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# A clinical approach to the management of the febrile infant and young child

Fever is a common presenting symptom of infectious and non-infectious diseases in children. Up to 20% of paediatric visits to outpatient or emergency departments are estimated to be for fever with or without other symptoms.<sup>1</sup> In private practice, 50% of after-hours consultations may concern fever.<sup>2</sup>

## MEASUREMENT AND DEFINITION OF FEVER IN INFANTS AND CHILDREN

Rectal temperature measurement is the gold standard for assessment of body temperature and a significant fever is regarded as a temperature  $> 38^{\circ}\text{C}$ .<sup>3</sup> Rectal temperature is recommended in infants less than 3 months.<sup>4</sup> In this age group hypothermia (rectal temperature  $< 36^{\circ}\text{C}$ ) may be an important sign of sepsis. Axillary temperature is widely used in children under the age of 5 - 6 years but may give a reading  $0.8 - 1.0^{\circ}\text{C}$  lower than rectal temperature. Oral and tympanic temperature may be up to  $0.5^{\circ}\text{C}$  lower than rectal temperature.<sup>4-6</sup>

Tympanic thermometers work by measuring naturally occurring infrared emissions from the eardrum and surrounding structures. Otitis media causes only a very minor ( $< 0.1^{\circ}\text{C}$ ) difference in the reading while mastoiditis and otitis externa may cause greater differences because of increased blood flow. Cerumen (wax),

which is translucent to infrared emissions, does not affect readings. Tympanic recordings are much less sensitive in infants  $< 3$  months of age and may miss up to 30% of significant fevers. This is because the narrow, tortuous external ear canal can collapse, resulting in measurements from the cooler canal rather than the warmer tympanic membrane.<sup>4,5</sup>

Zambian mothers have been shown to use touch to assess a fever greater than  $37.8^{\circ}\text{C}$  in children with a sensitivity of 94% but only 44% specificity.<sup>7</sup> This suggests that while mothers may overestimate the presence of fever they rarely miss it.

Additional factors in the assessment of fever are diurnal rhythm (a difference of up to  $0.9^{\circ}\text{C}$  may occur between 04h00 (lowest) and 18h00 (highest), age (normal young infants may have a baseline temperature up to  $37.8^{\circ}\text{C}$ ), vaccinations (elevated temperature is common after vaccination) and over-bundling (this may artificially elevate an infant's temperature, which should be re-measured 30 minutes after un-bundling).<sup>4</sup>

Clinically, fever may be divided into four categories (Table I). Our focus is on the clinical evaluation of acute febrile illness in children under the age of 3 years in which the aetiology of the fever is not apparent after a careful history and examination.

**Table I. Categories of fever in children**

- Fever of short duration with localising signs and diagnosis by clinical history and physical examination
- Fever of short duration without localising signs for which the history and examination do not suggest a diagnosis but laboratory tests may establish diagnosis (occult bacteraemia)
- Fever of unknown origin (or PUO)
- Recurrent fever

## FEVER WITHOUT SOURCE AND OCCULT BACTERAEMIA

Fever without source (FWS) is a fever present for less than 1 week with no identifiable cause on initial history and examination. Up to 20% of febrile children have FWS.<sup>8</sup> These fevers generally represent a self-limited viral process, but occasionally occult bacterial infection is present. Occult bacteraemia (OB) is the unexpected presence of bacteraemia. These patients have often been discharged home with or without treatment after an outpatient evaluation. They do not have obvious sepsis (e.g. shock or purpura), they are not 'toxic' in appearance, do not have significant underlying chronic medical conditions and do not have foci of infection on examination.<sup>1</sup> 'Toxic' refers to a clinical picture consistent with the sepsis syndrome: lethargy and reduced activity, unresponsiveness or irritability, signs of poor perfusion, hypo- or hyperventilation, cyanosis.<sup>1</sup>

Febrile infants and young children are at increased risk for unrecognised serious bacterial infection (SBI) including meningitis, sepsis, bone and joint infections, urinary tract infections, pneumonia and enteritis. Immaturity of the immune system, as well as non-specific and inconsistent clinical presentation are contributing risk factors. Clinical evaluation alone, including an assessment of whether the child appears 'toxic', is inadequate to reliably exclude SBI. Specific clinical and laboratory criteria have been used to define a population of low-risk, non-toxic-appearing febrile infants 1 - 3 months of age who can be managed safely as outpatients (Tables II and III). This may reduce the number of infants hospitalised unnecessarily and help to identify infants who may safely be managed

