

Core Messages

- › Fever is a very common complaint in children accounting for as many as 20% of paediatric visits to doctors.
- › How sick the child looks is more important than the level of fever.
- › Normal body temperature does not preclude serious infection.
- › Most children aged 0–36 months who have fever have a focus of infection, which can be identified by careful history and examination. A viral upper respiratory tract infection is the most common focus.
- › Most children aged 0–36 months without an obvious focus of infection have viral infections, but they may harbor two important serious bacterial infections (SBI): urinary tract infection or bacteremia.
- › Febrile neonates and ill-looking children, regardless of age, are at high risk for SBI and need antibiotic coverage, hospital admission, and comprehensive septic work-up. This entails blood and urine cultures, full blood cell count (FBC), C-reactive protein (CRP), and, when indicated, chest X-ray, LP and stool studies.
- › Children aged 1–36 months without a focus may be treated more selectively: if the temperature is $>39^{\circ}\text{C}$, WBC count is $>15,000\text{mm}^{-3}$ and CRP is $>40\text{mg L}^{-1}$; urine and blood cultures should be ordered; and a third-generation cephalosporin (ceftriaxone or cefotaxime) considered.
- › The distribution of the diseases causing pyrexia of unknown origin (PUO) differs according to the geographic area and the socioeconomic status of the country.
- › In PUO, atypical presentation of a common disease is more common than a rare and exotic disease.

1.1

Definitions

Fever (pyrexia) may be defined in both pathophysiological and clinical terms:

Pathophysiologically, fever is an interleukin-1 (IL-1) mediated elevation of the thermoregulatory set point of the hypothalamic center. In response to an upward displacement of the set point, an active process occurs in order to reach the new set point. This is accomplished physiologically by minimizing heat loss with vasoconstriction and by producing heat with shivering. Behavioral means of raising body temperature include seeking a warmer environment, adding more clothing, curling up in bed, and drinking warm liquids.

Clinically, fever is a body temperature of 1°C (1.8°F) or greater above the mean at the site of temperature recording. For example, the range of body temperature at the axilla is 34.7–37.4°C, with a mean of 36.5°C; 1°C above the mean is 37.5°C. The following degrees of temperature are accepted as fever (see also Chap. 5):

Rectal temperature	≥38.0°C
Oral temperature	≥37.6°C
Axillary temperature	≥37.4°C
Tympanic membrane	≥37.6°C

The importance of at least 1°C higher than the mean temperature lies in the diurnal variation of normal body temperature, which reaches its highest level in early evening (5–7 p.m.). Diurnal temperature fluctuations are greater in children than in adults and are more pronounced during febrile episodes.

In young children, a relatively high rectal temperature predominates, with a gradual decrease towards adult levels beginning at 2 years of age. This trend stabilizes soon after puberty.

1.2

Patterns of Fever

The importance of febrile patterns has diminished in medical practice because only a few diseases are known to show a specific pattern of fever, and occasionally the same disease may present in different patterns of fever. In addition, the diagnosis can often be established nowadays by means of laboratory investigations, even before a specific pattern emerges. Several patterns may occur in clinical practice, which sometimes have clinical value, such as malaria with its characteristic fever pattern (Table 1.1).

Patterns of fever include the type of onset (insidious or abrupt), variation in temperature degree during a 24-h period and during the entire episode of illness, cycle of fever, and response to therapy. Further patterns are as follows:

- **Continuous or sustained fever** is characterized by a persistent elevation of body temperature with a maximal fluctuation of 0.4°C during a 24-h period. Normal diurnal fluctuation temperature is usually absent or insignificant.

Table 1.1 Fever patterns found in pediatric diseases

Fever pattern	Diseases
Continuous	Typhoid fever, malignant falciparum malaria
Remittent	Most viral or bacterial diseases
Intermittent	Malaria, lymphoma, endocarditis
Hectic or septic	Kawasaki disease, pyogenic infection
Quotidian	Malaria caused by <i>P. vivax</i>
Double quotidian	Kala azar, gonococcal arthritis, juvenile rheumatoid arthritis, some drug fevers (e.g., carbamazepine)
Relapsing or periodic	Tertian or quartan malaria, brucellosis
Recurrent fever	Familial Mediterranean fever

- **Remittent fever** is characterized by a fall in temperature each day but not to a normal level. This is the most common type of fever in pediatric practice and is not specific to any disease. Diurnal variation is usually present, particularly if the fever is infectious in origin.
- In **intermittent fever** the temperature returns to normal each day, usually in the morning, and peaks in the afternoon. This is the second most common type of fever encountered in clinical practice.
- **Hectic or septic fever** occurs when remittent or intermittent fever shows a very large difference between the peak and the nadir.
- **Quotidian** fever, caused by *P. vivax*, denotes febrile paroxysms which occur daily.
- **Double quotidian** fever has two spikes within 12 h (12-h cycles).
- **Undulant fever** describes a gradual increase in temperature that remains high for a few days, and then gradually decreases to normal level.
- **Prolonged** fever describes a single illness in which duration of fever exceeds that expected for this illness, for example, >10 days for a viral upper respiratory tract infection.
- **Recurrent fever** is an illness involving the same organ (e.g., urinary tract) or multiple organ systems in which fever recurs at irregular intervals.
- **Periodic and relapsing fevers** are discussed next.

