Current challenges in the diagnosis and management of fever

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Purpose of review
We review recommendations from recent publications on the management of fever with antipyretics, the classification and diagnosis of fevers of unknown origin (FUO), and the evaluation of fever in infants under 90 days of age.

Recent findings
Anxiety about fever persists in the population, while the toxicity of antipyretics is an increasing concern. The numerous opportunities for overdosing with antipyretics have been emphasized by the American Academy of Pediatrics (AAP). The practice of alternating acetaminophen and ibuprofen has limited value. Nonclassic FUO and pseudo-FUO are as important to consider as true FUO, and clinicians should become familiar with the variety of periodic fever syndromes. The clinical utility of low-risk criteria to identify febrile infants at low risk for serious bacterial infection (SBI) was demonstrated in a systematic review of studies.

Summary
Pediatricians should spend more time educating parents about fever and antipyretic use. Not all persistent fever is FUO, and testing should be targeted to the child's clinical condition. Existing low-risk criteria should be used to identify febrile infants who can be managed without extensive work-up and antibiotics. Adherence to evidence-based recommendations will lessen the morbidity and mortality associated with febrile illnesses in children.

Keywords
antipyretics, febrile infant, fever, fever phobia, FUO, low-risk criteria, periodic fever, SBI

INTRODUCTION

Fever is one the most common symptoms of illness in infants and children, and the approach to its diagnosis and management is constantly evolving. One of the current challenges is to curb antipyretic use. Fear of fever is widespread, and antipyretics are relied upon excessively in an attempt to reduce temperatures to normal. Pediatricians need to educate parents on the adverse consequences of excessive antipyretic use, which are organ toxicity and occasional death. Another issue that pediatricians commonly confront is recurrent or persistent fevers. These are often labeled as fever of unknown origin (FUO), but the definition of FUO has changed. In an era of easy accessibility to expensive and invasive investigations, especially computed tomography (CT) scanning and magnetic resonance imaging, the approach to recurrent or persistent fever needs to be refined. This includes consideration of the clinical setting, and a return to the basics – meticulous and repeated history and physical examination. The approach to evaluation of young febrile infants has also changed. In developed countries there has been a near-elimination of vaccine-preventable bacteremia and meningitis, yet many infants are subjected to a 'full sepsis evaluation'. There are clinical criteria to screen infants at low risk for these forms of serious bacterial infection (SBI). If these criteria are used, much of the morbidity, inconvenience and expense associated with referral of febrile infants to the emergency room can be avoided.

FIGHTING FEVER PHOBIA

Fever is a beneficial physiological response to many infectious and noninfectious illnesses. It is a very

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KEY POINTS

- Pediatricians should counter fever phobia by emphasizing that most fever is not harmful and that overuse of antipyretics can cause organ damage.
- Antipyretics should not be prescribed as a preventive during a vaccination visit, and have no role in the prevention of febrile seizures.
- Alternation of antipyretics has no clinically significant benefit, and increases the chance of dosing errors.
- True FUO should be distinguished from pseudo-FUO and nonclassic FUO by careful history and examination, and a step-wise approach to the work-up should be employed.
- Febrile infants 30–90 days old identified as low-risk for serious bacterial infection can undergo limited laboratory screening and can frequently be observed as outpatients without empiric antibiotics.

useful sign of illness, but it also evokes inordinate fear and anxiety. Schmitt [1] in 1980 found that 52% of parents surveyed feared that fever 40°C or even less can result in neurological damage. He introduced the term 'fever phobia' [1]. Three decades later, most misconceptions about fever persist. Poirier *et al.* [2] investigated the incidence of fever phobia in an urban pediatric emergency department setting to identify specific misconceptions held by caregivers. Among a convenience sample of 230 persons surveyed, 32% named the main danger of fever as seizures, 18% as death, and 15% as brain damage. Thirty-one percent each would use cold or warm water to bring down the temperature, and 9% would use alcohol – measures that are no longer recommended. Seventy-seven percent reported that they would awaken their child to administer antipyretics. In a cross-sectional convenience sample survey on fever perceptions and treatment in Baltimore, Maryland, the likelihood to treat normal temperatures and to administer acetaminophen more frequently than recommended was the same among Caucasian, African-American and Latino families [3].