**Table II. Suggested clinical data set for febrile infants < 3 months of age<sup>9</sup>**

History		Laboratory evaluation	
Prematurity	Antibiotic therapy	WBC: < 5 or > 15 x 10 <sup>9</sup> /l	Bands: >1 x 10 <sup>9</sup> /l
Chronic illness	Prior hospitalisation	Urinalysis 5 WBC/hpf	If crackles/tachypnoea – CXR
Physical examination		If diarrhoea – 5WBC/hpf	Blood culture
Temp, pulse, RR, BP, (Sats)	Hydration abnormal	Urine culture	CSF culture
Perfusion abnormal	Activity abnormal	Social situation	
Otitis media	Skin infection/rash	Home telephone	Car available
Bone/joint infection		Parental maturity	Thermometer
		Distance to travel < 30 mins	

**Table III. Low-risk criteria for febrile infants<sup>8</sup>**

Clinical criteria	
• Previously healthy, term infant	• Non-toxic clinical appearance
• No focal bacterial infection (except otitis media)	• Good social situation
Laboratory criteria	
• WCC 5 - 15 x 10 <sup>9</sup> /l, < 15 bands x 10 <sup>9</sup> /l, or band/neutrophil ratio < 0.2	• Negative Gram stain of unspun urine, or negative urine dipstix, or < 5 WBCs/hpf
• When diarrhoea present, < 5 WBCs/hpf in stool	• CSF: < 8 WBCs/mm <sup>3</sup> and negative Gram stain

**Table IV. Probability of bacterial infections in infants ≤ 3 months of age by clinical and laboratory findings<sup>9</sup>**

	Infant risk category		
	Low risk	Non-toxic	Toxic
SBI (%)	1.4 (0.4 - 2.7)	8.6 (3.7 - 15.6)	17.3 (8.0 - 30.0)
Bacteraemia	1.1 (0.2 - 2.6)	2.0 (0.8 - 3.8)	10.7 (6.7 - 15.7)
Meningitis	0.5 (0.0 - 1.0)	1.0 (0.2 - 2.4)	3.9 (1.7 - 7.1)

Figures refer to risk ratio and 95% confidence interval.

as outpatients.<sup>8</sup> The probability of a low-risk infant developing a serious bacterial infection is extremely low compared with an ill or toxic child (Table IV).

The frequent empirical use of antibiotics for febrile children<sup>10</sup>

contributes to the emergence of high-level resistant bacterial strains, of which multi-resistant *S. pneumoniae* is of particular concern. The clinical utility and cost-effectiveness of empiric antibiotic treatment of febrile children at risk for OB has been difficult to study

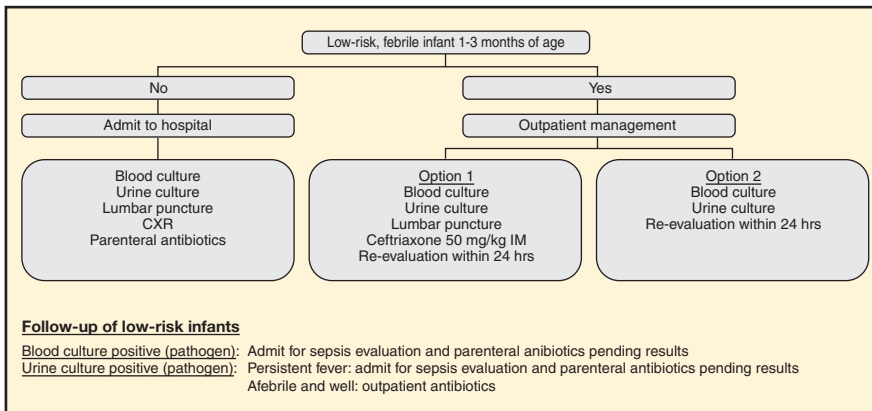


Fig. 1. Clinical approach to fever without source in 1 - 3-month-old infant.

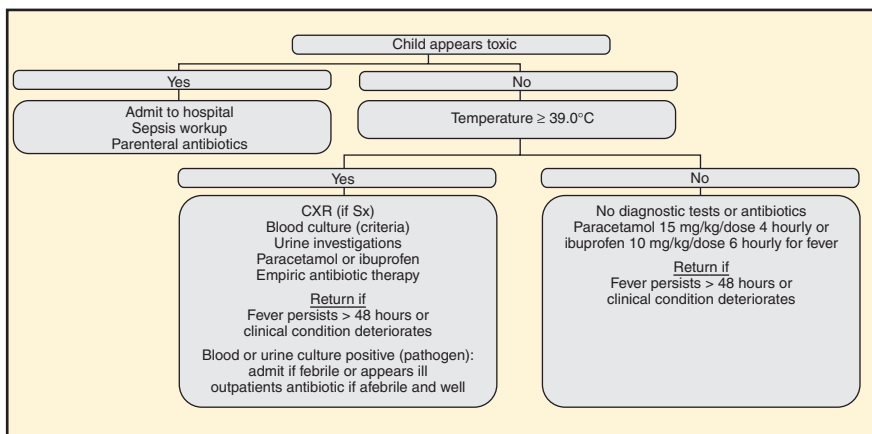


Fig. 2. Clinical approach to fever without source in 3 - 36-month-old child.