1.2.1

Periodic and Relapsing Fever

- **Periodic fever (PF)** is characterized by episodes of fever recurring at regular or irregular intervals. Each episode is followed by one to several days, weeks or months of normal temperature. Examples are seen in malaria (termed *tertian* when the febrile spike occurs every third day, and *quartan* when the spike occurs every fourth day) and brucellosis.
- **Relapsing fever (RF)** is the term usually applied to recurrent fevers caused by numerous species of *Borrelia* and transmitted by lice (louse-borne RF) or ticks (tick-borne RF). Lice transmit *Borrelia* (*B. recurrentis*) from infected humans to other humans. Ticks

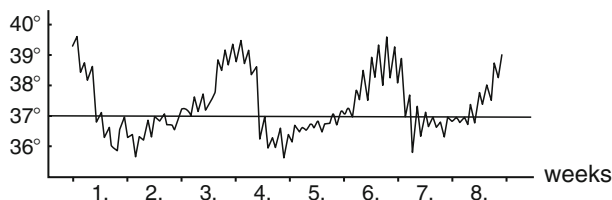


Fig. 1.1 Fever pattern in Pel–Ebstein fever

acquire the *Borrelia* (e.g. *B. duttonii*) from rodents (rats, mice, squirrels). The disease is characterized by rapid onset of high fever, which recurs in paroxysms lasting 3–6 days, followed by an afebrile period of similar duration. The maximum temperature is 40.6°C in tick-borne RF and up to 39.5°C in louse-borne. Associated complaints include myalgia, headache, abdominal pain, and alteration of sensorium. The resolution of each febrile episode may be accompanied within a few hours (6–8 h) by the **Jarish–Herxheimer reaction** (JHR), which usually follows antibiotic treatment. The reaction is caused by the release of endotoxin when the organisms are destroyed by antibiotics. JHR is very common after treating patients suffering from syphilis. It is less commonly seen with cases of leptospirosis, Lyme disease, and brucellosis. Symptoms range from mild fever and fatigue to a full-blown anaphylactic reaction.

- **Rat-bite fever** is another example, caused by *Spirillum minus* and *Streptobacillus moniliformis*. A history of rat bites 1–10 weeks prior to the onset of symptoms suggests the diagnosis.
- **Pel–Ebstein fever** (Fig. 1.1), described by Pel and Ebstein in 1887, was originally thought to be characteristic of Hodgkin's lymphoma (HL). Only a few patients with Hodgkin's disease develop this pattern, but when present, it is suggestive of HL. The pattern consists of recurrent episodes of fever lasting 3–10 days, followed by an afebrile period of similar duration. The cause of this type of fever may be related to tissue destruction or associated hemolytic anemia.

1.2.2

Genetic PF Syndromes (Autoinflammatory Diseases)

Genetic causes of PF syndromes that have been identified in the past few years are shown in Table 1.2. The term autoinflammatory disease has been proposed to describe a group of disorders characterized by attacks of unprovoked systemic inflammation without significant levels of autoimmune or infective causes [1]. Episodes of fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) are the most common clinical features. Each episode is followed by a symptom-free interval ranging from weeks to months. Some of the disorders have regular periodicity, whereas others do not. Most patients have mutations in either the protein pyrin or the TNF-receptor superfamily of molecules. Both play an important role in the inflammatory pathways of the immune system. Pyrin is present in neutrophils and their precursors. It is believed that pyrin decreases inflammation, particularly in neutrophils.

Table 1.2 Hereditary periodic fever syndromes

Disorder	Inheritance	Fever duration	Periodicity	Clinical features	Lab tests/etiology	Amyloidosis	Treatment
FMF	AR	1–3 days	3–6 weeks	Polyserositis (abdominal, chest pain), synovitis, myalgia	Inflammatory markers, gene mutations MEFV on chromosome 16, leading to protein defect	+	Colchicine
Cyclic neutropenia	AD	5–7 days	21 days	Pharyngitis, gingivitis, mouth ulcers, lymph-adenopathy, cellulites	Neutrophils <200, mutations of the gene neutrophil elastase: (ELA2): chromosome 19	No	GCSF
TRAPS	AD	Weeks	Irregular	Muscle cramps, migratory arthralgia, migratory erythematous rash	Inflammatory markers, mutation in TNFRSF1A gene: chromosome 12	Rare	NSAIDs, steroids
HIDS	AR	4–6 days	4–8 weeks	Abdominal pain, headache arthralgia, lymph-adenopathy, diarrhoea	IgD, IgA, TNF-low activity of mevalonate kinase, MVK: chromosome 12	No	Simvastatin?
PFAPA	Sporadic	3–5 days	3–6	Aphthous stomatitis, pharyngitis, Lymphadenitis	Inflammatory marker	No	Steroids, cimetidine
MWS/FCUS/ NOMID/ CINCA	AD	Irregular	Irregular	Urticaria, progressive deafness, arthritis, chronic meningitis, cutaneous rash, arthropathy, abdominal pain	Mutations in CIASI gene on chromosome 1q44	+	Anakinra, NSAIDs, steroids

FMF familial mediterranean fever; *TRAPS* tumor necrosis factor receptor-associated periodic syndrome; *HIDS* hyperimmunoglobulinemia d and periodic fever syndrome; *NOMID* neonatal-onset multisystem inflammatory disease; *CINCA* chronic infantile neurologic cutaneous and articular syndrome; *PFAPA* periodic fever, aphthous stomatitis, pharyngitis, and adenitis; *MWS* muckle-wells syndrome; *FCUS* familial cold urticaria; *AR* autosomal recessive; *AD* autosomal dominant; *GCSF* granulocyte colony stimulating factor; *NSAIDs* nonsteroidal antiinflammatory drugs

1.3
Phases of Fever

Fever is characterized by three phases:

- **The phase of temperature rise** is often characterized by discomfort and is the result of decreased heat loss through vasoconstriction and increased heat production through shivering. The patient feels cold and the skin also feels cold to the touch.
- **The phase of temperature stabilization (fastigium)** then occurs at the new level of the thermoregulatory set point. Heat production and heat loss are balanced as in normal health, but at the higher hypothalamic set point. A flushed or pink appearance signifies that the fever has peaked. Once this phase is reached, the child usually feels comfortable without shivering.
- **The phase of falling temperature or defervescence** occurs either by lysis (falling gradually within 2–3 days to a normal level) or by crisis (falling within a few hours to a normal level).

Table 1.3 shows mechanisms leading to normal and abnormal body temperatures.

1.4
Manifestations during Fever

The subjective perception of fever is generally absent in children, and fever is usually detected by the parents. Manifestations associated with fever vary considerably and depend on the child's age, how acute and how high the fever is, and the nature of the disease that has caused the fever. Common manifestations are summarized in Table 1.4.

