Clinical Manual of Fever in Children

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Second Edition

Springer

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ISBN 978-3-319-92335-2 ISBN 978-3-319-92336-9 (eBook)
https://doi.org/10.1007/978-3-319-92336-9

Library of Congress Control Number: 2018953720

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

I was contacted at the end of 2016 by Springer to write a new edition of this book (*Clinical Manual of Fever in Children*), which I was delighted to do. In the past few years and since the first edition of the book was published in 2009, remarkable advances have been made in understanding the mechanisms of fever and its management. The remarkable scientific progress on fever gave me the impetus to write this new edition. Understandably, the results of this latest research needed conversion into a practical, concise, informative and reader-friendly text. I hope that I have achieved this goal and provided the reader with the most up-to-date information on the subject of fever. There is a huge amount of information available to parents and carers on the Internet, but it is of variable quality and difficult to keep up with. This book is evidence-based and consistent with up-to-date knowledge.

This manual provides the latest scientific evidence in the understanding of fever in children. It offers clearly defined and proven approaches to the major problems affecting febrile children. This should result in an improved care of the febrile child. In this book I have attempted to cover the entire spectrum of fever, based on my own concepts and experience of the problems of fever and its management in clinical practice, and on the available research.

Febrile illnesses have their highest incidence in early child, and fever is the leading cause of bringing children to medical professionals (particularly paediatricians and primary care physicians). Despite the high prevalence of fever and the scientific knowledge about fever mechanisms, there is a lack of information about fever, in particular about the pathogenesis and management in paediatric textbooks. Primary care physicians have little time to address the subject. Lectures addressing the subject of fever are very few in number. There are hardly any books on the subject. A speciality or sub-speciality which could promote the subject of fever does not exist. This book is meant to provide the reader with the latest advances on these issues.

Although the book is written primarily for the senior and junior paediatricians, I hope that all medical professionals (primary care physicians and nurses) will find this book useful when dealing with a febrile child. Medical students are usually required to perform scientific projects, including those related to fever, and I hope that this book will be of benefit to them. There is a great interest among nursing staff about certain aspects of fever, in particular "measurement of body temperature".

The book is structured into 14 clinical chapters covering the entire breadth of fever in paediatric practice, presenting the evidence base where relevant. Chapter 1

introduces fever, its definition, causes and management in clinical practice and fever of unknown origin. The chapter also discusses drug fever and whether or not fever can cause malformation. The chapter is followed by hyperthermia (Chap. 2). Many physicians often equate the term fever with hyperthermia. This chapter differentiates between the two causes of elevated body temperature, discussing in some detail the causes and features of hyperthermia and their management. Because over a century ago hyperthermia (or fever) therapy 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 reader is likely to be surprised by the complexity of fever induction but also how effective the temperature regulation is in a healthy state and at the height of fever so that body temperature does not climb relentlessly. Measurement of body temperature (Chap. 4) is a subject that is often neglected in medical teaching. It is also often done inaccurately. The pros and cons of each thermometer and each site to measure body temperature are discussed. From my own experience, paediatric nurses in particular will find this chapter practical when they measure body temperature.

Chapters 5 and 6 are related to fever in infectious and non-infectious diseases, focusing on the incidence and pattern of fever in each disease, touching on management and, whenever possible, on the question of whether or not the presence of fever is beneficial for that disease. I 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 be included. Chapter 7 covers febrile seizures. This subject is included for two reasons: first, fever is an essential precursor of the event; second, the degree of fever has an important influence on the recurrence rate of seizures. Chapter 8 reviews the latest advances on the subject of childhood hypothermia, its causes in neonates and older children, as well as the therapeutical application of hypothermia. As hypothermia in neonates is associated with high mortality in developing countries, preventative measures in the delivery room and at home are provided.

As indicated in the previous edition, I felt that the book would be incomplete without asking the important question: Is fever beneficial? (Chap. 9). Few issues in medicine have been more controversial than this subject. The views of those who consider fever beneficial and those who consider it harmful are presented and a conclusion is drawn.

Special attention is given to the Management of Fever (Chap. 10). This is one of the most important chapters in the book. In recent decades remarkable progress has been made in paediatric care which now has a much stronger evidence base. In the past few decades, fever management used to be inadequate and not evidence-based. This chapter provides health professionals with almost all clinical information needed to understand how a febrile child should be managed. Antipyretics, their mechanisms, doses, and possible side effects are discussed in a concise way. The chapter also includes “Management of Fever” in hospital and at home, as well as guidelines for parents, and for 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 and drug antipyretics. Fever may present as the 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 the 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 provide the reader with a glossary of the terms related to fever (Chap. 14). The reader will be surprised by the multiplicity of medical disorders related to the term "fever".

London, UK A. Sahib El-Radhi

Acknowledgments

The author is grateful to his family for their encouragement and understanding while this book was being prepared. I must give special thanks to the two co-authors of the previous edition of this book published in 2009: Professor James Carroll and Professor Nigel Klein. I am grateful for their excellent contribution to the previous edition of the book. I also wish to thank those Editors at the Springer Publisher for their work in completing the book to produce a new edition of this book that I hope the reader will find useful.

Introduction

Man is a homeotherm, that is, he maintains his body temperature within a limited range of ±2 °C despite a wide variation 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 its role in disease, have evolved over many centuries. Fever was initially regarded not as a symptom but rather as the disease itself. For most of 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 civilisations, 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, and the later introduced antipyretics 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 nervous fever. The multiplicity of names for fever reflects the lack of a breakthrough into 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. The 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 were generally 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-L (IL-1), the effects of which 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 no consensus as to whether fever is beneficial, neutral or harmful in the current literature.

Fever, even when it is associated with multiple symptoms, is often considered as the dominant feature of the illness. This may be due to fever phobia and also to the wrong perception that when fever is reduced, we assume that the severity of the disease is also 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 and the pain. This is the most important reason why the antipyretics have maintained their popularity over a century.

As emphasized throughout this 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 is not to be equated with hyperthermia (e.g. heat stroke), 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 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 and 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 20–30% 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 harbour two important serious bacterial infections (SBI): urinary tract infection or bacteraemia.
- 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, FBC, 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 >40 mg/L; urine and blood cultures should be ordered and a third-generation cephalosporin (ceftriaxone or cefotaxime) considered.
- The distribution of the diseases causing PUO differs according to the geographic area and the socio-economic status of the country.
- In PUO, atypical presentation of a common disease is more common than a rare and exotic disease.

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_1

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 centre. 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. Behavioural 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 36.4 °C; 1 °C above the mean is 37.4 °C. The following degrees of temperature are accepted as fever:

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

Fever is also defined a core temperature of 38.3 °C or higher, i.e. just above the upper limit of a normal body temperature (see also Chap. 4).

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 late afternoon (4–6 pm) and lowest prior to awakening (4–5 am). This rhythm is regulated by a hypothalamic light-sensitive suprachiasmatic nucleus (SCN) that responds to light entering the eyes. 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).

Table 1.1 Fever patterns found in paediatric 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, JIA, drug fever (e.g. carbamazepine)
Relapsing or periodic	Tertian or quartan malaria, brucellosis
Recurrent fever	Familial Mediterranean fever

JIA juvenile idiopathic arthritis

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:

- 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. This pattern is not usually associated with chills or rigour. Normal diurnal fluctuation temperature is usually absent or insignificant. This pattern is characteristic of typhoid fever, and it may be associated with bacterial endocarditis, Tb and drug fever.
- Remittent fever is characterized by a fall in temperature each day but not to a normal level. The amplitude of fever is more than 0.3 °C and less than 1.4 °C. This is the most common type of fever in paediatric 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. The amplitude of fever is the same as with remittent fever. 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 (> 1.4 °C) between the peak and the nadir.
- Quotidian fever, caused by *P. vivax*, denotes febrile paroxysms which occur daily. Common viral and bacterial infections can also cause it.
- Double quotidian fever has two spikes within 12 h (12-h cycles). This may occur in malaria or drugs such as carbamazepine.
- Undulant fever describes a gradual increase in temperature, which remains high for a few days and then gradually decreases to normal level. Brucella may cause this type of fever.

- Prolonged fever describes a single illness in which duration of fever exceeds that expected for this illness, e.g. >10 days for a viral upper respiratory tract infection.
- Recurrent fever, relapsing and periodic fevers are discussed next.

Recurrent Fevers

Recurrent fevers (RF) are defined as three or more febrile episodes during a 6-month period, with symptom-free intervals of at least 7 days separating the episodes. Causes of RF are either infectious or non-infectious (Table 1.2). Infections such as viral upper respiratory tract infections (URTIs) are by far the most common causes of RT in children. These infections occur at irregular intervals and usually resolve within a week. Young children will commonly develop one to two episodes of URTI monthly, especially if they attend a preschool nursery (Chap. 5). Children with viral URTIs usually have symptoms other than fever (e.g. runny nose, cough) that give clues as to the cause of the fever. In endemic areas, malaria is the most common cause of RF, termed tertian fever when the febrile spike occurs every 48 h with *P. vivax* and *P. ovale* and quartan when the spike occurs every 72 h with *P. malariae*. Paroxysms of fever are less evident in children. After excluding infections, clinicians are faced with a diagnostic challenge as to the aetiology of a child with RF. Autoimmune, malignancy and periodic fever syndromes should be considered.