prospectively. This is because adverse outcomes of OB are uncommon. As a result, practice guidelines have been in use since the early 1990s.

### FEBRILE INFANTS YOUNGER THAN 1 MONTH OF AGE

Most authors favour hospitalisation, full sepsis evaluation and empiric parenteral antimicrobial therapy in infants younger than 1 month of age (neonates) presenting with fever. Sepsis evaluation includes full blood count and differential, blood culture, urine and cerebrospinal fluid microscopy, culture and sensitivity, chest radiograph and stool microscopy and culture, if diarrhoea is present.<sup>9</sup> Appropriate first-line empiric antimicrobial therapy is ampicillin and gentamicin. If meningitis is

suspected, gentamicin should be substituted for cefotaxime or ceftriaxone.

Algorithms outlining practice guidelines for febrile infants older than 1 month of age and young children are shown in Figs 1 and 2.<sup>8</sup>

### OTHER CATEGORIES OF FEVER

#### Recurrent fever

Recurrent or periodic fever refers to 3 or more episodes of fever in a 6-month period, with no defined medical illness explaining the fevers and with an interval of at least 7 days between febrile episodes. This definition differentiates recurrent fevers from daily, persistent fevers, which after 3 - 4 weeks would meet the criteria for fever of unknown origin (FUO). The aetiologies of FUO are far

more diverse than those of recurrent fever, so defining a fever as recurrent rather than persistent is an important distinction.<sup>11</sup>

The differential diagnosis for the child with recurrent fever may be divided into those with fever occurring at regular and irregular intervals. The likely causes of fever occurring at regular intervals include PFAPA syndrome (periodic fever, aphthous ulcers, pharyngitis and adenopathy), cyclic neutropenia, relapsing fever (*Borrelia* spp.), familial Mediterranean fever, hyper-IgD syndrome and Epstein-Barr virus infection. The initial workup for a child with recurrent fever includes a careful history, including detailed family history, and physical examination, full blood count with differential, erythrocyte sedimentation rate and C-reactive protein, urine culture and blood culture if clinically indicated.<sup>11</sup>

#### Fever of unknown origin

Most authorities would define a FUO as the presence of a fever for longer than 3 weeks and failure to establish a diagnosis despite 1 week of intensive hospital investigation. In most cases children with FUO are not overwhelmingly ill.

The differential diagnosis of FUO is protean. About 40% are due to infections and 10% each may be due to inflammatory, collagen vascular and oncological disorders. In about 20 - 30% of cases no cause is found. FUO may also be caused by drugs such as the beta-lactam antibiotics, phenothiazines, phenytoin and sulfa drugs. The spectrum of causes varies from country to country. In developing countries infections predominate while in developed countries the other causes predominate.

The investigation and management of the patient should be individualised. The history and examina-

tion must be comprehensive and include history of travel, drug ingestion, and exposure to animals and animal products. Special investigations are dictated by the possible differential diagnoses that are considered. As a minimum a chest X-ray, tuberculin skin tests, blood film for malaria, blood and urine cultures and basic serological tests should be done.

## Fever in immunocompromised children

Fever in patients who are immunocompromised as a consequence of a primary or secondary immunodeficiency disorder or from the use of agents that depress one or more components of the immune system warrants a different approach from that outlined above. Fever may be the only manifestation of serious infection and requires urgent evaluation and intervention with broad-spectrum antimicrobial cover.<sup>12</sup>

Febrile HIV-infected infants and children are common. Westwood *et al.*<sup>13</sup> found 25% of blood cultures to be positive in 136 presumed infective episodes in HIV-infected children collected over a 1-year period, 44% of which were caused by pneumonia. Factors placing HIV-infected children at higher risk of serious bacterial infection include malnutrition, poor socioeconomic circumstances, high risk of HIV-TB co-infection, neutropenia as a result of bone marrow suppression and vaccine failure. Immune reconstitution disease following the introduction of highly active antiretroviral therapy (HAART) is being increasingly recognised as contributing to infective episodes in the immediate post-HAART period. The overall high-risk medical and social settings that often accompany febrile HIV-infected children favour inpatient management.