- **Symptoms** directly related to fever include chills or rigor, which characteristically herald the onset of high fever. Young children do not often report chills, and the chills may be so subtle that they pass unnoticed. Chills are more characteristic of some

Table 1.3 Peripheral mechanisms responsible for normal and abnormal body temperature

Mechanism	Example	Relation of body temperature to the hypothalamic set point
Heat production = loss	Health, second phase of fever	Body temperature = set point
Heat production > loss	First phase of fever, MH	Body temperature > set point
Heat loss < production	Heat stroke	Body temperature > set point
Heat production < loss	Hypothermia	Body temperature < set point

MH malignant hyperthermia

Table 1.4 Summary of the clinical changes noted during fever

Manifestation	Clinical findings
Symptoms	Chills (rigor), myalgia, headaches, anorexia, excessive sleep, fatigue, thirst, delirium, scanty urine (oliguria)
Signs	Drowsiness, irritability, tachycardia, tachypnoea, increased BP, flushed face, grunting, decrease in GFR, proteinuria. Accentuation (or appearance) of an innocent (functional) murmur and third heart sound
ECG changes	Shortening QT-intervals, increase in supraventricular ectopic beats

BP blood pressure; *GFR* glomerular filtration rate

diseases such as bacteremia and lobar pneumonia. They may also occur in viral diseases and in noninfectious diseases, such as lymphoma. Other symptoms of fever include tachycardia, myalgia, anorexia, and fatigue.

- **Signs** of fever include tachycardia, with the pulse rate rising 10 beats per minute for every 1°C temperature elevation. Tachypnoea during fever is an increase of respiratory rate by approximately 2.5 breaths per minute for each 1°C elevation of body temperature, occasionally associated with grunting (arousing the suspicion of pneumonia). In pneumonia and malaria, the temperature effect on the respiratory rate is even higher at 3.7 breaths per minute per °C [2]. The reason for the difference between 2.5 and 3.7 breaths is related to the comorbid features in these diseases, such as anemia and acidosis and the role of cytokines. While the initial phase of fever is accompanied by a rise in blood pressure and a decrease in glomerular filtration rate (GFR), sustained fever is associated with a fall in blood pressure and a slight increase in the GFR. Proteinuria occurs in 5–10% of children with fever without pre-existing renal diseases.
- An occasionally encountered sign during fever is **relative bradycardia**, which is a pulse rate disproportionately low for the degree of fever. Normally, for every 1°C (1.8°F) rise in fever, the pulse rate increases by 10. For example, a patient with a temperature of 40°C (whose pulse normally is 70 per minute) and a pulse rate lower than 100 per minute has relative bradycardia. Classic causes of relative bradycardia are typhoid fever, drug fever, central nervous system (CNS) lesions, brucellosis, leptospirosis, and factitious fever. **Relative tachycardia** is a pulse rate disproportionately elevated in relation to the degree of fever. Examples include hyperthyroidism and myocarditis.

1.5 Metabolic Effects of Fever

The host metabolic response during fever depends on a number of factors, including the age of the child, the height and duration of the fever, and the severity and duration of the underlying illness. A summary of the metabolic response during fever is shown in Table 1.5. Most of the requirements for cellular energy are supplied by glucose, while free fatty acids

Table 1.5 Summary of the metabolic changes [increase (↑) or decrease (↓)] occurring during fever

↑ Energy expenditure (10% for each°C ↑)	↓ Liver albumin
↑ O ₂ consumption (10–12% for each°C ↑)	↓ Nitrogen balance
↑ Insensible water loss (10% for each°C ↑)	↓ Sodium
↑ Glucose production	↓ Iron, zinc
↑ Amino acids release	
↑ C-reactive protein, haptoglobin, ceruloplasmin, fibrinogen, triglyceride	
↑ Hormones: cortisol, ACTH, growth hormone, arginine vasopressin	
↑ Copper	

are used to a lesser extent. Glucose production is increased in the liver by using amino acids as substrates. These amino acids are released during proteolysis in the muscles and are transported via plasma into the liver. Despite the increase in uptake of amino acids, production of albumin in liver decreases. Nitrogen balance begins to be negative soon after the onset of fever, reaching a loss of about 10g daily if the fever is high. While plasma iron and zinc concentrations decline rapidly, depriving invading microorganisms of essential nutrients, that of copper increases.

Increase in serum cortisol of up to fivefold may occur in severe bacterial infections. Arginine vasopressin (AVP) is also increased and is responsible for the maintenance of homeostasis of body fluid during fever. Hyponatremia often occurs in association with acute febrile diseases, particularly with pneumonia and meningitis, as a result of inappropriate secretion of AVP. AVP is an endogenous antipyretic, which is secreted in an attempt to control the fever.

Although some of these changes appear harmful, healthy children usually recover rapidly after febrile episodes. Wasting of body fat and muscle may occur if the fever is prolonged.

1.6
Potential Complications (See Box 1.1)

Complications directly related to fever are rare. Morbidity and mortality are closely linked to the severity of the underlying disease but not to the level of fever. Complications are the following:

- **Dehydration** may occur owing to increased body temperature and the therapeutic effects of drugs that promote sweating. Fever and infection increase the metabolic rate to <1.5 times the basal metabolic rate. For every 1°C rise of body temperature, there is a 10% increase of insensible water loss. Dehydrated children are prone to heat stroke,

Box 1.1 Practical Tips

- › Fever should not be equated with hyperthermia; the latter is due to imbalance between heat production and loss and is not controlled centrally.
- › Fever is not dangerous. If there is morbidity or mortality, it is due to the underlying disease. The associated fever may be protective.
- › The principal complication of fever is dehydration, which can be easily prevented and treated by providing extra fluid to the child.
- › Fever does not damage the central nervous system. It also does not climb up relentlessly because it is well controlled by a hypothalamic center.

particularly if the child is excessively wrapped. It is essential to prevent this complication by offering oral fluids to the febrile child frequently.