Physicians' perception of fever and its treatment may also contribute to fever phobia. This has been documented among pediatricians [4]. Pediatricians commonly advise parents to treat fever less than 102°F, and many allow the liberal use of alternating antipyretics. The overzealous use of antipyretics cannot be curbed without education by the clinician. The American Academy of Pediatrics (AAP) has published a Clinical Report that reviews evidence on the efficacy and toxicity of antipyretics [5▪▪]. This document is a comprehensive review of fever treatment practices, and provides an excellent basis for educating parents on rational use of antipyretics. Key physiologic principles about fever as reviewed in this study are summarized below. These should be taught to parents and other caregivers:

(1) Other than in hyperthermia (e.g. in heatstroke), severity of illness has no correlation with degree of fever.
(2) Treating fever does not improve the course of the illness, with the exception of chronically or critically ill children who have borderline metabolic reserves.
(3) Treating fever does not prevent febrile seizures.
(4) Prevaccination antipyretics have no role, and were shown to diminish the antibody response to several common vaccines. Antipyretics may be used as necessary to treat fever after vaccination.
(5) Fever should only be treated in order to improve the comfort of the child, rather than to make the temperature 'normal'. The effect of acetaminophen and ibuprofen may be more as analgesia, as research is lacking into whether normalizing the temperature really alleviates discomfort.
(6) It is more important that the parent or caregiver monitors the activity and hydration of the child, and is vigilant for new symptoms that may indicate serious illness, than watches the temperature.

The AAP Clinical Report discusses the following key pharmacologic principles about antipyretics [5▪▪].

(1) Acetaminophen versus ibuprofen: Contrary to popular perception, ibuprofen has not been demonstrated to be superior to acetaminophen by any parameter of fever control, except in a slightly longer duration of antipyretic effect (6–8 h, compared with 4–6 h for acetaminophen). The safety of acetaminophen and ibuprofen is generally comparable, but gastritis and gastrointestinal mucosal ulceration are more common with ibuprofen. The potential nephrotoxicity of ibuprofen is a major concern in children with renal insufficiency, such as in a dehydrated child or one on concomitant nephrotoxic drugs. Ibuprofen acts by inhibition of synthesis of prostaglandins, which are important for maintenance of renal blood flow. Babies under age 6 months may be more prone to this risk. An association between ibuprofen use and invasive group A streptococcal infection in children with varicella has been described.

(2) Alternating acetaminophen and ibuprofen: A limited body of evidence suggests there is a modest short-term benefit to alternating these two drugs. Specifically, lower temperatures and a greater percentage of children who became afebrile 4–8 h after initiating treatment have been observed, compared with single-drug treatment groups, but fever still recurred. The implications of prompt fever response for alleviation of discomfort are unclear. Moreover, one must keep in mind the increased possibility of confusion in dosing strengths and intervals, leading to risk of toxicity. Most importantly, the advice to use alternating antipyretics serves to reinforce fever phobia.
(3) Ample opportunity for dosing errors:
   (a) Neither administration of an initial loading dose nor rectal dosing of acetaminophen improves its efficacy. Both of these modalities increase the risk of hepatotoxicity due to dosing errors.
   (b) Chronic overdosing of acetaminophen is a risk, such as with doses more than 15 mg/kg/dose or administered more frequently than every 4 h.
   (c) Confusion due to packaging and labeling ambiguity, coupled with low health literacy, is very common. This leads to inadvertent overdosing and occasional fatalities. It is vital that we instruct parents on the strength of the antipyretic formulation, and the precise volume and intervals for administration.
   (d) Acetaminophen is the single leading medication implicated in pediatric emergency room visits for drug overdoses. Dosing devices sold with products with different concentrations should never be mixed and matched. Over the counter cough-and-cold medications should not be used in children, not only because of the adverse effects of sympathomimetic drugs, but because of danger of overdosing from simultaneous additional use of the component antipyretic, usually acetaminophen.

Both parental anxiety and the incidence of life-threatening drug toxicity can be diminished if the practitioner takes time to explain these principles.

WHAT CONSTITUTES FEVER OF UNKNOWN ORIGIN?