Rat-bite fever is caused by *Spirillum minus* and presents with recurrent fevers that may last weeks and months. Symptoms include chills, headaches, enlarged lymph nodes in the proximity of the rat bite, skin rash, arthralgia and myalgia. Afebrile intervals are usually short and last 3–7 days. Diagnosis is confirmed by a history of contact with rats and by direct dark-field microscopy from the wound discharge.

Pel-Ebstein fever. Fever is one of the most important presenting symptoms of Hodgkin's lymphoma (HL). It is present in about 35% of cases, usually as intermittent fever. Pel-Ebstein fever was described by Pel and Ebstein in 1887. The pattern was originally thought to be characteristic of Hodgkin's lymphoma. Only a few patients with Hodgkin's disease develop this pattern, but when present, it is

Table 1.2 Main causes of recurrent fever

Infectious causes	Non-infectious causes
• Viral (URTI, EBV)	Immune-mediated (CD, SLE)
• Bacterial (UTI, *Brucella*)	Neoplasms (Chap. 6)
• Fungal (histoplasmosis)	Drug fever
• Parasitic (malaria, toxoplasmosis)	Periodic fever syndromes,
• Relapsing fever (*Borrelia*)	Auto-inflammatory diseases (see next)

URTI upper respiratory tract infection, *EBV* Epstein-Barr virus, *CD* coeliac disease, *SLE* systemic lupus erythematosus

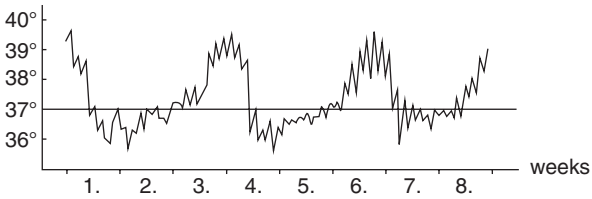

Fig. 1.1 Fever pattern in Pel-Ebstein fever

suggestive of HL. The pattern consists of recurrent episodes of high fever, often reaching 40 °C and lasting 3–10 days, usually a week, followed by an afebrile period of similar duration (Fig. 1.1). The cause of this type of fever may be related to tissue destruction or associated haemolytic anaemia.

Relapsing Fever

Relapsing fever is the term usually applied to recurrent fevers caused by numerous species of *Borrelia* and transmitted by lice or ticks. Human body lice transmit *Borrelia recurrentis* (the causative organism of the epidemic louse-borne RF) from infected human to other humans. Ticks are the vectors for at least 15 different species of *Borrelia* that acquire the *Borrelia* from rodents (rats, mice, squirrels) and cause endemic tick-borne RF. The most well-known tick-borne disease is Lyme disease (see Chap. 5) caused by *B. burgdorferi* and transmitted to humans by the bite of a tick infected with these bacteria.

Relapsing fever 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 RF. Associated complaints include myalgia, headache, abdominal pain and alteration of sensorium. A rash may appear on the trunk after the initial febrile episode that lasts about 2 days. Diagnosis is confirmed by thick blood smear obtained from patients during febrile episodes.

The resolution of each febrile episode may be accompanied within a few hours (6–8 h) by the Jarisch-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 with syphilis. It is less common with cases of leptospirosis, Lyme disease and brucellosis. Symptom severity ranges from mild fever and fatigue to a full-blown anaphylactic reaction.

Periodic Fever Syndromes (Auto-Inflammatory Diseases)

Periodic fevers are also relapsing fever but tend to have rhythmic recurrences. They are mostly genetic and characterized by organ-specific inflammation causing overlapping symptoms including arthralgia/arthritis, skin rash, abdominal pain,

conjunctivitis and occasionally neurological symptoms. Onset of symptoms usually occurs in early childhood and often before the age of 1 year (e.g. cryopyrin-associated periodic syndromes, CAPS). Whereas fever in some syndromes (HIDS and PFAPA) tends to be high, 39–40 °C, low-grade fever is more typical in CAPS. Some syndromes (PFAPA and cyclic neutropenia) have regular periodicity (21–28 days); others do not. While some syndromes (e.g. HIDS) are lifelong conditions, children with other syndromes (e.g. PFAFA) are likely to outgrow the condition later on in life.

The term auto-inflammatory disease has been proposed to describe a group of disorders characterized by attacks of unprovoked systemic inflammation without significant levels of autoimmune (low detectable autoantibodies) or infective causes. The abnormally increased inflammation is caused by a defect in the innate immune system [1].

Syndromes that have been identified during the past 20 years are shown in Table 1.3. FMF and PFAPA are much more common than other syndromes. Non-steroidal anti-inflammatory drugs (NSAID) are far more effective than paracetamol in controlling fever in these fever syndromes. Anakinra is a receptor antagonist that works by blocking the biological activity of IL-1 [2]. IL-1 is a cytokine that is induced in response to inflammatory stimuli to produce inflammatory reactions (Chap. 3).

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) 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). Sweating occurs at this phase.

Table 1.4 shows mechanisms leading to normal and abnormal body temperatures.

Table 1.3 Periodic fever syndromes

Disorder	Inheritance	Fever duration	Periodicity	Main features	Diagnostic tests	Amyloidosis	Treatment
FMF	AR	1–3 days	3–6 weeks	Polyserositis (abdominal, chest pain, arthritis)	Inflammatory markers, gene mutations MEFV on chromosome 16, leading to protein defect	+	Colchicine, Anakinra
CN	AD	5–7 days	3–4 weeks	Pharyngitis, stomatitis, repeated bacterial infections, lymphadenopathy, cellulites	Neutrophils <500; mutation of the gene neutrophils elastase on chromosome 19	No	CSF, antibiotics
TRAPS	AD	7–28 days	Invariable	Muscle cramps, migratory arthralgia, exanthem	Raised CRP, WBC, ESR, TNFRSFIA gene testing	Occasional	Prednisolone, anti-TNF therapy
HIDS	AR	4–6 days	4–8 weeks	Abdominal pain, headache arthralgia, lymph-adenopathy, diarrhoea	High CRP, WBC, IgD level, genetic testing of MVK gene, raised mevalonate in urine	Rare	Prednisolone, simvastatin
PFAPA	Familial/	3–6 days	3–4-weeks	Aphthous stomatitis, pharyngitis, lymphadenitis	Diagnosis: Clinical; high CRP, WBC and pro-inflammatory cytokines	No	Prednisolone, tonsillectomy
CAPS MWS	AD	2–3 days	Irregular	Urticaria, progressive deafness	NLRP3 gene testing raised pro-inflammatory cytokines	+	Anakinra, prednisolone
	FCAS	12–24 h	Irregular	Cold-induced urticaria			
	NOMID	Irregular	Irregular	Neonatal rash, arthropathy			

FMF familial Mediterranean fever, *CN* cyclical neutropenia, *TRAPS* tumour necrosis factor receptor-associated periodic syndrome, *HIDS* hyperimmunoglobulinaemia D and periodic fever syndrome, *CAPS* cryopyrin-associated periodic syndromes, *MWS* Muckle-Wells syndrome, *FCAS* familial cold auto-inflammatory syndromes, *NOMID* neonatal-onset multisystem inflammatory disease, *PFAPA* periodic fever, aphthous stomatitis, pharyngitis, and adenitis, *AR* autosomal recessive, *AD* autosomal dominant, *CSF* colony-stimulating factors

Table 1.4 Peripheral mechanisms leading to 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 1.5 Summary of the clinical changes noted during fever

Manifestation	Clinical findings
Symptoms	Chills (rigour), 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

1.4 Manifestations during Fever

The subjective perception of fever is generally absent in children, and fever is usually detected by the parents. Symptoms include feeling cold, achiness, headaches and weakness. Manifestations associated with fever vary considerably and depend on the child's age, how acute and how high the fever is and on the nature of the disease that has caused the fever. Common manifestations are summarized in Table 1.5.

Symptoms directly related to fever include:

- Chills or rigours, which characteristically herald the onset of high fever as a result of cytokine and prostaglandin release, causing rapid muscle contraction and relaxation. Young children do not often have chills, or the chills are so subtle that they pass unnoticed. Chills are more characteristic of some diseases, such as bacteraemia and lobar pneumonia. They also occur in viral diseases and in non-infectious diseases, e.g. lymphoma.
- Other symptoms of fever include myalgia, anorexia and fatigue and altered sensorium.
- Fever may unmask Brugada syndrome which is a rare genetic disease associated with a characteristic ECG pattern leading to dangerous ventricular arrhythmia. The disease usually affects young and middle-aged people.

Signs of fever include:

- Tachycardia, with the pulse rate rising 10 beats/min for every 1 °C temperature elevation.
- Tachypnoea during fever is an increase of respiratory rate by approximately 2.5 breaths/min for each 1 °C elevation of body temperature, occasionally associated with grunting (arousing the suspicion of pneumonia). In pneumonia with malaria, the temperature effect on the respiratory rate is even higher at 3.7 breaths per minute per I°C [3]. The reason for the difference between 2.5 without and 3.7 with malaria is related to the co-morbid features in these diseases, such as anaemia, 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.
- Hypotension may occur to suggest septic shock.
- Relative bradycardia is an occasionally encountered sign during fever, which is by 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/min) and a pulse rate lower than 100/min has relative bradycardia. Classic causes of relative bradycardia are typhoid fever, drug fever (particularly in association with β-blockers), 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.

Capillary refill time (CRT) in febrile children is essentially the same as in those without fever (2–3 s). CRT has an important diagnostic value in seriously ill children with shock and dehydration.