- Three to four percent of genetically susceptible children younger than 5 years experience **fever-induced seizure (febrile seizure)**, which occurs when the temperature of a susceptible child rises rapidly.
- Some young children experience **delirium** in association with a high degree of body temperature. This is a nonspecific sign, occurring in viral as well as with bacterial infections. Delirium often recurs, causing considerable anxiety to the parents.
- **Hyperpyrexia** is a rectal temperature of 41.1°C or higher (for axillary or tympanic temperature, 40°C is taken instead of 41.1°C), as defined by Dubois, who observed this degree of temperature elevation in about 5% of 1,761 patients with severe bacterial infections [3]. In a recent study of 130,828 consecutive pediatric patients seen over a two-year period, only 103 (1 per 1,270 patient visits) had a fever of 41.1°C or higher [4]. Of the 103 subjects, 20 (18.4%) had serious bacterial infection. This report and others [5] emphasized the significant association between such a degree of temperature elevation and serious bacterial infections, such as bacterial meningitis. Apart from infection, hyperpyrexia up to 41.8°C has been reported in newborn infants presenting with intraventricular haemorrhage [6].
- **Herpes labialis** (cold sore) results from activation of a latent herpes simplex infection in association with febrile illnesses. It occurs less often in children than in adults, and is more common with certain bacterial infections, such as pneumococcal or meningococcal infection.

1.7**Classification of Fever (Tables 1.6 and 1.7)****1.7.1****Fever with Localized Signs**

Table 1.6 The principal three classes of fever encountered in pediatric practice

Class	Commonest cause	Usual fever duration
Fever with localizing signs	URTI	<1 week
Fever without localizing signs	Viral infection, UTI	<1 week
Fever of unknown origin	Infection, JIA	>1 week

URTI upper respiratory tract infection; *UTI* urinary tract infection; *JIA* juvenile idiopathic arthritis

Table 1.7 Definitions of terms used in Sect. 1.7

Term	Definition
Fever with localization	Acute febrile illness with a focus of infection, which can be diagnosed after a history and physical examination
Fever without localization	Acute febrile illness without apparent cause of the fever after a history and physical examination
Lethargy	Poor or absent eye contact; no interaction with the examiner or parents, no interest in surroundings
Toxic appearance	Clinical signs characterized by lethargy, evidence of poor perfusion, cyanosis, hypo- or hyperventilation
Serious bacterial infections	Suggest serious diseases, which can be life threatening. Examples are meningitis, sepsis, bone and joint infection, enteritis, urinary tract infection, pneumonia
Bacteraemia and septicemia	Bacteremia indicates the presence of bacteria in blood, evident by a positive blood culture; septicemia indicates in addition tissue invasion of the bacteria, causing tissue hypoperfusion and organ dysfunction

Table 1.8 Main causes of fever due to diseases of localized signs

Group	Diseases
Upper airway infections	Viral URTI, otitis media, tonsillitis, laryngitis, herpetic stomatitis
Pulmonary	Bronchiolitis, pneumonia
Gastrointestinal	Gastroenteritis, hepatitis, appendicitis
CNS	Meningitis, encephalitis
Exanthems	Measles, chickenpox
Collagen	Rheumatoid arthritis, Kawasaki disease
Neoplasma	Leukaemia, lymphoma
Tropics	Kala azar, sickle cell anaemia

URTI upper respiratory tract infection

The most common febrile illnesses encountered in pediatric practice belong to this category (Table 1.8). Fever is usually of short duration, either because it settles spontaneously or because a specific treatment, such as an antibiotic, is administered. Diagnosis may be suggested by the history and physical examination and confirmed by simple investigation, such as a chest X-ray. As children <36 months experience the highest rate of febrile illnesses with localizing signs, a brief discussion of this subject in this age group is presented.

Fever in children <3 days of age

Fetal temperature. Fever is unusual in the fetus, rare in neonates, and infrequent in the pregnant mother before parturition. It has been assumed that fever suppression in these groups may be caused by the action of the arginine vasopressin hormone, which acts as an endogenous antipyretic. Fetal temperature at about 38.0°C is 0.5–0.9°C higher than the mean maternal core temperature, allowing a continuous heat transfer along the gradient from the fetus to the mother through the umbilical circulation. At birth, the body temperature of the neonate and mother briefly maintains this difference. Heat is produced via nonshivering thermogenesis, which begins shortly after birth.

Fever in children 1–3 days of age, elevated body temperature (fever or hyperthermia) in the first hours of life may be caused by the following:

- **Maternal fever.** The major cause of such an intrapartum fever is the use of epidural anesthesia, occurring in about 15% of women (7). The longer the labor, the greater the risk of fever development in women who are given an epidural.
- **Maternal infection.** A less frequent cause of intrapartum fever is maternal infection, such as chorioamnionitis. Infants of women who are febrile during labor are more likely to be evaluated for sepsis and to receive antibiotics than infants of afebrile women. These infants may also need resuscitation because of low Apgar score and hypotonia.
- **Hyperthermia.** Elevated body temperature during the first 1–3 days of life may be caused by placing the neonate under a radiant warmer or dehydration. Infection as a cause of fever at this age is rare.

Fever in children 4 days to <3 months of age

Children at this age have the highest incidence of serious bacterial infection (SBI), estimated to be 12% in neonates and 6% in children aged 1–2 months. Overall, children younger than 3 months of age have a 21-times higher risk of SBI than those older than 3 months [8]. Definite identification of SBI requires a positive culture of the cerebral spinal fluid (CSF), blood, stool, or urine or an identifiable bacterial focus by physical examination or radiograph.

Despite the high incidence of infection, febrile episodes are uncommon in this age group, and some seriously ill infants are hypothermic. In a series of consecutive infants younger than 3 months of age evaluated at an ambulatory clinic, only 1% had a rectal temperature >38.0°C, with a temperature >40.0°C occurring in only 6% of these febrile episodes [9]. The rate of SBI has been shown to be proportional to the height of fever, occurring in 9.5% with a temperature <40°C and in 36% with a temperature of 40°C and greater [10]. A normal temperature did not exclude infection: 30% of infants with SBI were afebrile on admission [11].

Infants usually present with nonspecific and subtle symptoms (Table 1.9). Organisms causing SBI are shown in Table 1.10.

Management of febrile children at this age is summarized in Fig. 1.2.

Table 1.9 Symptoms and signs of a child with serious bacterial infection

General	Reduced activity, weak cry, poor eye contact, absent smile
Body temperature	Instability, fever, hypothermia
Signs of shock	Clammy, mottled skin, reduced CRT
Respiratory	Apnoea, tachypnoea, shallow respiration, grunting
Gastrointestinal	Poor feeding, vomiting, abdominal distension, diarrhea
CNS	Drowsiness, sometimes alternating with irritability (in case of meningitis: bulging fontanelle, other meningeal signs such as neck stiffness are usually absent)

CNS central nervous system; CRT capillary refill time

Table 1.10 The most common organisms causing SBI in children younger and older than 3 months of age.