Fever of unknown origin was first described by Petersdorf and Beeson [6] in 1961 as well-documented fever (>38.3°C) of at least 3 weeks' duration with no apparent source after 1 week of inpatient investigations. Published definitions of both adult and pediatric FUO have since changed [7▪▪]. These vary widely, and encompass intermittent or daily low or moderate-grade fevers, in outpatient or inpatient settings, of 5-day to 3-week durations. Most children referred nowadays to a subspecialist for fevers of unknown cause do not meet even the modified definitions. A fresh look at what constitutes true FUO, as distinguished from pseudo-FUO and nonclassic FUO in children, is offered by Tolan [7▪▪].

Pseudo-FUO refers to repeated, self-limited febrile illnesses that appear to coalesce into one prolonged febrile illness, at least in the perception of the parent. The illnesses commonly are caused by viruses, so a patient explanation of the variety of viruses that a child is exposed to at home, daycare and school is helpful to allay anxiety. Fear of cancer stands out as a reason for anxiety, often triggered by a family history of cancer. As parents may be reticent about this, the absence of clues to a malignancy should be dealt with early and directly. A careful history, coupled with good documentation of temperature recordings, can go a long way to reassure the parent that the child does not have true FUO. In most instances, if the physical examination is normal, a comprehensive work-up beyond basic laboratory data will not be warranted unless fevers persist or symptoms worsen. A syndrome called 'deconditioning' is a common reason for referral of adolescents for specialist evaluation as FUO [8]. In this syndrome, possibly a variant of chronic fatigue syndrome, the adolescent becomes a victim of a downward spiral in energy level culminating in a home-bound and home-schooled state. Whereas this may follow a documented short illness, typically there are few documented fevers of note. Reassurance and an in-depth psychosocial evaluation are imperative.

Nonclassic FUO includes nosocomial FUO, FUO in HIV-infected children, FUO in other immunocompromised children and FUO in the developing world [7▪▪]. The differential diagnoses are very broad, and require expanded considerations of epidemiology and pathogens and of noninfectious causes of fever.

A discussion of the causes of true FUO is not within the scope of this article, but cardinal steps in the diagnostic approach, based on the review by Tolan [7▪▪], are:

(1) The evaluation of a child with FUO should be driven by a careful history and meticulous physical exam. The clues to the cause often lie therein, but can be missed.

(2) A symptom-focused approach is far superior to a 'shotgun' or 'running-the-list' approach.
(3) The overall condition of the child should be the guide to the pace of work-up, rather than the degree of anxiety of the family or the physician.
(4) Special populations, such as the immunocompromised or recently travelled, require an expanded approach.
(5) Diagnostic testing is best ordered in stages – a basic screening profile, followed by an extensive battery including invasive tests only if the child's condition suggests a high likelihood of pathology. In the authors' experience, low yield tests such as rheumatologic profiles, serology for infectious agents that do not match the clinical presentation, and tests involving large doses of radiation are performed too soon. This practice may not allay parental anxiety, but instead increase it.
(6) The majority of patients with FUO do not require admission for a work-up, and empiric antibiotics have little to no role in the diagnosis and treatment of FUO.
(7) Referral to a subspecialist is commonly needed.

On the basis of published series of children with FUO, infection accounts for 30–35% of cases, 20% are from rheumatologic or autoimmune diseases, 10% have a neoplastic condition, whereas 30% remain undiagnosed [7▪▪]. Most of the latter self-resolve. Chow and Robinson [9] performed a systematic review of 18 pediatric case series with 10 or more children, from both developing and developed countries. A limitation was that the definition of FUO varied widely. Among 1638 children with FUO, 51% were due to infection, 23% were unidentified, 11% were from rare noninfectious causes, 9% were collagen vascular diseases and 6% were eventually diagnosed as malignancy. Of note, a urinary tract infection was the leading bacterial cause in both developing and developed countries, and tuberculosis was the next most common cause in both settings.