Mottled skin (livedo reticularis, cutis marmorata) is mostly caused by fluctuation in body temperature following a drop in environmental temperature. This patchy skin discolouration is often seen in newborn infants and is harmless.

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 1.6. Metabolic processes include:

- Fever is associated with improved host survival by enhancement of immune-protective mechanisms such as activation of the bactericidal effect of neutrophils (see Chap. 9).
- Most of the requirements for cellular energy are supplied by glucose as the primary energy source during fever, while free fatty acids are used to a lesser extent.

Table 1.6 Summary of the metabolic changes (increase ↑ or decrease ↓) occurring during fever

↑ energy expenditure (13% 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 acid release	↓ phosphorus
↑ C-reactive protein, haptoglobin, ceruloplasmin, fibrinogen, triglyceride	
↑ hormones: Cortisol, ACTH, growth hormone, arginine, vasopressin	
↑ copper	

Basal metabolic rate is increased by 13% for each 1 °C. Glucose production is increased in the liver to build gluconeogenesis. O_2 consumption increases by 10%.

- 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, liver production of albumin decreases. Negative nitrogen balance begins soon after the onset of fever, reaching a loss of about 10 g daily with high fever.
- While plasma iron and zinc concentrations decline rapidly, depriving invading micro-organisms of essential nutrients, copper increases.
- Hormonal changes: 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. Hyponatraemia 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. Insulin and glucagon are released from the pancreas in response to IL-1 release.

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 Table 1.7)

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

- Dehydration may occur due to increased body temperature and the therapeutic effects of drugs that promote sweating. Fever and infection increase the meta-

bolic rate to less than 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, 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 4% of genetically susceptible children younger than 5 years experience fever-induced seizure (febrile seizure), which occurs when a temperature of a susceptible child rises rapidly.
- Some young children experience delirium in association with a high degree of body temperature. This is a non-specific sign caused by viral as well as bacterial infections and medications. Delirium has an acute onset causing disturbance of consciousness and reduced focus. It requires immediate medical attention to exclude other causes such as psychosis or acute anxiety state. Delirium often recurs, causing considerable anxiety on the part of parents. Antipyretics will rapidly ameliorate symptoms caused by fever. Other conditions usually respond to haloperidol or risperidone.
- 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 1761 patients with severe bacterial infections [4]. In another study, of 130,828 consecutive paediatric patients seen over a 2-year period, only 103 (1 per 1270 patient visits) had a fever of 41.1 °C or higher [5]. Of the 103 subjects, 20 (18.4%) had serious bacterial infection. There was a significant association between such a degree of temperature and serious bacterial infections, such as meningitis. Apart from infection, hyperpyrexia up to 41.8 °C has been reported in neonates presenting with intraventricular haemorrhage [6].
- Herpes simplex 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.

Table 1.7 Practical tips on "complications of fever"

• The principal complication of fever is dehydration, which can easily be prevented and treated by providing an extra fluid to the child
• Fever may be associated with lethargy and drowsiness caused in over 90% by a viral infection that lasts a few days
• Fever is a symptom and not a disease. It is not dangerous. If there is morbidity or mortality, it is due to the underlying disease, not to the fever
• Febrile seizures occur only in genetically susceptible children and are usually not dangerous
• Fever helps the body fight against infection; is one of the important defence mechanisms
• Fever does not damage the central nervous system. It also does not climb up relentlessly because it is well controlled by a hypothalamic Centre

1.7 Classification of Fever (Tables 1.8 and 1.9)

Classification of fever into three categories (fever with localized signs, without localized signs and persistent fever of unknown cause) is useful diagnostically. For example, urinary tract infection and bacteraemia predominately occur in those children who present with fever without localized signs. Although urinalysis is indicated in every febrile child (e.g. with cold symptoms), however, it is pivotal to request urinalysis including urine culture in any child who does not exhibit a source of infection.

1.7.1 Fever with Localized Signs

The most common febrile illnesses encountered in paediatric practice belong to this category (Table 1.10). Fever is usually of short duration, either because it settles spontaneously after a common viral infection or because a specific treatment, such as an antibiotic, has been administered. Diagnosis may be suggested by the history and physical examination and confirmed by simple investigation, such as a chest

Table 1.8 The principal three classes of fever encountered in paediatric 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 1.9 Summary of definitions of terms used in "classification of fever"

Term	Definition
Fever with localization	Acute febrile illness with a focus of infection, which can be diagnosed after a history and physical examination, usually lasting less than a week
Fever without localization	Acute febrile illness without apparent cause of the fever after a history and physical examination
PUO	Fever without localizing signs that persists for 1 week or longer during which evaluation in the hospital fails to detect the cause
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 infections, enteritis, urinary tract infection, pneumonia
Bacteraemia and septicaemia	Bacteraemia indicates the presence of bacteria in blood, evident by a positive blood culture; septicaemia indicates, in addition, tissue invasion of the bacteria, causing tissue hypoperfusion and organ dysfunction

PUO pyrexia of unknown origin

Table 1.10 The main causes of fever 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
Neoplasms	Leukaemia, lymphoma
Tropics	Kala azar, sickle cell anaemia

URTI upper respiratory tract infection

X-ray. As children younger than 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 Younger than 36 Months of Age

Foetal temperature. Fever is unusual in the foetus, 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 is acting as an endogenous antipyretic. Foetal 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 foetus to the mother through the umbilical circulation. At birth, the body temperature of the neonate and mother briefly maintains this difference. Heat in the neonate is produced via non-shivering thermogenesis, which begins shortly after birth (see Chap. 3).

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

- Maternal fever without infection. The major cause of an intrapartum fever is the use of epidural anaesthesia, occurring in about 19.2% of women [7]. The longer the labour, the greater the risk of fever development in women who are given an epidural. Maternal fever >38 °C (100.4 °F) was associated with adverse neonatal outcomes (such as hypotonia, early-onset seizures) compared to those who did not receive epidural or who received epidural and were afebrile. Although the cause of the fever is not entirely clear, elevated maternal serum levels of interleukin-1 (IL-1) and a high neonatal monocyte production of IL-1β and IL-6 have been proposed.
- Maternal infection. A less frequent cause of intrapartum fever is maternal infection, such as chorioamnionitis. Infants of women who are febrile during labour 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. In contrast to fever, rapid normalization of the body temperature occurs once the cause of the hyperthermia has been eliminated.

Children 3 days to less than 3 months of 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 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 normothermic or hypothermic. In a series of consecutive infants younger than 3 months of age evaluated at an ambulatory clinic, only 1% had a rectal temperature greater than 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 less than 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. Infants usually present with non-specific and subtle symptoms (Table 1.11). Organisms causing SBI are shown in Table 1.12.

Table 1.11 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, prolonged CRT >2–3 s
Respiratory	Apnoea, tachypnoea, shallow respiration and grunting
Gastrointestinal	Poor feeding, vomiting, abdominal distension, diarrhoea
CNS	Drowsiness, sometimes alternating with irritability (in case of meningitis, bulging Fontanelle, other meningeal signs such as neck stiffness are usually absent)

CRT Capillary refill time

Table 1.12 The most common organisms causing early-onset (<3 days) and late-onset SBI in developed and developing countries

Children <3 months of age	
Developed countries	
Early-onset	*E. coli*, CBS, *Staphylococcus epidermidis*
Late-onset	*E. coli*, GBS, CONS, *N. meningitidis*, *S. pneumoniae*, *Salmonella*, *Listeria* monocytogenes
Developing countries	
–	Non-typhoid salmonella, *Klebsiella*, *E. coli*, *Pseudomonas*, *Staphylococcus aureus, H. influenzae*, *S. pneumoniae*, *S. pyogenes*
Children >3 m	*S. pneumoniae*, *N. meningitidis*, *Salmonella*

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

Table 1.13 Factors that increase the risks of serious bacterial infections

Age	Infants <3 months (3–36 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 (e.g. GBS), catheter, central line
Older child	Sickle cell anaemia, immunosuppression, nephrotic syndrome, splenectomy, HIV infection
Others	Venous catheter, skin petechiae
History and signs	See symptoms and signs in Tables 1.11 and 1.14
Laboratory findings	WBC > 15,000
	CRP: >10 (neonates); >40 (older child)
	Procalcitonin: >0.5 ng/mL
	CSF: >8 WBC/mm^3
	Urine: Positive nitrate on dipsticks, urinalysis showing >10 wbc/hpf
	Chest radiograph: Infiltrate
	Stool: >5 wbc/hpf stool smear

hpf high-power field

Fever in children between 3 and 36 months have the highest incidence of fever during childhood, with approximately 6–12 febrile episodes per year. A self-limiting viral URTI is the most common infection, occurring in 50% of all febrile episodes. Temperature greater than 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 1.13 summarizes factors that increase the risk of SBI.

Management of a Child with Fever Is Summarized in Figs. 1.2 and 1.3

Management includes history, physical examination and laboratory investigation. The most important challenge facing a physician is to determine the aetiology of the illness, in particular confirming or excluding a serious disease. Management includes history taking, focusing on:

- Onset and duration of fever, the degrees of temperature recorded at home, the temperature-taking method.
- Presence of similar symptoms in other family members.
- Pattern of feeding, degree of activity, playfulness at home.
- Features suggestive of SBI.
- Pre-existing disease.
- Previous administration of antibiotics.
- Immunizations.