Children <3 months	
Developed countries	
Early-onset	GBS, <i>E. coli</i>
Late-onset	<i>E. coli</i> , GBS, CONS, <i>N. meningitidis</i> , <i>S. pneumoniae</i> , <i>Salmonella</i> , <i>Listeria monocytogenes</i>
Developing countries	<i>Klebsiella</i> , <i>E. coli</i> , <i>Pseudomonas</i> , <i>Salmonella</i> , <i>Staphylococcus aureus</i> , <i>H. influenzae</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i>
Children >3 months	<i>S. pneumoniae</i> , <i>N. meningitidis</i> , <i>Salmonella</i>

GBS group B streptococcus; CONS coagulase negative staphylococci; *S. Streptococcus*; *N. Neisseria*, *H. Haemophilus*

Fever in children 3 to 36 months of age

Children aged 3–36 months have the highest incidence of fever during childhood, with approximately six febrile episodes per year. An upper respiratory tract infection (URTI) is the most common infection, occurring in 50% of all febrile episodes. The highest degrees of fever are found in this age group. Temperature >40°C is common, occurring in 20% of all febrile episodes. Such a degree of fever may accompany bacterial or viral infection. In contrast to younger children, the vast majority of febrile illnesses are benign and self-limited. SBIs are uncommon (about 2–3%). Table 1.11 summarizes factors that increase the risk of SBI.

Management of a child with fever includes history, physical examination, and laboratory investigation. The most important challenge facing a physician is to determine the etiology of the illness, in particular confirming or excluding a serious disease. Management includes the following:

- **History taking**, focusing on:
 - Onset and duration of fever, the degrees of temperature recorded at home, and the temperature-taking method

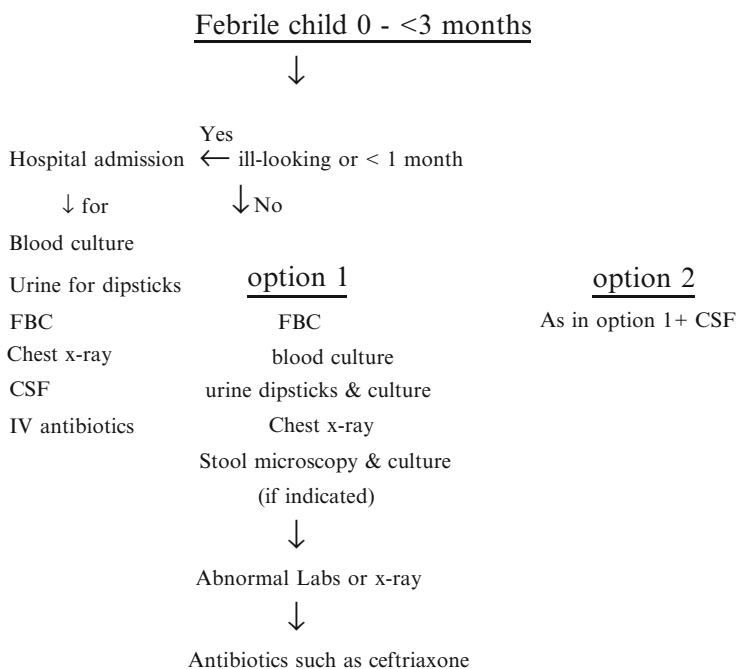


Fig. 1.2 Management of a child aged 0 to <3 months without a focus of infection

- Presence of similar symptoms in other family members
 - Pattern of feeding, degree of activity, playfulness at home
 - Features suggestive of SBI (Tables 1.9, 1.11, and 1.12)
 - Pre-existing disease
 - Previous administration of antibiotics
- **Physical examination**, performed in two parts, consisting of:
 - Observation of items to predict SBI (shown in Table 1.12). These items, combined with a history and physical examination, can identify most serious diseases in children. Those children who are unwell require immediate admission to hospital, appropriate investigation, and treatment. Those who appear well are managed according to the algorithm shown in Fig. 1.3
 - Physical examination, looking particularly for a focus to explain the fever
 - **Investigation**, taking into consideration that:
 - In a child with localized signs of infection, investigation should be minimal and focus on the diagnostic test most likely to provide a diagnosis
 - Screening tests include full blood cell count (FBC), looking particularly at the white blood cell (WBC) count, C-reactive protein (CRP) and urine dipsticks

Table 1.11 Factors that increase the prediction of SBI

Age	Infants <3 months
Temperature	
Neonates	Any degree of fever
Older child	>39.0°C, particularly >40°C
Pre-existing disorder	
Neonates	Prematurity, premature rupture of membrane, maternal infection, GBS
Older child	Sickle cell anaemia, immunosuppression, nephrotic syndrome, splenectomy, HIV-infection
Others	Venous catheter, skin petechiae
History and signs	See symptoms and signs in Table 1.9
Laboratory findings	WBC >15,000, CRP >10 (neonates); >40 (older child) CSF: >8 WBC mm ⁻³ Urine: positive nitrate on dipsticks, urinalysis showing >10 WBC per hpf Chest radiograph: infiltrate Stool: >5 WBC per hpf stool smear

hpf high power field; *CRP* C-reactive protein; *WBC* white blood cell; *CSF* cerebro spinal fluid

Table 1.12 Summary of observation items to identify a child with SBI

Item	Unwell	Very unwell
Appearance	Ill looking (lethargy, reduced activity)	Absent eye contact, does not recognize parents, no activity
Quality of cry	Whimpering	Weak cry, high-pitched cry
Response to cuddling	Slow response, unwilling	Too weak to respond
Alertness	Drowsiness	Frequently falls asleep, difficulty to arouse
Hydration	Slightly dry mouth	Dry mouth, sunken fontanelle, doughy skin
Color	Peripheral cyanosis or pallor	Mottled, pale face or ashen
Sociability/stimulation	Brief smiling and response	Not smiling, anxious face, expressionless

- In small children, chest auscultation is frequently unreliable and chest X-ray is usually necessary to establish the diagnosis of pneumonia
- Blood culture is an important test in a child thought to have SBI, particularly in a child who has no focus of infection.
- Pulse oximetry is a mandatory test for any ill child.