Periodic fever syndromes

Many children referred to subspecialists for frequently recurring fever have one of several periodic fever syndromes. In contrast to FUO, the febrile episodes are usually abrupt in onset, last only a few days to few weeks, and are self-limited. Episodes are either like 'clockwork' or have irregular periodicity [9]. The child is well between episodes. These syndromes are autoinflammatory conditions. The history indicates that no infectious cause has been identified for the majority of episodes. In a recent review of these syndromes, Wurster *et al.* [10▪▪] classified periodic fever syndromes as either hereditary or sporadic (Table 1). The sporadic type, known commonly as PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis), is the most common, and has a benign prognosis [11]. Unless clinical features suggest one of the hereditary periodic fever syndromes, a comprehensive work-up is not indicated, especially if the features are restricted to fever, aphthous stomatitis, pharyngitis, and cervical adenitis, there is no neutropenia, and the growth and development are normal. One of the hereditary syndromes should be suspected if there is a positive family history, and based upon the specific pattern of periodicity. Regular periodicity is characteristically present in familial Mediterranean fever and in cyclic neutropenia. More of a variable periodicity is observed in hyperimmunoglobulinemia D syndrome, tumor necrosis factor receptor 1-associated periodic syndrome, and familial cold autoinflammatory syndrome. The fever curve has more of a continuous pattern in Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease. The Gaslini diagnostic criteria, available at www.printo.it/periodicfever, are useful to determine the need for specific genetic testing [12].

EVALUATION OF THE YOUNG FEBRILE INFANT

Current practices in the evaluation and treatment of fever in young infants lag behind the evidence. It is still common for febrile infants to have extensive work-up including blood tests and lumbar punctures done, even if they lack risk factors for SBI. This practice is not consistent with the current epidemiology of bacteremia and bacterial meningitis. Management of the febrile infant younger than 90 days should be based upon age and other risk factors.

Most experts agree that, during the first 4 weeks of life of a full-term infant, the occurrence of any fever warrants a 'full sepsis evaluation' of blood, urine, and cerebrospinal fluid to rule out SBI, because symptoms of bacterial infection may be muted [13]. For well-appearing febrile infants older than 30 days of age, the concept of 'low-risk criteria' was introduced by investigators in Rochester, NY, in the mid-1980s to aid in the screening of infants in whom one can avoid unnecessary procedures, antibiotics, and hospitalization [14]. Briefly, the criteria are a previously healthy term infant who has not been treated recently with antibiotics, normal physical examination, normal white blood cell (WBC) and band cell counts, and normal urinalysis. Several variations of the Rochester criteria have been

Table 1. Periodic fever syndromes (compiled from Wurster *et al.* [10▪▪])

Syndrome	Genetics	Age of onset	Characteristic symptoms	Laboratory findings
Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome	Some cases familial	<5 years	Regularly recurring fevers, absence of respiratory symptoms, with or without aphthous stomatitis, pharyngitis, and cervical adenitis	Leukocytosis, neutrophilia, elevated ESR, CRP
Familial Mediterranean fever (FMF)	Autosomal recessive 16p	≤20 years, usually <10 years	Abdominal pain, monoarthritis, pleuritis, myalgias, erysipelas like erythema and bowel habit changes. Less commonly, pericarditis and scrotal swelling	CRP, Serum amyloid A (SAA), ESR elevated in early disease; bilirubin, IL-2, IL-10, and anti-CCP may also be elevated
Hyperimmunoglobulinemia D syndrome (HIDS)	AR; MVK gene on chromosome 12, >60 mutations described	First year of life; attacks may be provoked by illness, vaccination, or stress	Prodrome of malaise then fever for up to 6 days, then lymphadenopathy with possible splenomegaly, GI symptoms, joint pain, rashes, sterile arthritis, and oral or genital ulcers. Less commonly, headaches, hepatomegaly and conjunctivitis	Elevated WBC, CRP, ESR, and SAA. Hallmark: elevated polyclonal IgD. IgA is elevated in 75–80%. Elevated mevalonic acid in the urine or reduced MVK activity diagnostic
Tumor necrosis factor receptor 1 associated periodic syndrome (TRAPS)	AD; TNF-1 receptor gene on 12p13	≤3years; commonly triggered by injury, infection, hormonal changes, and exercise	Days to months of febrile attacks including abdominal pain, arthralgias, severe myalgia caused by a monocytic fasciitis	Elevated WBC, CRP, ESR, SAA and IgA; anemia
Cyclic neutropenia	Inherited or sporadic; heterozygous mutations in the ELANE (ELAstase Neutrophil Expressed)	≤1 year	Recurrent weeklong episodes of fever, pharyngitis, mouth ulcers, lymphadenopathy, cellulitis, sinusitis, otitis, and bronchiolitis	Neutropenia; ANC less than 200/μl for 3–5 days, then increased to 2000/μl for duration of cycle (21 days)
Cryopyrin-associated periodic syndromes (CAPS): a group of three disorders – familial cold auto inflammatory syndrome, Muckle-Wells syndrome, and neonatal onset multisystem inflammatory disease	Mutations in *CIAS1* (human cold-induced autoinflammatory syndrome 1) gene on chromosome 1q	<6 months	Urticaria-like rash, arthralgias, arthritis, sensorineural hearing loss, severe type AA amyloidosis, severe central nervous system involvement, skeletal deformities	Leukocytosis and elevated inflammatory markers, coagulopathy, eosinophilia