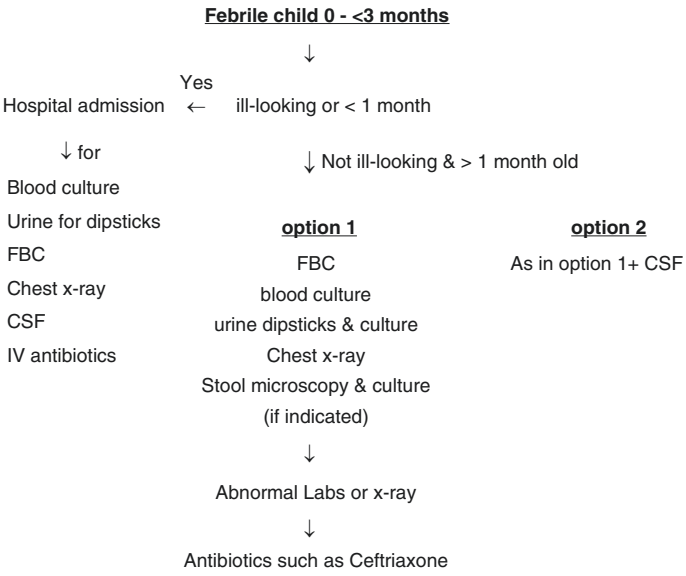

Fig. 1.2 Management of a child aged 0≤3 m without a focus of infection

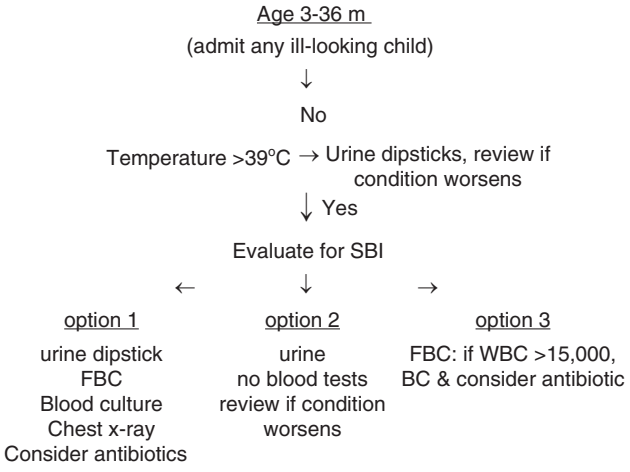

Fig. 1.3 Management of a child 3–36 m of age without a focus of infection

Physical examination, performed in two parts:

- Observation of items to predict SBI (shown in Table 1.14). 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.
- Physical examination, looking particularly for a focus to explain the fever.

Table 1.14 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, doughty skin
Colour	Peripheral cyanosis or pallor	Mottled, pale face or ashen
Sociability/ stimulation	Brief smiling and response	Not smiling, anxious face, expressionless

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 WBC count, CRP and urine dipsticks. These tests are particularly important for young children who may appear well, but the laboratory tests are abnormal (see Bacteraemia). Tests include WBC count, CRP and procalcitonin (PCT). PCT (>0.5 ng/mL) is an early sensitive and specific marker of bacterial infections.
- 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 mandatory test for any ill child.

Antipyretic treatment (see Chap. 10).

Antibiotic treatment should depend on the underlying disease, how ill the child is, age of the child and the height of the fever and the result of the laboratory findings. It is indicated for:

- Any ill-appearing child, irrespective of age.
- All febrile neonates (<28 days of age) should be hospitalized, undergoing a full sepsis evaluation, and receiving empirical intravenous antibiotic therapy.
- Children whose focus of infection is likely to be caused by bacteria.

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

1.7.2 Fever without Localized Signs (Bacteraemia)

When the history and physical examination fail to identify a specific source of fever in an acutely ill, nontoxic-appearing child, usually aged 3–36 months, the illness is termed "fever without localized signs or fever without a source, FWS". 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 (UTI) and bacteraemia. Table 1.15 shows the most common causes of this group. Serious bacterial infections (SBIs) include meningitis, septic arthritis, pneumonia, UTI, cellulitis, malaria in malaria-endemic areas and bacteraemia.

Bacteraemia indicates the presence of bacteria in blood, while septicaemia suggests the tissue invasion of the bacteria, causing tissue hypoperfusion and organ dysfunction. Neonates and young infants more often have septicaemia rather than bacteraemia. The overall incidence of bacteraemia in febrile children is around 2%, but higher risks exist in:

- Children aged 3–24 months who have the highest incidence, estimated to be 3–4% in those aged 7–12 months who have 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 bacteraemia 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. Duration of fever should not be used to predict the likelihood of serious illness.
- Underlying conditions such as immunocompromised status, neutropenia, malaria and malnutrition.

Table 1.15 Usual causes of fever without localized signs

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

HH-6 human herpes-6, *UTI* urinary tract infection, *JIA* juvenile idiopathic arthritis

Symptoms and signs of bacteraemia are often those noted in children with SBI (Table 1.11). Focus of infection on physical examination is absent, with fever above 39.0 °C and ill general appearance being the only manifestations of the disease. Occasionally, bacteraemic patients may present with alarming symptoms such as hypotension, impairment of consciousness, disseminated intravascular coagulopathy (DIC) and renal failure.

Although bacteraemia occurs more frequently as a primary isolated disease, many infectious diseases are known to be associated with septicaemia. These include meningitis (in up to 80% depending on organisms and age), pneumonia (in about 10%), malaria (5%) and otitis media (1.5%) [11]. Bacteraemic pneumococcal pneumonia has been found to have an increased fatality compared to cases of pneumococcal pneumonia without bacteraemia.

The predominant bacteria isolated from blood culture in neonates and early infancy used to be group B streptococcus (GBS), which were responsible for over 50% of early-onset neonatal septicaemia. GBS has declined dramatically since the early 1990s. The most common cause of bacteraemia in febrile infants <3 months of age is currently *E. coli* (42%) followed by GBS (23%) [12]. *E. coli* bacteraemia is very often associated with urinary tract infection. The most common isolates in malaria are non-typhoid salmonella. Prior to the H influenzae type b (Hib) vaccine, Hib was the most common causative bacteria of bacteraemia and bacterial infection in older children. In recent years *Streptococcal pneumoniae* became the most common causative agent.

Summary of Management of a Febrile Child Is Shown in Table 1.16

The prognosis of bacteraemia 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 bacteraemia without antibiotics in 40–60% of cases. The remainder may develop bacterial complications, including bacterial meningitis in about 10% of cases.

Table 1.16 Summary on management of a febrile child

• The majority of children who present with fever are <3 years of age
• The challenge for the clinician is in differentiation children with viral from those with serious bacterial infections, 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 exclude UTI
• The management of a child who appears ill or who have an evident focal infection is straightforward. The vast majority of children without localized signs of infection are usually have UTI, bacteraemia or a viral infection
• Signs of SBI, such as meningitis, bacteraemia 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

Impact of Vaccination

The introduction of routine immunization of infants with the conjugate vaccines (1990 for the H influenzae type B Hib; 2000 for the *Streptococcus pneumoniae*) has dramatically altered the prevalence of invasive diseases caused by these organisms. For example the risk of meningitis from bacteraemia in unimmunized child used to be around 10%, almost all due to Hib. The incidence of bacteraemia in well-appearing febrile child has fallen dramatically to below 1%. Frequent bacterial isolates from blood cultures include *E. coli*, *Staphylococcus aureus*, *N. meningitides*, *Salmonella* and group A *Streptococcus*. Children with high risk of bacteraemia should receive empirical parenteral antibiotic (ceftriaxone). An appropriate follow-up appointment should be arranged within 24 hours whenever possible, particularly for those with incomplete immunization (less than two doses of Hib). Those in whom follow-up is uncertain should be admitted for parenteral antibiotic therapy.

1.7.3 Persistent Pyrexia of Unknown Origin (PUO)

This term is usually applied when fever without localizing signs persists for 1 week or longer during which evaluation in the hospital fails to detect the cause. This means that fever without localized signs can progress to PUO if no cause is found after 1-week fever. In 1961 PUO was defined as a duration of fever greater than 38.3 °C on several occasions of at least 3 weeks and uncertainty of diagnosis after a 1-week investigation in the hospital [13]. 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.
- 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, 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 1.17 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	The absence of clinical signs (abdomen, dental)
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
Cat scratch fever	Blood culture often negative (in contrast to PCR)
Collagen (about 20%)	
JIA	Pre-arthritic manifestation
SLE	Atypical manifestations
Neoplasms (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
Auto-inflammatory	No diagnostic criteria diseases

EBV Epstein Barr virus, *JIA* juvenile idiopathic arthritis, *SLE* systemic lupus erythematosus

Table 1.17 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 the majority of 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:

- 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 less than 1% of PUO in children.
- Checking for tenderness over the sinuses, bones and muscles and palpation of lymph nodes.
- 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 1.18) 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.
- Immunization schedule.

Table 1.18 Suggested investigations for a child 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)	Salmonella
Chest X-ray	Viral study
Tuberculin test	Radiology of sinuses, mastoid
Lumbar puncture	Ultrasound of abdomen and heart (for vegetation)
Liver function tests	
Antinuclear antibody	Blood for IgD
	Bone marrow aspiration, liver biopsy
	Isotope bone scan
	CT scan of abdomen

FBC full blood count, *CRP* C-reactive protein, *ESR* Eryth. sedimentation rate

Naproxen test may be utilized to differentiate between infectious fever (no response) and patients with underlying neoplastic condition who promptly respond with normalization of temperature (see Chap. 6).