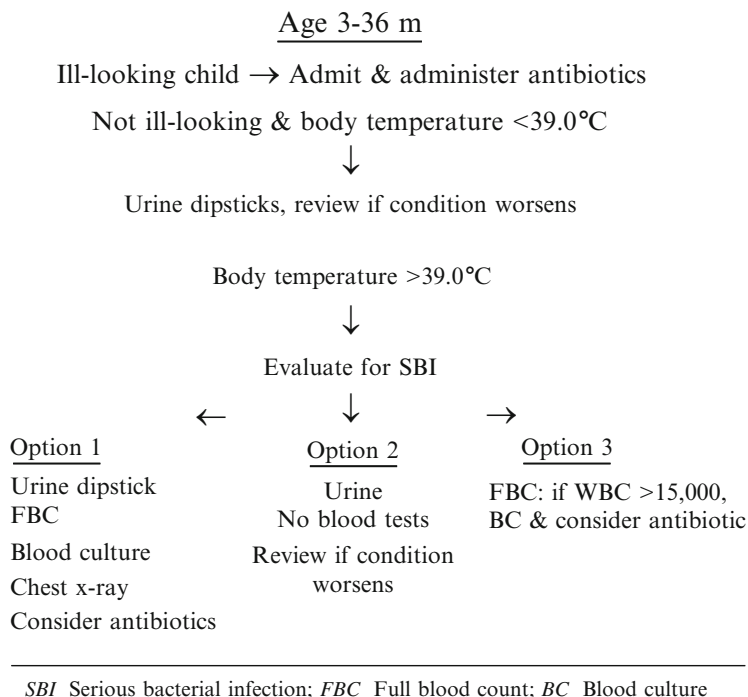


Fig. 1.3 Management of a child 3–36 m of age without a focus of infection

- Antibiotic treatment, depending on the underlying disease, how ill the child is, age of the child, and the height of the fever. It is indicated for:
 - Any ill-appearing child, irrespective of age
 - Neonates
 - Children whose focus of infection is likely to be caused by bacteria
 - Children aged 1–2 months who appear well but the initial laboratory tests (e.g., CRP) are abnormal

For children 3 months of age and older, antibiotics are not indicated in most infections, which tend to be viral as an underlying cause.

1.7.2

Fever without Localized Signs (Bacteremia)

About 20% of all febrile episodes demonstrate no localizing signs on presentation. The most common cause is a viral infection, mostly occurring during the first few years of life. Such an infection should be considered only after exclusion of urinary tract infection

Table 1.13 Usual causes of fever without localized signs

Causes	Examples	Clues for diagnosis
Infection	Bacteremia/sepsis Most viruses (HH-6) UTI Malaria	Ill looking, high CRP, leukocytosis Well appearing, normal CRP, WBC Urine dipsticks In malarial area
PUO	JIA	Pre-articular, rash, splenomegaly, high ANF (antinuclear factor), CRP
Post-vaccination	Triple vaccination, measles	Time of fever onset in relation to the time of the vaccination
Drug fever	Most drugs	History of drug intake, diagnosis of exclusion (see Sect. 1.9)

HH-6 human herpes-6; UTI urinary tract infection; JIA juvenile idiopathic arthritis; CRP C-reactive protein; WBC white blood cell

(UTI) and bacteremia. Table 1.13 shows the most common causes of this group. SBIs include UTI, malaria in malaria endemic areas, and bacteremia.

Bacteremia indicates the presence of bacteria in blood, while septicemia suggests the tissue invasion of the bacteria, causing tissue hypoperfusion and organ dysfunction. Neonates and young infants more often have septicemia rather than bacteremia. The overall incidence of bacteremia in febrile children is around 1%, but higher risks exist in:

- Children aged 3–24 months who have the highest incidence, estimated to be 3–4%, with children aged 7–12 months demonstrating twice the incidence of those aged 13–18 months
- Association with high fever. While the risk of bacteraemia is negligible with temperatures of 38–39°C, a strong correlation exists between the incidence of bacteremia and higher temperatures. The incidence is 7% with temperatures of 40–40.5°C, 13% with a temperature of 40.5–41.0°C, and 26% with a temperature higher than 41.0°C

Symptoms and signs of bacteremia are often those noted in children with SBI (Table 1.9). Abnormal findings on physical examination may be absent, with fever above 39.0°C and ill general appearance being the only manifestations of the disease. Occasionally, bacteremic patients may present with alarming symptoms such as hypotension, impairment of consciousness, disseminated intravascular coagulopathy (DIC), and renal failure.

Although bacteremia occurs more frequently as a primary isolated disease, many infectious diseases are known to be associated with septicemia. These include meningitis (in up to 80% depending on organisms and age), pneumonia (in about 10%), and otitis media (1.5%) [12]. Bacteremic pneumococcal pneumonia has been found to have an increased fatality compared to cases of pneumococcal pneumonia without bacteremia [13].

The predominant bacteria isolated from blood culture in the neonatal period are group B streptococcus (GBS), which were responsible for over 50% of early-onset neonatal

Box 1.2 Summary for the Clinician on Management of a Febrile Child

- › Most children who present with fever are <3 years of age
- › The challenge for the clinician is in differentiating children with viral infection from those with SBI. Careful history-taking and observation (while the child in the parent's arms) by an experienced clinician can provide such differentiation.
- › A urine sample should be tested with urine dipsticks in any child with fever, particularly in a child without a source of infection. The presence of nitrate entails submitting the urine for culture and antibiotic treatment; negative nitrate and WBC almost certainly excludes UTI.
- › The management of a child who appears ill or who has an evident focal infection is straightforward. The vast majority of children without localized signs of infection are usually have UTI, bacteremia, or a viral infection.
- › Signs of SBI, such as meningitis, bacteremia and pneumonia are subtle in small infants; culture of blood and CSF as well as a chest X-ray are required for definite identification of the SBI.

septicemia in a series of 410 cases from Finnish hospitals, followed by *E. coli* [14]. Prior to the discovery of the H influenzae type b (Hib) vaccine, Hib was the most common causative bacteria of bacteremia and bacterial infection in older children. In recent years *S. pneumoniae* has become the most common causative agent.

