Clinical Manual of Fever in Children

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Preface

Febrile illnesses have their highest incidence in early childhood, and fever is the leading symptom bringing children to see the pediatricians and primary care physicians. Despite the high prevalence of fever and the increased scientific knowledge about fever mechanisms, there is a lack of information about fever pathogenesis and management in pediatric textbooks. Primary care physicians have little time to study the subject. Medical students receive insufficient teaching about fever. Lectures addressing fever are few or nonexistent. Books on the subject of fever are hardly available. One important reason for all these is that there is no specialty or subspecialty to foster and promote the subject.

In the past few decades, remarkable advances have been made in understanding the mechanism of fever and its management. The current knowledge on fever is the result of evidence-based research. The remarkable scientific progress on fever on the one hand and the incomplete dissemination of information of it on the other gave us an impetus to write the book. The results of the research needed conversion into a practical, concise, and reader-friendly text. We are hoping that we have achieved this goal.

Although the book is written primarily for the senior and junior pediatricians, we hope that all medical professionals (primary care physicians and nurses) will find the book useful when dealing with a febrile child. Medical students are usually required to perform scientific projects, including those related to fever, and it is hoped that this book can provide the information they may need to do that.

This Manual provides scientific evidence in the understanding of children with fever. It offers clearly defined, practical, and proven approaches to the major problems affecting these children. This should result in an improved care for the febrile child. In this book, we have attempted to cover the entire spectrum related to fever, emphasizing also facts observed by others and presenting our own concepts of the problems of fever and its management in clinical practice. Chapter 1 introduces fever, its definition, causes and management in various age groups and fever of unknown origin. The chapter also discusses drug fever and whether or not fever can cause malformation. This chapter is followed by hyperthermia (Chap. 2). Many physicians often equate the term fever with hyperthermia. This chapter differentiates the two causes of elevated body temperature, enumerating the causes and features of hyperthermia and their management. Because hyperthermia (or fever)

therapy over a century ago had a definite role in the treatment of various infectious diseases, such as syphilis, the subject is included in this chapter.

The remarkable progress made over the past few decades on the pathogenesis of fever is summarized in Chap. 3. The readers will not only confirm the complexity of fever induction but also how effective the temperature regulation is in healthy state and at the height of fever so that body temperature does not climb up relentlessly. Measurement of body temperature (Chap. 4) is a subject that is often neglected in medical teaching. It is also often inaccurately done. The pros and cons of each thermometer and each site to measure body temperature are discussed. Pediatric nurses in particular will find the measurement of body temperature evidence-based and practical when they measure body temperature.

Chapters 5 and 6 are related to fever in infectious and noninfectious diseases, focusing on the incidence and pattern of fever in each disease, a brief management and, whenever possible, on the question whether or not the presence of fever is beneficial for that disease. We did not intend to write an account on infectious diseases as there are excellent books on the market dealing with this subject. It was, however, unavoidable that a short description of each disease was added. Chapter 7 covers the whole aspects of febrile seizures. This subject is included for two reasons. First, fever is an essential precursor of the event and second the degree of fever has an important influence on the recurrence rate of seizures. Chapter 8 reviews the latest advance in hypothermia, its causes in neonates and older children, as well as therapeutic application of hypothermia. As hypothermia in neonates is associated with high mortality in developing countries, preventative measures in delivery room and at home are discussed.

We felt that the book would be incomplete without discussing the important subject "Is fever beneficial" (Chap. 9). Few issues in medicine have been more controversial than this subject. The views of those who consider fever as beneficial and those who consider it as harmful are presented and a conclusion is drawn. Special attention is given to the management of fever (Chap. 10). Despite the intensive research on fever during the past few decades, fever management is often inadequate and not evidence-based. This chapter provides health professionals with almost all clinical information needed to understand how a febrile child should be treated. Antipyretics, their mechanism, doses, and possible side effects are discussed in a concise way. The chapter also includes management of fever in hospital and at home, guidelines for parents, and for the practicing physicians. The chapter ends with a section on "Fever Phobia" and its management.

Alternative medicine (Chap. 11) has become increasingly popular in recent years and many of its methods are used to treat fever. Clinicians need to know whether these methods are effective for fever treatment and whether they can compete with conventional physical and drug antipyretics. Fever may present as the only sign of a disease (e.g. PUO) or in association with other symptoms and signs. Diagnosis in both presentations can be difficult. Chapter 12 ("Differential Diagnosis") provides clinicians with a guide to clinical and laboratory means to reach a diagnosis of the most common febrile diseases. Chapter 13 covers the history of fever from BC to present. In this chapter, the concepts of the ancients, including scholars and lay people, are presented, along with views and practice of Middle Age and European scholars. Finally, we provided the readers with a glossary of the terms related to fever (Chap. 14). The readers will be surprised to see the multiplicity of medical disorders related to the term fever.

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Introduction

Man is a homeotherm, that is, he maintains his body temperature within a limited range of ±2°C despite wide variations in ambient temperature. Temperature regulation in health and during fever is maintained by both behavioural and physiological processes. Along with pulse and respiration, body temperature remains the third vital sign.