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 less than 5% of the patients primarily due to neoplastic cases.

1.8 Foetal 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 causal relationship between fever (or hyperthermia) during pregnancy and congenital anomalies in human [14, 15]. 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 [16]. As shown in Table 1.19, a wide variety of foetal malformations have been reported, particularly involving those of 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 [17].

Despite these reports, evidence for maternal fever or hyperthermia causing foetal malformations is inconclusive for the following reasons:

- 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 foetal 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 foetal malformation [18]. A

Table 1.19 List of reported congenital defects

Location	Defect
CNS	Neural tube defect, anencephaly, encephalocele, microcephaly and 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

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 foetal death [19]. Uncertainty about the relationship between heat produced by hot tube in pregnancy and neural tube defects was also reported in more recent studies [20, 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 was very low in Finland of only 0.32/1000 in contrast to an incidence of 1/1000 in other European countries and the USA [22]. In general, pregnant Finnish women are not advised against the use of saunas. Ten to 30 min 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)

This condition is common, and 3–7% of all febrile episodes are attributed to drug reaction. It is one of the most important diagnoses in PUO (see above).

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 (usually within 24 h), with no other cause for the fever evident after a careful physical examination and laboratory investigation [23].

Clinical characteristics include:

- A classical example of DF is a child taking an antibiotic with resolving infection who develops fever after initial defervesce.
- A characteristic fever pattern is generally lacking. Hectic, continuous intermittent or remittent fever may occur. Patients usually do not appear toxic, and the body temperature ranges from 38.8 °C (102 °F) to 40.0 °C (104 °F) [24]. Classically, the fever is without a focus.
- Drug fever is difficult to diagnose since it is a diagnosis of exclusion.
- Conditions predisposing to the development of DF include polypharmacy (more than four drugs simultaneously), concurrent diseases of the CNS and immune disorders, repetitive exposure to the drug, high-risk drugs such as antibacterial (particularly β-lactam antibiotics, sulfa), antiepileptics (particularly carbamazepine), cytotoxic drugs, immunosuppressants and off-label and unlicensed medicines.
- Drug fever may develop immediately following initiation of therapy but more commonly is delayed for 7–10 days. A faster onset occurs with cytotoxic drugs (median: 0.5 days) and antibiotics (median: 6 days).
- Cutaneous manifestations are frequently observed (18–29%), particularly maculopapular or urticaria. Morbilliform skin eruption may occur in association with drug hypersensitivity syndromes (also called drug reaction with eosinophilia) that also include lymphadenopathy, haematological changes (leukocytosis, increased eosinophilia, atypical lymphocytes) and organ involvement. Fever tends to be high 38–40 °C. The reaction typically occurs with antiepileptic drugs such as carbamazepine or phenytoin.

- A pulse that is disproportionately low in relation to the degree of temperature (relative bradycardia). This is one the most important diagnostic clues.
- Definite tests, including drug antibodies, to confirm the diagnosis are usually absent, and a re-challenge is generally discouraged. Eosinophilia count and hepatic transaminases are sometimes raised.

Drugs may induce fever by several mechanisms:

- The most common mechanism is hypersensitivity reaction, probably mediated by humoral immune response; the drug acts as an antigen. An example of this mechanism is penicillin.
- Another example is Jarisch-Herxheimer reaction where endotoxin is released from bacteria that were destroyed by an antibiotic such as penicillin. There is usually an abrupt onset of fever with myalgia occurring about 6–8 h after starting the antibiotic. This reaction is associated with increased levels of interleukin-1 (IL-1), IL-6 and tumour necrosis factor (TNF).
- Antibiotics and some cytotoxic drugs, such as bleomycin and asparaginase, are derived from micro-organisms and may occasionally be contaminated by endotoxin, which can provoke fever.
- Some drugs, e.g. cocaine, may have a direct pyrogenic effect on the hypothalamic centre.
- Cytotoxic drugs often cause immunosuppression with subsequent infections and are responsible for the majority of febrile episodes.
- Altered thermoregulation. 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 for drug-induced hyperthermia).

Almost any drug may provoke a temperature rise as an adverse reaction. These include antibiotics (especially beta-lactams and sulphonamides), anticonvulsants (especially carbamazepine and phenytoin) antiarrhythmics (especially quinidine and procainamide) and cytotoxic drugs. However, certain drugs have more predictable pyrogenic effects in causing hyperthermia/fever and are shown in Table 1.20.

Other drugs, which are associated with high incidence of fever include:

- Prostaglandin in treatment of patent ductus arteriosus (PDA): 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 patency of the ductus. The procedure is particularly important if the child is born outside a tertiary centre (with facility of cardiac surgery) so that the baby is transported to an appropriate centre 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).

Table 1.20 The main drugs that can cause a rise of body temperature

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

- Interferon treatment. Interferons are endogenous pyrogens that are capable of inducing fever. Interferon-alpha 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 weeks treatment [25].
- Maternal fever during labour (intrapartum fever) caused by the use of epidural anaesthesia (see above Sect. 1.7).

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Hyperthermia

2

Core Messages

- Hyperthermia is a peripherally (skin and muscle) mediated elevation of body temperature, which greatly differs from fever. Temperature is uncontrolled because the hypothalamic centre is not involved.
- Hyperthermia, in contrast to fever, is uncommon, but it has to be considered in the differential diagnosis of elevated body temperature.
- Although hyperthermia and fever cannot usually be differentiated clinically on the basis of the height of temperature, a temperature above 42 °C suggests hyperthermia. A normal temperature excludes fever but not hyperthermia.
- Hyperthermia has different causes, symptoms and signs than fever. Its management is specific and is also different from that of fever, e.g. antipyretics are ineffective while physical methods are effective.
- Drugs play a major role in causing hyperthermia. In contrast to fever, hyperthermia can largely be prevented.
- Hyperthermia has many causes of which malignant hyperthermia (prototype of increased heat production) and heat stroke (prototype of decreased heat production) are the most common and serious causes.

2.1 Definition

Hyperthermia is a state of thermoregulatory failure resulting from the inability to dissipate heat at a sufficient rate (e.g. heat stroke) or excessive heat production with a normal rate of heat loss (e.g. malignant hyperthermia). Dehydration, the most common cause of hyperthermia, leads to vasoconstriction and decreased sweating, which impair heat dissipation usually causing a mild rise of body temperature. Hyperthermia may coexist with fever: hyperthermia, caused by dehydration, may occur on the top of fever due to infection. In another situation, intense muscular contraction during a febrile seizure (FS)

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_2

Table 2.1 Main differences between fever and hyperthermia

Criteria	Fever	Hyperthermia
Occurrence	Commonest sign	Relatively rare
Clinical findings	Feeling cold, cold skin	Feeling hot, dry flushed skin
Temperature	Usually 38–41 °C	May exceed 42 °C
Principal therapy	Antipyretics	Physical measures
Central regulation	Yes	No
Central set point	Elevated	Normal
Mortality	Unusual	High (excluding minor forms such as dehydration)

may cause hyperthermia, leading to a further increase of fever in FS caused by infection.

In contrast to fever, hyperthermia is not mediated by pyrogen or interleukin-1 (IL-1), and the body temperature is higher than the hypothalamic set point, which is usually normal. Because hyperthermia is not regulated centrally, a temperature in excess of 42 °C is common, and the presence of such degree makes hyperthermia a likely diagnosis. This very high degree of temperature rarely occurs, if ever, with fever alone, even with the most severe infections. Despite this difference, a febrile range of temperature of 38–42 °C does not exclude hyperthermia. Table 2.1 shows the main differences between fever and hyperthermia.

Characteristically, patients with hyperthermia feel warm and attempt to eliminate the heat by stretching out, drinking cold liquid, seeking a cooler environment and removing clothes.

2.2 Physiology

The body temperature is regulated by mechanisms involving the autonomic nervous system (mainly via skin) and the hypothalamus. These are:

- Heat production by muscle activity (increase in muscle tone or shivering) and cellular metabolisms, mainly within the liver, heart and brain through the catabolism of the intracellular proteins, carbohydrates and fats.
- Heat dissipation from the skin and, to lesser extent, the lungs through conduction, convection, radiation and evaporation. The loss is dependent on the humidity and the ambient temperature of the body's surroundings.

Heat production and loss are usually so balanced that a constant body temperature is maintained between 36.6 and 37.9 °C measured rectally.

During the neonatal period, the dominant source of heat production is through non-shivering thermogenesis that increases the metabolic rate without shivering.

This may begin as early as 15 min after birth. The site of non-shivering thermogenesis is brown adipose tissue, which is found predominately in the interscapular area, axillae, perirenal area and around the large vessels in the chest.

When the body is exposed to extreme levels of heat, excessive heat production or impaired heat loss, the thermoregulatory system fails causing heat stress and hyperthermia.

2.3 Effects of Hyperthermia

Not all forms of hyperthermia are dangerous. Hyperthermia is a physiological response to intense exercise, and moderate temperature of 39–40 °C can be found in athletes during hard exercise.