The prognosis of bacteremia is generally good, provided the possibility is considered in any febrile child without a focus of infection and appropriate antibiotic is initiated early. Recent reports indicate a spontaneous resolution of bacteremia without antibiotics in 40–60% of cases. The remainder may develop bacterial complications, including bacterial meningitis in about 10% of cases. (See Box 1.2)

1.7.3**Persistent Pyrexia of Unknown Origin (PUO)**

This term is usually applied when fever without localizing signs persists for 1 week during which evaluation in the hospital fails to detect the cause. In 1961 PUO was defined as a duration of fever of at least 3 weeks and uncertainty of diagnosis after a 1 week investigation in the hospital [15]. As the progression of disease in children is more rapid and has more profound effects on the child's health than in an adult, using the duration of fever of 3 weeks is impractical in children.

Several comments are of practical importance to the diagnosis of PUO:

- The patient's history should be searched for animal exposure, travel abroad, and prior use of antibiotics.
- Repeated physical examinations are more helpful in establishing a diagnosis than extensive investigations.

Table 1.14 Principal causes of PUO

Cause	Reason for being a case of PUO
Infection (60%–70%)	
Localized	
Sinusitis	Standard sinus radiograph not performed or negative
Endocarditis	Previously unsuspected of having a cardiac defect
Occult abscess (abdomen, dental)	Absence of clinical signs
Systemic	
Viral (e.g. EBV)	Fever as the only sign of the disease
TB	Extrapulmonary, tuberculin test negative
Kawasaki disease	Incomplete presentation, diagnosis not considered
Brucellosis	Diagnostic test for brucella not performed
Collagen (about 20%)	
JIA	Prearthritic manifestation
SLE	Atypical manifestations
Neoplasma (5%)	
Leukaemia	Atypical presentation; blood tests negative
Lymphoma	Unusual localization
Neuroblastoma	Disseminated
Miscellaneous (5–10%)	
Drug fever	Diagnosis not considered, suspected drug not stopped
Factitious fever	Diagnosis not considered, thermometer left to patient

EBV Epstein–Barr virus; *JIA* Juvenile idiopathic arthritis; *SLE* systemic lupus erythematosus

- A child with the initial diagnosis of PUO on presentation to the hospital may often prove to have either a self-limiting benign disorder, such as viral infection, or a common disease that can be diagnosed easily with simple initial investigations, such as urine culture or a chest X-ray. Therefore, provided that the child's condition is satisfactory, extensive investigations initially are not required. An atypical presentation of a common disease is more common than a rare and exotic disease.
- With the exception of bone marrow aspiration, an invasive technique such as laparotomy, laparoscopy, or biopsy is rarely indicated nowadays to diagnose PUO. Rheumatoid arthritis in a child with established diagnosis of PUO is often the single most common diagnosis.

Table 1.14 shows the main causes of PUO.

- Infections are the most common causes, accounting for 60–70% of all cases. The younger the child, the higher the relative percentage of infection. Although most viral infections rarely cause prolonged fever, about 15% of the infectious cases of PUO are due to viral infection.
- Collagen diseases account for about 20%, of which the most common cause is rheumatoid arthritis as a pre-arthritic presentation.
- Malignancy presenting as fever without other manifestations is unusual in children compared to adults, but may occur in up to 5%.

- Miscellaneous diagnoses account for 5–10% and undiagnosed in the remaining 5%. Previously, a high percentage of PUO (up to 25%) was categorized as undiagnosed, but with recently developed techniques, in particular imaging, the percentage of undiagnosed cases has greatly decreased.

Physical examination of a patient with PUO should include the following:

- A thorough examination on admission, which should be repeated during hospitalization
- Measurement of temperature by a nurse attending to the procedure to eliminate the rare possibility of factitious fever, occurring in <1% of PUO in children
- Checking for tenderness over the sinuses, bones, and muscles, and palpation of lymphnodes
- Eye examination (looking in particular for uveitis as an early clue for rheumatoid arthritis, bulbar conjunctivitis for leptospirosis, choroid tubercles, and toxoplasmosis lesions)
- Noting that an absence of sweat with high fever may suggest heat stroke, dehydration, anhidrotic ectodermal dysplasia, or familial dysautonomia

The tempo of laboratory investigation (Table 1.15) is based on the child's condition, while the extent of investigation is based on clues obtained from history:

- Travel abroad
- Exposure to animals
- Ingestion of raw milk
- Exposure to infection
- Consideration of ethnic group

Initial investigations (chest X-ray, blood and urine culture) may rapidly establish a diagnosis of unexplained fever. If these investigations fail to reach a diagnosis, further investigations and occasionally invasive techniques will be required.

Table 1.15 Suggested investigations for a case with PUO

Initial tests	Further investigations
FBC, CRP, ESR, blood film	Serum albumin: globulin ratio
Blood culture	Serology for brucellosis, toxoplasmosis
Urine (microscopy and culture)	Cytomegalovirus, mononucleosis
Stool (microscopy and culture)	<i>Salmonella</i>
Chest X-ray	Viral study
Tuberculin test	Radiology of sinuses, mastoid
Lumbar puncture	Ultrasound of abdomen and heart (for vegetation)
Liver function tests	Bone marrow aspiration
Antinuclear antibody	Isotope bone scan

FBC full blood count; *CRP* c-reactive protein; *ESR* erythrocyte sedimentation rate

The prognosis of PUO is better in children than in adults, mainly because of the higher incidence of infection and lower incidence of malignancy. Fatality may occur in <5% of the patients primarily due to neoplastic cases.

1.8
Fetal Malformation and Fever

A woman early in pregnancy with high body temperature increases her skin blood flow and ventilation at the expense of blood flow to the uterus and placenta. This reduces the heat removal efficiency of the placenta and results in a high fever in the fetus, which, theoretically, may lead to the loss of the fetus.

