a specific diagnosis. When approaching a child with prolonged fever, it is helpful to remember that the child more often has an occult presentation of a common disease than a truly rare disease.

What are the key parts of the evaluation of a FUO?

The most important information is generally revealed by the history and physical examination. Significant clues may be identified only after *serial* histories and exams. Important elements of the history and examination include:

- Fever pattern, weight loss, and other constitutional symptoms, such as anorexia and night sweats (not discriminatory among diagnoses, but an indicator of disease severity)
- Exposures: ill contacts, residence and travel, animals, insects, unpasteurized dairy products, wild game, medications, tuberculosis contacts, HIV risk factors

- Symptoms/signs that may help discriminate among possible diagnoses, e.g., rash, joint findings, cardiac/respiratory or genitourinary symptoms/signs, or other localizing abnormalities. A normal examination suggests a favorable prognosis.

What laboratory tests should be done for a child with a FUO?

Screening laboratory evaluations can be extremely helpful in identifying clues and assessing the “degree of worry” one should have. These can be obtained over the course of several evaluations or they can be “front-loaded”, with more tests done at the first evaluation if the child is clinically concerning. Repeating basic hematology and chemistry tests and cultures over time may be revealing. A recommended screening approach includes the following:

First Level Screening Laboratory Evaluation

- Complete blood count
- Erythrocyte sedimentation rate
- C-Reactive protein
- Urinalysis
- Blood culture – *shouldn't be forgotten!*
- Urine culture – *even in the absence of suggestive symptoms!*
- Chest radiograph – *relatively high yield even without respiratory symptoms!*

Second Level Screening Laboratory Evaluation

- Repeat complete blood count, erythrocyte sedimentation rate, C-reactive protein, urinalysis
- Repeat blood culture, urine culture
- Liver function tests, lactate dehydrogenase (LDH), uric acid, blood urea nitrogen, creatinine
- Stool heme test
- Antinuclear antibody, rheumatoid factor
- Mantoux skin test (PPD)
- Save serum for additional testing as needed

What evaluations should be done if screening testing doesn't provide the answer?

Extensive “shotgun” laboratory evaluations are generally not very helpful in discerning the cause of a FUO. The yield is greater if additional work-up is individualized according to the clues from the history, physical exam, and screening laboratory studies. Tests that may be useful in pursuing clues include:

- Stool cultures (gastroenteritis symptoms; possible enteric fever)
- Serologies (cat scratch disease – cat/dog exposure; Epstein-Barr virus)
- Imaging targeted to organ-specific symptoms/signs (sinus CT scan; cranial CT or MRI; skeletal imaging; gastrointestinal imaging; etc.)
- Tissue biopsy of an involved organ
- Abdominal imaging (ultrasound or CT scan) may also be warranted and has a relatively high yield

During this phase of the evaluation, consultation with appropriate subspecialists (Infectious Diseases, Rheumatology, and/or Oncology) may be helpful to further organize the diagnostic evaluation.

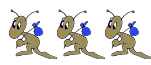
Should the child with prolonged fever be hospitalized?

Because the prognosis for children with prolonged fever is generally favorable (more so than in adults), one can generally be patient in the evaluation of a child with FUO. The tempo of the workup should be tailored to the degree of illness and the level of worry suggested by screening laboratory results.

Hospitalization can be considered if the clinical and laboratory picture is worrisome, if the fever history is unreliable, or if it would assist in coordination of consultations and diagnostic tests.

Should empiric therapy (e.g., antibiotics or corticosteroids) be tried?

Empiric therapy such as antibiotics or corticosteroids should generally not be administered unless a specific diagnosis warranting their use is uncovered. In the absence of a diagnosis, such empiric treatment often provides transient responses (at best) and frequently masks the diagnosis, resulting in a more prolonged course.



Human Metapneumovirus: Details and Diagnosis

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Virology and Molecular Diagnostics*

Human metapneumovirus (hMPV) is a recently-discovered paramyxovirus that is responsible for a significant proportion of acute upper and lower respiratory tract disease in children worldwide. In Colorado, hMPV infections occur in 10-15% of hospitalized children under the age of 5, mostly during the winter and spring. Immunocompromised patients of any age and the frail elderly are also susceptible. Clinical syndromes associated with hMPV are similar to those associated with RSV and range from upper respiratory tract infections and severe bronchiolitis to pneumonia. Some fatalities have been reported. Co-infection with hMPV and other common respiratory viruses is frequent and may result in more severe disease than solo infections. A link between hMPV infection and asthma has been proposed.

Detection of hMPV infection by conventional virology methods is difficult. The virus does not grow well in standard tube culture and reagents for its identification by direct immunofluorescence (DFA) or immunoassay are not yet FDA-cleared. Currently, hMPV infections must be diagnosed by reverse transcriptase polymerase chain reaction (RT-PCR).

A sensitive, real-time RT-PCR for hMPV in respiratory tract specimens is now available in the Children’s Hospital Laboratory. This assay uniformly detects all 4 subgroups of the virus, which is important because the hMPV genotype can change season to season and even within a season with no change in symptoms. We recommend the hMPV PCR for hospitalized pediatric patients whose DFA is negative for other respiratory viruses and if the result will improve patient management.

hMPV RT-PCR	
Preferred Specimens:	Nasopharyngeal washes or aspirates, tracheal aspirates, BAL, or lung tissue.
Ordering:	Write-in on Microbiology requisition.
Test Schedule:	Wednesdays. In by 7 AM, results by 4 PM.
Charge:	Call Client Services at 303-864-5795.
For a hMPV Fact Sheet, call our TCH Microbiology Laboratory at 303-861-6703.	





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