Hyperthermia, particularly when excessive, can induce cellular damage. The brain is especially sensitive to extremes of body temperature. Although it has been difficult to establish a thermal threshold or critical thermal maximum (CTM) in man (defined as the temperature above which tissue damage may occur), a temperature of 42 °C is likely to induce such damage [1]. Complications and mortality above this temperature are related more to the severity of the underlying disease than to the height of the temperature. The upper thermal limit for the survival of most organisms is about 45.0 °C because proteins tend to denature above this temperature. However, it has been difficult to differentiate the clinical effects caused by hyperthermia per se from those caused by related manifestations or complications of hyperthermia, such as hypoxia, hypotension, metabolic acidosis, disseminated intravascular coagulation, azotaemia, hypoglycaemia, circulatory failure or seizures. These secondary disturbances play a part in the pathogenesis of organ damage and in the poor prognosis of hyperthermia. Table 2.2 summarizes the effects of hyperthermia during anaesthesia (see malignant hyperthermia).

Table 2.2 Summary of the effects of hyperthermia during anaesthesia (features are related to hypermetabolic response to anaesthetic agent

• Body temperature: increase of core temperature at a rate of 1–2 °C every 5 min
• Cardiac: tachycardia (earliest sign), decreased output by direct damage of the myocardium causing congestive cardiac failure
• Respiratory: hypoxia, respiratory acidosis
• Renal: failure, acute tubular necrosis, hyperkalaemia, metabolic acidosis
• Gastrointestinal: diarrhoea, liver damage, pancreatitis
• Blood: DIC
• Neurologic: confusion, seizure, cerebral oedema
• Muscular: muscle rigidity, rhabdomyolysis, increased creatinine kinase, myoglobulinaemia, myoglobinuria
• General: widespread vital organ dysfunction

DIC disseminated intravascular coagulopathy

Hyperthermia (e.g. heatstroke) may also cause adverse effects on organs including:

- Renal: Reduction of the glomerular filtration rate when the body temperature increases by 2 °C causing increased concentrations of creatinine and urea.
- Gastrointestinal: Increase of gastrointestinal permeability with loss of the barrier integrity leading to an increase of bacterial toxins.
- Cardiovascular: Hypotension despite hyper-dynamic circulation and increased cardiac output. This is due to blood redistribution and vasodilatation. ECG with high temperature usually shows conduction defects with arrhythmia, QT, ST and T wave abnormalities.
- Cerebral: Initial irritability is soon replaced by lethargy and inactivity, loss of cognitive dysfunction and chronic damage.
- Hepatic: Liver dysfunction with increased enzyme concentrations occur at a temperature of greater than 40.0 °C leading to hepatocellular damage.
- Blood: Coagulopathy is common and contributes to multi-organ dysfunction. Also common are thrombocytopenia, prolonged clotting time, increased plasma fibrin degradation products, spontaneous bleeding and DIC.

2.4 Causes of Hyperthermia

There are several causes of hyperthermia, which are listed in Table 2.3. (The differential diagnosis of the forms of hyperthermia is discussed in Chap. 12).

Table 2.3 Causes of hyperthermia

Hyperthermia caused by increased heat production
• Malignant hyperthermia
• Neuroleptic malignant syndrome
• Serotonin syndrome
• Drug-induced
• Exercise-induced hyperthermia
• Endocrine hyperthermia
• Miscellaneous clinical disorders
Hyperthermia caused by decreased heat loss
• Neonatal hyperthermia
• Dehydration
• Heat stroke
• Haemorrhagic shock and encephalopathy
• Sudden infant death syndrome (SIDS)
• Drug-induced
Unclassified
• Factitious fever
• Induced illness
• Induced illness by proxy

2.4.1 Hyperthermia Caused by Increased Heat Production

Exercise-Induced Hyperthermia

Increase in body temperature and sweating are two normal responses to physical activity. With dehydration (e.g. less than 2% loss of body weight) and hyperthermia, fatigue may occur unless fluid is replaced. This may occur in older children following intense and prolonged exercise, particularly in a hot climate. Maximal exercise produces a nearly 15-fold increase in cutaneous blood flow. The greater surface area to mass ratio in children compared to adults allows greater transfer of heat. For example, an 8-year-old child has a surface area to mass ratio of 360–380 cm^2/kg as compared to 240–260 cm^2/kg in a medium-sized adult [2]. Although the greater surface area produces more sweat, the resulting dehydration may eventually limit heat loss. Children generate more metabolic heat per mass unit than do adults, as evidenced by the higher oxygen uptake seen in children performing the same work as adults. Children have a limited capacity for sweating: secretion per gland in the adult is nearly 2.5 times as high as that in an 8–10-year-old child.

For these reasons, the American Committee on Sport Medicine [3] recommended:

- Caution should be used with prolonged (over 30 min) and intense exercise in environmental temperatures exceeding 30 °C and relative humidity of more than 90%.
- Periodic drinks should be available, e.g. 150 mL of cold tap water every 30 min.
- Clothing should be light, limited to one layer of absorbent material to facilitate evaporation, and sweat-saturated garments should be replaced by dry ones.

Malignant Hyperthermia

Malignant hyperthermia (MH) is an autosomal dominant myopathy causing a hypermetabolic state including massive heat production. Most of the commonly used anaesthetic agents and muscle relaxants can induce MH, but the agents most commonly incriminated are halothane, isoflurane, sevoflurane, desflurane and muscle relaxant succinylcholine. The condition is due to several gene mutations, the commonest being in the skeletal ryanodine receptor gene (PYR1) located on chromosome 19q 13.1. Patients with this gene defect are usually asymptomatic. Some patients have no detectable gene defect. During an acute episode of MH, intracellular calcium increases in skeletal muscle, causing uncontrolled muscle contractions and hyperthermia.

Body temperature during anaesthesia may increase at an alarming rate (1–2 °C every 5 min), reaching a level greater than 44 °C. The hypothalamic thermoregulatory centre functions normally, and therefore antipyretics are ineffective. Normothermia does not exclude MH. Core temperature monitoring should be used instead of skin temperature monitoring for patients at risk of MH.

MH is a potentially fatal condition with a mortality rate ranging between 50 and 70% if untreated. Increased understanding of the condition has led to a decreased

mortality rate to below 5%. The reported incidence ranges from about 1/10.000 to 1/50.000 anaesthetic procedures, with children being at higher risk (1/15000) than adults. Even very young children may be affected.

Risk factors for MH include:

- Genetically susceptible patients who appear normal with an underlying, subclinical muscle disease.
- Susceptibility to heat stress, such as exertional heat stroke.
- Parents of babies who died of SIDS related to high body temperature.
- Patients with chronic myopathy, e.g. central core disease, Duchenne muscular dystrophy, chondrodystrophic myotonia (Schwartz-Jampel syndrome) and those with Noonan syndrome. Interestingly, MH and central core disease have been found to reside near one another on chromosome 19q13.1.
- Some patients with characteristic clinical features, including spinal deformities, ptosis and cryptorchidism.

Clinical features result from the abnormal muscular contractions and are:

- Muscle rigidity, particularly of masseter muscle, causing rhabdomyolysis.
- An increase in end-tidal carbon dioxide, which is often an early sign.
- Tachycardia, rising blood pressure, cardiac arrhythmia, tachypnoea and hyperpnoea (as a result of respiratory and metabolic acidosis).
- A rapid rise in body temperature, reaching a temperature as high as 44.0 °C. When temperature exceeds 41 °C, disseminated intravascular coagulopathy (DIC) is the usual cause of death.

A summary of the effects of MH on the body is shown Table 2.2.

Diagnostic clues include:

- A history of hyperthermia or death among relatives.
- Elevated serum CPK screening.
- In vitro response of the patient's biopsied muscle to halothane (caffeine-halothane contracture test). This gold standard diagnosis is confirmed when both caffeine and halothane test results are positive, while negative results to both caffeine and halothane exclude the diagnosis.
- Deoxyribose nucleic acid (DNA) markers to identify the region on chromosome 19 that carries the gene for MH susceptibility.
- Molecular genetic sampling for MH in the umbilical cord blood [4].

Treatment in established cases during surgery includes:

- Local anaesthesia other than lignocaine should be used whenever possible, e.g. procaine. Also spinal, epidural or regional blocks are recommended. For general anaesthesia, thiopentone (or diazepam) and nitrous oxide are safe.

- Termination of anaesthesia and surgery while continuing ventilation.
- Initiating rapid and aggressive total body cooling with ice packs or ice water, through a nasogastric tube, i.v. and rectally. Antipyretics are ineffective.
- Hundred percent oxygen.
- Correction of acidosis with sodium bicarbonate (1 mg/kg and higher).
- Other medications: i.v. furosemide (1 mg/kg) and mannitol (1 g/kg as 20% solution) to maintain urine output and reduce cerebral oedema; insulin and dextrose to treat hyperkalaemia; hydrocortisone (100 mg 4 hourly).
- Dantrolene, the specific antidote, given in a dose of 2.5 mg/kg and then every 5–10 min. The drug prevents an increase in cytoplasmic calcium. Mortality rate has been reduced to 10% using dantrolene.
- Arrhythmia treatment with lignocaine or procainamide hydrochloride.

Neuroleptic Malignant Syndrome (NMS)

This is a rare but potentially fatal drug-induced syndrome following treatment with dopamine antagonists (neuroleptics such as haloperidol). NMS has the following features:

- Increased extrapyramidal disturbance, altered mental status (particularly delirium), muscle rigidity and hyperthermia.
- An incidence, which varies between 0.02 and 3.2% of patients treated with neuroleptics [5]. Drugs triggering NMS are shown in Table 2.4.
- Cases mostly occur after intake of typical or atypical antipsychotic drugs.
- Certain diagnostic criteria [6] are shown in Table 2.5.
- Symptoms usually subside 5–7 days after discontinuation of the triggering drug. The symptoms may last longer with the use of depot preparations.