Fever or hyperthermia has been shown to be teratogenic in experimental animals, and several retrospective studies have suggested a casual relationship between fever (or hyperthermia) during pregnancy and congenital anomalies in human [16,17]. Fever of 38.9°C or higher or the use of a hot sauna for 15 min or longer was used as the marker of excessive heat [18]. As shown in Table 1.16, a wide variety of fetal malformations have been reported, particularly involving the CNS. It has been postulated that during early gestation at the time of neural tube closure (22–28 days), the rapidly proliferating cells may be sensitive to heat, causing a disruption of mitosis. Skeletal malformations, such as arthrogryposis, were found to occur in animal experiments at a higher temperature than those associated with abnormalities in the CNS [19].

Despite these reports, evidence for maternal fever or hyperthermia causing fetal malformations is inconclusive because:

Table 1.16 List of reported congenital defects

Location	Defect
CNS	Neural tube defect
	Anencephaly
	Encephalocele
	Microcephaly
	Mental deficiency
Face	Micrognathia
	Microphthalmia
	Cleft palate
Heart	Congenital defects (atrial septal defect Hypoplastic left heart syndrome)
Limb/skeletal	Clubfoot
	Arthrogryposis
	Limb reduction defect
Genitals	Hypospadias
	Micropenis
Intestine	Hirschsprung's disease

- Most studies were based on birth registries, and history was ascertained as far as 10 years back. The accuracy of such a history is therefore difficult to evaluate.
- A temperature of 38.9°C or higher is not uncommon with infection during pregnancy. If there is, indeed, a relationship between temperature elevation and fetal malformation, it is difficult to explain the rarity of these congenital malformations. A large prospective study involving 55,000 women could not confirm an association between febrile illness during pregnancy and fetal malformation [20]. A more recent study from Denmark involving over 24,000 women found no evidence that fever in the first 16 weeks of pregnancy was associated with the risk of fetal death [21].
- The use of saunas as a possible source of teratogenic hyperthermia has been challenged by Finnish authors on the grounds that their surveys did not show an increase in CNS abnormalities and that the incidence of anencephaly is very low in Finland [22] (only 0.32/1,000 in contrast to an incidence of 1/1,000 in other European countries and the United States). In general, pregnant Finnish women are not advised against the use of saunas. Ten to thirty minutes in an ambient temperature of 70–100°C usually does not raise body temperature higher than 38.5°C. Body temperature rises by 1.6°C during a 10-min sauna in children under 5 years of age and 0.9°C in those over 15 years of age.

1.9 Drug Fever (DF)

DF is a common condition, with fever often appearing as the sole manifestation of an adverse reaction of drugs.

- **Definition:** A disorder characterized by elevation of body temperature with the administration of a drug and the disappearance of the fever after discontinuation of the drug, with no other cause for the fever evident after a careful physical examination and laboratory investigation [23].
- **Diagnostic features include.**
 - DF is a diagnosis of exclusion.
 - Definite tests to confirm the diagnosis are usually absent, and a rechallenge is generally discouraged.
 - A characteristic fever pattern is lacking.
 - Drug fever may develop immediately following initiation of therapy but more commonly is delayed for 7–10 days.
 - Diagnosis is suggested by prompt defervescence (usually within 24 h) after discontinuation of the offending drug.
 - Conditions predisposing to the development of DF include atopic disorders, severe infection (e.g., meningitis) and systemic lupus (SLE).
 - Patients usually do not appear toxic, and the body temperature is usually of moderate degree. However, a high temperature may occur, including hectic patterns and chills. The highest temperatures are caused by cytotoxic drugs and by those drugs inducing hyperthermia.

- Cutaneous manifestations are frequently observed, particularly urticaria, along with eosinophilia, and a pulse that is disproportionately low in relation to the degree of temperature (relative bradycardia).

Drugs may induce fever by several mechanisms:

- IL-1 can be produced by an antigen–antibody complex with leukocytes; the drug acts as an antigen. An example of this mechanism is penicillin.
- Antibiotics and some cytotoxic drugs, such as bleomycin and aspraginase, are derived from microorganisms and may occasionally be contaminated by endotoxin, which can provoke fever.
- Cytotoxic drugs often cause immunosuppression with subsequent infections and are responsible for most febrile episodes.
- Drugs can also elevate the body temperature by inducing hyperthermia in several ways: by increased heat production (e.g., drugs inducing malignant hyperthermia, severe salicylate intoxication, and thyroxine), by reduction of sweating (e.g., anticholinergic drugs such as atropine), or by inducing vasoconstriction, as with adrenaline (see Chap. 2).
- Some drugs, for example cocaine, may have a direct pyrogenic effect on the hypothalamic center.
- Almost any drug may provoke a temperature rise as an adverse reaction. However, certain drugs have more predictable pyrogenic effects in causing hyperthermia/fever, which are shown in Table 1.17.

Other drugs that are associated with high incidence of fever include:

A neonate with suspected congenital heart defect, especially a ductus arteriosus-dependent defect (e.g., pulmonary stenosis, tricuspid atresia, hypoplastic left heart syndrome) should receive prostaglandin infusion as soon as possible to maintain the

Antimicrobial	Antihypertensive
Penicillin	Hydralazine
Ampicillin	Methyldopa
Rifampicin	Oxprenolol
Sulphanamide	Antiepileptic
Isoniazid	Carbamazepine
Cephalosporins	Diphenylhydantoin
Co-trimoxazole	Phenothiazines
Nitrofurantoin	Promethazine
Amphotericin B	Chlorpromazine
Cytotoxic drugs	Haloperidol
Bleomycin	Others
Chlorambucil	Blood
6-Mercaptopurine	Aspirin
Daunorubicin	Quinidine
L-Asparaaginase	Procainide

Table 1.17 The main drugs that can cause a rise of body temperature

patency of the ductus. The procedure is particularly important if the child is born outside a tertiary center (with facility of cardiac surgery) so that the baby is transported to an appropriate center for surgery. The most frequent complication of prostaglandin infusion is fever, with an incidence of around 60%. This complication should disappear once the dose is moderately reduced. Other side effects include apnoea and tachycardia (or bradycardia, hypotension, and cardiac arrhythmia).

- **Interferon treatment.**

Interferon are endogenous pyrogens capable of inducing fever (see Chap. 3). Interferon- α has been the most effective treatment for patients suffering from hepatitis B and C, and melanoma. In a study of 100 children (mean age 7 years) treated for hepatitis B, fever was observed in 72%, occurring either periodically or throughout the whole 20-week treatment [24].

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