FUO is also common in HIV-positive patients. It occurs in 20 - 40% of patients and is associated with significant morbidity and mortality. Most are due to unrecognised opportunistic infections and generally tend to occur in individuals who are more immunocompromised.

## LABORATORY MARKERS OF BACTERIAL INFECTION

Widely used laboratory screening parameters include urine and cerebrospinal fluid white blood cell counts, peripheral white blood cell count, band to neutrophil ratio and C-reactive protein (CRP). Other markers including interleukin 6 and 8, interleukin-1 receptor antagonist, soluble tumour necrosis factor receptor and interferon alpha have been studied but are not in widespread clinical use.<sup>14</sup>

Recently, procalcitonin (the precursor of calcitonin) has been shown to be a good marker of severe bacterial infection in neonates, children and adults.<sup>15</sup> It is also useful as a marker of prognosis in severe sepsis and shock.<sup>16</sup> Procalcitonin (PCT) is a stable polypeptide present in the plasma of healthy subjects (< 0.5 ng/ml).<sup>15</sup> It has a shorter half-life than CRP. Under experimental conditions, it shows a marked rise in response to the administration of endotoxin to healthy volunteers.<sup>15</sup> Measured in patients, PCT shows a mild to moderate rise (0.5 - 2 ng/ml) in response to viral infection, bacterial colonisation, postoperative trauma or localised bacterial infection (such as pneumonia or pyelonephritis). PCT concentrations of 2 - 10 ng/ml are found with systemic bacterial, fungal or parasitic infections and severe burns or polytrauma while values greater than 10 ng/ml are strongly suggestive of severe sepsis and shock.

PCT measurement has been shown to be a sensitive and specific tool in meningococcal sepsis,<sup>17</sup> meningitis,<sup>18</sup> pyelonephritis<sup>19</sup> and perinatal disease.<sup>20</sup> There are some conflicting reports with regard to differentiating bacterial from viral community-acquired pneumonia.<sup>21,22</sup> A semi-quantitative rapid test has been developed and is available in the larger centres in South Africa.

## FEVER PHOBIA

Misinformation and ignorance have led to the belief among some people that fever is itself a disease rather than a symptom or sign of illness. This view may also originate from previous experience of 'aggressive' laboratory testing and presumptive treatment for occult bacteraemia in children presenting with fever. This can result in undue caution and inappropriate management of fever on the part of parents. A study in Baltimore revealed some interesting responses to a child's fever including measuring the temperature every hour when febrile, antipyretics given when the temperature was below 37.8°C, and ibuprofen and paracetamol given too frequently. Interestingly, 46% of parents in the study said they were acting on information given by their doctor.<sup>23</sup>

## TREATMENT OF FEVER

Therapy should be directed at the cause of the fever and not the fever *per se*. The specific treatment of fever is also controversial and some would argue that it is unnecessary except in situations where the temperature is exceedingly high. The main indication for treating fever in such cases would be to reduce the child's level of discomfort (not the parents' or doctor's). Other indications include those children at risk of cardiac or respiratory

decompensation as a result of high fever, children with neurological disorders and children at increased risk of febrile seizures. There is, however, limited evidence that active treatment of fever is effective in preventing febrile seizures.

The rationale for favouring pharmacological treatment over physical heat loss measures, such as sponging and fanning, is that fever results from an elevated set-point

of the thermoregulatory centre in the hypothalamus.<sup>4</sup> Sponging and fanning may themselves be a source of considerable discomfort for the child.<sup>24</sup> The initial drug of choice is paracetamol in adequate dosage (15 mg/kg/dose 4 - 6 hourly) to provide both antipyretic and analgesic effect. Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and mefenamic acid, should be reserved for short-term, second-

line use. Avoid the use of aspirin in children because of the risk of Reye's syndrome. There is no evidence that alternating doses of paracetamol and NSAIDs is more effective than either agent used alone. A response to antipyretics (i.e. drop in temperature) does not indicate a viral aetiology for the fever.

References available on request.

## SINGLE SUTURE

A little of what you fancy ...

As drinking and abstinence behaviour changes over time, some view the conventional J-shaped mortality curve (which depicts abstainers and heavy drinkers as having a higher mortality risk than those who indulge moderately) with scepticism. When researchers prospectively studied the relation by using two measurement points, they found that risk for consistent abstainers was not raised, but for men who consistently drank heavily the all-cause mortality risk was higher. Abstainers who started drinking did not improve their survival rate; heavy drinkers who reduced consumption did.

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