Table 2.4 Medications that can induce neuroleptic malignant syndrome

Phenothiazine	Monoamine oxidase inhibitors
Thioridazine	Phenelzine
Chlorpromazine	
Benzodiazepine	Antimanics
Diazepam	Lithium
Butyrophenones	Tricyclic antidepressants
Haloperidol	Imipramine, amitriptyline
Anticonvulsants	Serotonin reuptake inhibitors (SSRIs)
Carbamazepine	Fluoxetine
Phenytoin	
Atypical antipsychotic	Antiemetics
Olanzapine	Metoclopramide
Risperidone	Promethazine
Amisulpride	

Table 2.5 Diagnostic criteria for neuroleptic malignant hyperthermia (modified from reference [6])

Essential	Recent use of antipsychotics, or recent use of other dopaminergic, or recent withdrawal of dopamine agent (e.g. Parkinson's medication carbidopa-levodopa)
Major	Elevated body temperature > 38.0 °C.
	No other cause is found for the temperature
	Muscular rigidity
	Elevated CPK >3 times than normal
Minor	Tachycardia, arrhythmia, dystonia, tremor, tachypnoea, altered consciousness, unstable BP, myoglobinuria

CPK creatinine phosphokinase, *BP* blood pressure

The hyperthermia, often in excess of 41 °C, is partly due to sustained muscle contraction and partly due to central disturbance of dopaminergic pathways within the hypothalamic thermoregulatory centre. NMS is a potentially life-threatening disorder with a reported mortality rate of around 10% of cases [7].

This complication of neuroleptic drugs is to be distinguished from the more common and benign side-effects of these drugs, which may produce fever. Infants with dehydration, fever or coexisting brain damage are at high risk of developing NMS.

Laboratory tests are not diagnostic, but an increased CPK suggests the diagnosis.

Therapy is similar to that of malignant hyperthermia, including stopping medication, rapid cooling measures, close monitoring and the use of dantrolene as a muscle relaxant. Bromocriptine has been used with success. Anticholinergics are of little value.

Serotonin Syndrome (SS)

SS overlaps with NMS. Although clinical features are common to both disorders (elevated body temperature, muscle rigidity, delirium, autonomic instability and high CPK), more typical presentation of SS includes features of:

- Behavioural: confusion and agitation or restlessness.
- Autonomic: tachycardia, hypo- or hypertension, mydriasis.
- Neurologic: myoclonus seizures, clonus, tremor, hyperreflexia.
- Intestinal: diarrhoea.

Hyperthermia in SS is a less consistent finding, compared to malignant hyperthermia and neuroleptics malignant syndrome, and is present in about 50% of cases [8].The syndrome is caused by excessive serotonin stimulation. It has been most commonly associated with an intake of monoamine oxidase inhibitors, tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac) and sertraline, and the use of cocaine and ecstasy.

Sympathomimetic Syndrome

Sympathomimetics are the most common drugs responsible for hyperthermia. Common symptoms include mental status changes (agitation, confusion, panics, hallucination).They interfere with heat loss and increase heat production through increased muscle activity. Life-threatening hyperthermia caused by these agents is idiosyncratic and not related to duration and mode of administration. The most used drugs are:

- Amphetamine enhances the release of noradrenaline, dopamine and 5-HT from presynaptic nerve terminals and inhibits their reuptake from the synapses.
- Ecstasy (3,4-methylenedioxymethamphetamine = MDMA) is an amphetamine derivative, which causes sympathomimetic activity by releasing serotonin from neurons in the CNS. It was used briefly in the 1970s and 1980s as an adjunct to psychotherapy. Since then, this drug has become popular and abused by teenagers and young adults as an illicit drug, causing a number of adverse events and fatalities. The hyperthermia is mainly attributed to "rave" parties involving high ambient temperatures, excessive dancing and dehydration. In severe cases, particularly with co-use of other illicit drugs, rhabdomyolysis, DIC, seizures, renal and liver failure and cardiac arrest may occur. There is a correlation between the extent of hyperthermia and survival rates in patients taking ecstasy.
- Cocaine stimulates the release of endogenous catecholamines and prevents their reuptake leading to increased metabolism and impairment of heat loss. Intoxication with these two drugs can cause mortality, which is directly related to the degree of the hyperthermia.
- Methylphenidate is a CNS stimulant which is widely used for the management of ADHD in children. Side-effects with the usual daily dose of 10–60 mg include insomnia, irritability, tachycardia and jitteriness. With overdose, symptoms are similar to those of amphetamine overdose, such as agitation, hallucinations, psychosis, tremors, seizures and hyperthermia.
- Baclofen. This drug is used for spasticity and is being increasingly given intrathecally via an implantable pump, where it achieves a high CSF concentration (100 times greater than that achieved by oral route). Its rapid withdrawal (e.g. pump or catheter malfunction) causes a syndrome characterized by altered mental status, tachycardia, hypo- or hypertension, seizures, rebound spasticity (causing muscle rigidity that sometimes progress to fatal rhabdomyolysis) and hyperthermia, which results from increased muscle activity. Baclofen is known to inhibit sympathetic activity at the spinal cord level, and so its withdrawal may cause rebound sympathetic activity. The syndrome may be fatal unless treated promptly by restoration of the drug intrathecally, supportive care and the use of benzodiazepines.

Endocrine Hyperthermia (EH)

Endocrine hyperthermia is a rare endocrine disorder in children compared to adults. Table 2.6 summarizes the main endocrine disorders that may increase body temperature.

Table 2.6 Summary of the main endocrine disorders causing hyperthermia

Disorder	Underlying mechanisms of hyperthermia
Hyperthyroidism	Combination of increased metabolic rate and enhanced sensitivity to amines
Diabetes mellitus	Similar mechanisms to malignant hyperthermia
Pheochromocytoma	Catecholamines causing excessive heat production, peripheral vasoconstriction and IL-6 may be present in the tumour acting as an endogenous pyrogen
Adrenal insufficiency	Dehydration, possibly due to polyuric hypercalciuria
Etiocholanolone fever	Stimulate formation of leukocyte pyrogens

- Hyperthyroidism. About two thirds of all endocrine hyperthermia are due to thyroid diseases [9]. Thyrotoxic crisis and subacute thyroiditis (de Quervain's thyroiditis) may cause a raised body temperature by increasing the metabolic rate and the hypothalamic set point. In contrast to the extreme hyperthermia in thyrotoxic crisis (can reach 41 °C), hyperthermia due to subacute thyroiditis is usually low-grade, often associated with tenderness and pain in the thyroid area, tachycardia and high ESR. It may present with fever alone as a case of PUO. The thyroiditis, which is caused by a viral infection, can be confirmed by abnormal thyroid function tests (high or low T4/T3 levels) with reduced isotope uptake on thyroid scan. Levels of thyroid- stimulating hormone (TSH) are unchanged with increasing body temperature, but T3 levels decrease with high body temperatures.
- Diabetes mellitus. Hyperglycaemic, hyperosmolar non-ketotic syndrome (HHNS) is usually associated with type 2 diabetes mellitus (DM) and is rare in children. Several cases of malignant hyperthermia-like syndrome have been reported in children in association with HHNS in type 1 DM, resulting in rhabdomyolysis and fatality [10]. The underlying aetiology remains unclear (defect in fatty acid oxidation? genetic predisposition?). A rare endocrine abnormality is insulinoma that may be associated with elevation of body temperature and severe hypoglycaemia [11]. A removal of the tumour normalizes the body temperature.
- Hyperparathyroidism is the third most common endocrine disorder after thyroid diseases and diabetes. It is due to increased parathyroid hormone, mostly from parathyroid adenoma, hypercalcaemia (>2.5 mmol/L), bone demineralization and nephrolithiasis. Polyuria may cause hyperthermia. It is one of the rare causes of pyrexia of unknown aetiology.
- Pheochromocytoma with increased catecholamine production may cause excessive heat production as well decreased heat loss subsequent to peripheral vasoconstriction. The presence of a large tumour and tumour necrosis increases the likelihood of hyperthermia that occurs in about a third of patients. Exercise may trigger both sudden hyperthermia and hypertension.

- In adrenal insufficiency, hyperthermia is not common. Elevated temperature may be due to dehydration, related to polyuric hypercalciuria and electrolyte imbalance, autoimmune disorders or tuberculosis.
- Etiocholanolone fever. Etiocholanolone is a major metabolite of testosterone and androstenedione. It acts as a pyrogen causing fever due to the release of interleukin-1 from the leukocytes.

2.4.2 Hyperthermia Caused by Decreased Heat Loss

Neonatal Hyperthermia

A rapid rise in body temperature on the second and third day of life may be due to:

- Dehydration (so-called dehydration fever) is the result of fluid loss, mainly due to evaporation of the amniotic fluid from the baby's body or exposure to a high environmental temperature. This problem results from the infant's greater surface area per unit weight as compared to adults, causing a higher fluid loss through the skin. This condition was identified in 68 out of 358 (19%) febrile neonates, making it the third most common cause of temperature elevation after infection and birth trauma [12]. Hyperthermia should not be confused with fever, which is a response to infection, although both may cause elevated body temperature. Table 2.7 shows the main difference between neonatal hyperthermia and infectious fever. Up to 10% of breast-fed children are said to develop this complication due to insufficient breast secretion and/or infant's reluctance to feed. This incidence can be lowered to about 1% following fluid supplement (through frequent breast feeding to replace fluid loss), which is about the same incidence found in formula-fed babies.