AD, autosomal dominant; ANC, absolute neutrophil count; AR, autosomal recessive; CCP, cyclic citrullinated peptides; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; IL, interleukin; MVK, mevalonate kinase; SAA, serum amyloid A; WBC, white blood cell.

used since, but a consensus is lacking. In an effort to re-evaluate the use of these criteria, Huppler *et al.* [15▪▪] determined their performance in a well-designed and timely review of 21 studies of management of fever in infants less than 90 days of age. They categorized studies as retrospective, prospective with empiric antibiotic treatment for all infants, and prospective with antibiotics withheld (termed prospective/no antibiotics for the purpose of the current review). The rates of SBIs in low-risk infants were calculated from data pooled from studies within each category.

The authors hypothesized that low-risk criteria would provide the greatest clinical utility in the prospective/no antibiotics studies, because SBIs that were potentially missed would become apparent. This category of studies yielded 1858 infants, of whom 870 were deemed low risk. Six low-risk

infants had SBIs (either bacteremia or possible urinary tract infection), a rate of 0.67%, and the infants had benign outcomes with treatment. This rate was significantly lower than the rate of SBIs when compared with all other studies. In order to further assess the validity of low-risk criteria in pooled data, the relative risk of SBI in high-risk versus low-risk infants was measured. The relative risk ranged from 31 in prospective/no antibiotics studies to 7 in retrospective studies. This means that 'absence of low-risk' in all types of studies predicted a greater risk of SBI, with the strongest evidence being from prospective/no antibiotics studies. In other words, infants who fulfilled low-risk criteria and were observed without empiric antibiotics had the lowest risk of SBI.

These analyses strongly indicate that low-risk criteria are useful in stratifying febrile infants into those that need work-up beyond complete blood count and urinalysis, and possible treatment, and those that do not, but can be observed safely if follow-up is assured. The latter group consists of about 30% of febrile infants under 90 days of age. The dramatic decline in incidence of occult bacteremia and bacterial meningitis, since the introduction of conjugate bacterial vaccines, further lends support to the low-risk criteria approach in immunized populations [16▪]. In addition, the widespread use of rapid viral diagnosis has the potential to decrease the number of infants being hospitalized [17].

Pediatricians and Emergency Medicine physicians are constantly reviewing their management of febrile young infants. However, they lack definitive guidelines, and many emergency medicine physicians use guidelines that are based on data from the preconjugate vaccine era [16▪]. Experts have called for updates of management protocols and consensus guidelines [16▪,18]. A model for updated guidelines is the 2011 AAP guideline for management of febrile seizures, which takes into account the current epidemiology of SBIs [19▪].

CONCLUSION

It is incumbent on pediatricians to counter fever phobia by teaching parents that fever is a beneficial response, and that temperature does not need to be lowered to normal. Incorrect dosing of antipyretics is common. Alternation of antipyretics has no clinically significant benefit, and increases the chance of dosing errors. Antipyretics should not be prescribed as a preventive during a vaccination visit, and have no role in the prevention of febrile seizures. The approach to work-up of children with recurrent or persistent fever needs to be thoughtful and focused, rather than based on batteries of tests. Most periodic fevers are the PFAPA syndrome but some are hereditary syndromes that require further investigation. In an era of conjugate bacterial vaccines and rapid viral diagnosis, febrile infants 30–90 days old should be screened to see if they fit low-risk criteria for serious bacterial infection, because most will not need extensive laboratory screening or hospitalization.

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Conflicts of interest

There are no conflicts of interest.

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