Of the many symptoms and signs of diseases, fever has received the most attention throughout medical history. For thousands of years, simple palpation has been performed to assess the status of well-being of people by confirming the presence or absence of fever. Many decisions concerning the investigation and treatment of children are based on the results of temperature measurement alone. Without detecting fever a serious underlying illness could be missed, which could result in death.

The views on fever, particularly on its role in disease, have evolved gradually over many centuries. Fever was initially regarded not as a symptom but rather as the disease itself. For most of the history, it was feared by ordinary people as a manifestation of punishment, induced by evil spirits or a marker of death. However, medical scholars of ancient civilizations, particularly the Greeks, believed in the beneficial effects of fever, a concept that prevailed until it underwent a radical transformation in the nineteenth century. Scholars began to regard fever as harmful. The later introduced antipyretics were regarded as beneficial.

During the nineteenth century, fever was still regarded as both part of a symptom complex (as it is today) and a disease in its own right. Examples of fever being regarded as a disease were *autumnal fever, jail fever and hospital fever*. Fever could also be described in terms of the severity of the disease, for example, *malignant fever* or *pestilential fever*, or even in terms of the supposed pathology of the fever, *bilious fever* or *nervous fever*. The multiplicity of names for fever reflects the lack of a breakthrough into an understanding of the causes of febrile illnesses. The breakthrough came with the science of bacteriology, which was able to reveal the aetiology of many infectious diseases, such as the identification of the typhoid bacillus in 1880, and the discovery of the tubercle bacillus in 1882. These discoveries relegated fever to a sign of disease.

With the introduction of fever therapy in the twentieth century, renewed interest in the role of fever began. The best results of fever therapy were observed in gonorrhoea and

syphilis, including their complications, such as arthritis, keratitis and orchitis. Approximately 70–80% of the cases treated were arrested using artificial hyperthermia or malarial fever in the range of 40.5–41.0°C. Despite this therapeutic success, the prevailing concepts over two centuries remained negative on the role of fever. Only in the past four decades has there been successful research into the role of fever in disease. The effects of elevated temperatures on body defence have been extensively studied. One of the most important outcomes of this research has been the discovery of a single mononuclear cell product, interleukin-1 (IL-1), whose effects include induction of fever by its action on the hypothalamic centre and activation of T lymphocytes. The fever induction, which occurs simultaneously with lymphocyte activation, constitutes the clearest and strongest evidence in favour of the beneficial role of fever. Despite this recent progress, there is currently no consensus as to whether fever is beneficial, neutral or harmful.

Fever, even when it is associated with multiple symptoms, is often considered as the dominant feature of an illness or as the illness itself. This may be due to *fear of fever* and also by us feeling better when the fever is reduced, thus assuming that the severity of the disease is reduced. It is thought that during infections both fever and pain (such as muscle pain and headaches) are caused by cytokine-mediated production of prostaglandins. Antipyretics, such as paracetamol, reduce both the elevated body temperature as well as the pain. This is the most important reason why the antipyretics have maintained their popularity over a century.

As emphasised throughout the book, fever should not be regarded as a passive by-product of infection. Rather, fever is the result of an active rise in regulated body temperature. As such, fever should not be equated with hyperthermia (e.g. heatstroke), which is unregulated. With fever, unlike hyperthermia, body temperature is well regulated by a hypothalamic set point that balances heat production and heat loss so effectively that the temperature will not climb up relentlessly and does not exceed an upper limit of 42°C. Within this upper range of 40–42°C, there is no evidence that fever is injurious to tissue. If there is morbidity or mortality, it is due to the underlying disease. The associated fever may well be protective.

Contents

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Fever 1

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°C, WBC count is >15,000 mm^{-3} and CRP is >40 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.

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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 *P. vivax*
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

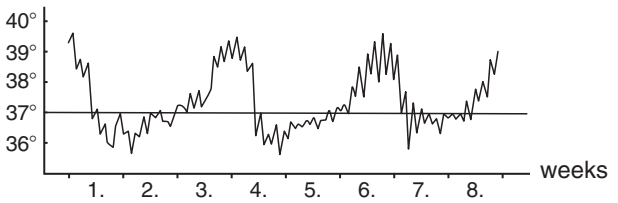

Fig. 1.1 Fever pattern in Pel–Ebstein fever

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 neutrophils elastase: (ELA2): chromosome 19	No	GCSF
TRAPS	AD	Weeks	Irregular	Muscle cramps, migratory arthralgia, migratory erythematous rash	Inflammatory markers, mutation in TNFRSFIA 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* hyperimmunoglobuliaemia 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

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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 10 g 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 chorioaminionitis. 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, *E. coli*
Late-onset	*E. coli,* GBS, CONS, *N. meningitidis, S. pneumoniae, Salmonella, Listeria monocytogenes*
Developing countries	
	Klebsiella, E. coli, Pseudomonas, Salmonella, Staphylococcus aureus, H. influenzae, S. pneumoniae, S. pyogenes
Children > 3 months	*S. pneumoniae, N. meningitidis, Salmonella*

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