Table 2.7 Differentiating neonatal hyperthermia from infectious fever

Criteria	Hyperthermia	Fever
Incidence	1–10%	1%
Main risk	Dehydration, overheating	Prematurity, PRM[a]
Appearance	Well at initial stage	Unwell
Symptoms	Usually none if hyperthermia is short. If prolonged: tachypnoea, tachycardia, hot and red skin, irritability	Numerous (see Ch 1)
Response of °C to fluid	Rapid normalisation	No change
Leg-rectal temperature[b]	< 1.5 °C	> 3.2 °C
Laboratory findings	Hypernatraemia, high urea	CRP ↑, leucopenia

[a]Premature rupture of membrane
[b]Measurement of the skin temperature of the anterior mid-lower leg simultaneously with rectal temperature or tympanic temperature

- Overheating from mechanical or electrical failure of a warming device or servo-controlled incubators that can cause overheating if the skin sensor becomes detached from the infant or if the baby is left under a radiant warmer for a long period. Overwrapped infants left in a warm room are also at risk.
- Birth trauma may cause a rise in body temperature occurring on the second and third day of life. This phenomenon occurred in 86 out of 358 (24%) infants [12]. Temperature usually subsides within 1–3 days but occasionally persists in the presence of excessive restlessness or convulsions. A probable cause of this hyperthermia is the inability of the sick infant to maintain normal body temperature owing to inadequately developed thermoregulatory mechanisms.

The treatment of hyperthermia in the newborn consists of cooling the infant rapidly by undressing and exposing him or her to room temperature and by frequent breast-feeding. If the skin temperature is higher than 39.0 °C, sponging with tepid water at about 35.0 °C should be initiated until the skin temperature reaches 37.0 °C.

Heat Stroke

Clinical descriptions of 14 different heat-related disorders are recognized in the medical literature (e.g. heat cramps, heat exhaustion, sunburn, etc.), of which heat stroke is the most important heat-related illness and is a medical emergency. It is sometimes called siriasis, based on the biblical reference that occurred coincidentally with the appearance of the Dog Star, Sirius [13]. Heat stroke was described in medicine over 1000 years ago as "another form of fever" by Rhazes (Chap. 13: History of fever). Its recognition in Europe did not occur before the eighteenth century when soldiers were sent to warm countries. Risk factors predisposing to heat-related illness are shown in Table 2.8.

Heat stroke is defined as a core temperature greater than 40.6 °C, accompanied by hot, dry skin and CNS abnormalities such as convulsion, delirium and coma. The two principal causes are high ambient temperature and water deprivation. If the

Table 2.8 Risk factors predisposing to heat-related illness

Age	Environmental
Very young and old	High ambient temperature
	High humidity
	Lack of wind
Dehydration	Drugs
Fever	Lithium, antihistamine, anticholinergic, selective serotonin reuptake inhibitors
Inadequate fluid intake	
Gastroenteritis	
Diuretic use	
Sport (exertional heat stroke)	
Clothing	Condition
Wrapping	Physical or mental disability

temperature rises above 40.2 °C cell deaths occur, and the condition is associated with high mortality of 80%. Heat exhaustion is associated with a core temperature < 40.0 °C.

Heat stroke is due to failure of the heat-regulating mechanisms of the hypothalamus subsequent to inhibition of sweating. Cytokines in the CNS leads to increased intracranial pressure, thus reducing the blood flow and causing neural injury. Initially, there may be sweat loss leading to dehydration, which aggravates the hyperthermia.

Heat stroke has been reported from a number of geographical areas including:

- In the USA [14] and Italy [15], infants who were left sleeping in a parked automobile under the sun with inadequate ventilation may suffer heat stroke. In 2003, the number of children reported who died from heat stroke after being left unattended in motor vehicles was 42.
- In the UK and other European countries where excessive wrapping is sometimes practiced in infants (mainly from lower socioeconomic classes). This swaddling, which in an ancient practice, has become increasingly popular as a sleep-promoting intervention, sometimes resulting in fatalities [16].
- In Melbourne, Australia, heat stroke occurred during a recent heat wave.
- In the tropics, heat stroke may occur in children as a result of combined salt and water deprivation or severe sunburn.

The cardinal features of heat stroke include:

- Body temperature: > 40.6 °C.
- Skin: hot, dry and red (sweating may or may not be present).
- CNS abnormalities: alteration of consciousness, dizziness, headache, convulsion and coma, uncontrollable muscle twitching.
- Cardiac: Tachycardia, arrhythmia and failure as a result of extensive haemorrhage in the myocardium.
- Gastrointestinal: diarrhoea, nausea, vomiting, cramps, jaundice (liver failure).

In addition, children are usually in shock (due to maldistribution of the blood to the circulation), with metabolic acidosis. Clinical evaluation may confirm the presence of renal failure, DIC, rhabdomyolysis (due to severe muscular contraction), hepatic enlargement with elevation of the enzymes and anaemia due to increased RBC destruction, thrombocytopenia and hyperkalaemia, with characteristic ECG abnormalities.

A child with heat stroke should:

- Be referred to an intensive care unit with facilities for continuous monitoring and ventilation. The two main goals of therapy are cooling and support of circulation.
- Undergo rapid cooling, best achieved by removing the clothes, sponging with ice water (or better immersing into ice water) until body temperature reaches

38.5 °C. Then the patient is moved to a bed and wrapped in a blanket. In severe or resistant cases iced-intravenous solution, iced-saline gastric lavage and cold saline enema may be needed.
- Be vigorously massaged to promote vasodilatation and fanning to increase convection. Continuous oxygen therapy is usually given routinely.
- Have IV fluid therapy aimed at correction of dehydration and balancing electrolytes. Plasma expanders and mannitol (1 g/kg of 20% solution, infused over 15–20 min) are required to treat cerebral oedema and renal under-perfusion.
- Be treated for hyperkalaemia with glucose and insulin. Renal failure may require early dialysis, along with adequate fluid, electrolytes and bicarbonate.

Despite intensive treatment, the prognosis of heat stroke is poor, with a mortality ranging from 17 to 70%, depending on severity of the heat stroke and age of the patient. Post-mortem examination reveals cerebral oedema and haemorrhage in various organs.

Haemorrhagic Shock and Encephalopathy (HSE)

This form of hyperthermia was described by Levin et al. in 1983 [17].Despite extensive investigations, including viral and bacteriological studies, no specific cause has been found. Although clinical features are similar to heat stroke, the majority of reported cases had no evidence of wrapping, fluid deprivation or high environmental temperature. It was later suggested that HSE may be a manifestation of a genetic defect in the production or release of serum protease inhibitor alpha-1-trypsin [18].

The median age of affected children is 5 months (range 17 days to 15 years), and nearly 90% have been less than 1 year of age. Usually, the children have been completely well with only mild non-specific symptoms, such as an upper respiratory tract infection or febrile gastroenteritis, 2–5 days prior to the onset of HSE. Then abruptly they develop:

- Severe shock, manifested clinically by collapse, pallor, cyanosis and mottled skin. Hypotension is a late sign of shock.
- Encephalopathy manifested with sudden onset of seizures and coma.
- Hyperthermia a constant finding, with a temperature usually above 41 °C.
- Bleeding due to DIC, with diarrhoea, may be striking, resulting in severe anaemia requiring transfusion.

Examination reveals hepatomegaly and acidosis with shallow respirations. During the next few hours, renal failure becomes established with increased creatinine, hyperkalaemia and acidosis. Additional laboratory abnormalities include leukocytosis, hypernatraemia, elevated serum levels of creatinine phosphokinase (CPK), liver enzymes and trypsin, hypoglycaemia and hypocalcaemia, thrombocytopenia, reduced factors II, V, hyperfibrinogaemia and alpha-1-antitrypsin.

Haemorrhagic shock and encephalopathy must be differentiated from:

- Heat stroke with its history of fluid deprivation and high ambient temperature.
- Septicaemia with its less abrupt presentation.

- Reye's syndrome with its elevated plasma ammonia and characteristic histological findings of the liver; possible aspirin intake.
- Haemolytic uremic syndrome with its haemolysis, pronounced anaemia.
- Toxic shock syndrome and Kawasaki disease (both have a less dramatic onset) and accidental intake of toxin.

There is no specific treatment for HSE, and management is similar to that discussed for malignant hyperthermia and heat stroke. Prognosis is poor with a mortality of 80% and severe neurological squeal in the majority of surviving cases. CT scan and autopsy show focal haemorrhage in many organs and cerebral oedema.

Drug-Induced Hyperthermia

- Anticholinergic poisoning. The dominant clinical features are:
  Central: confusion, agitation, hallucination and seizures
  Peripheral: dry mucous membranes, thirst, flushed face, blurred vision, dilated pupils and hyperthermia

  The hyperthermia is mainly caused by decreased sweating.
  Drugs with anticholinergic activity include

Antispasmodic	For example, belladonna, propantheline
Antiemetic	For example, hyoscine, cyclizine, promethazine
Atypical antipsychotics	For example, olanzapine
Bronchodilator	For example, ipratroprium
Antihistamine	For example, chlorpheniramine
Antidepressant	For example, amitriptyline, imipramine

Hyoscyamine is one of the principal alkaloid components of belladonna. Hyoscyamine sulphate drops are sometimes prescribed for infantile colic. Herbal tea and Chinese herbal medicine have also caused anticholinergic poisoning and hyperthermia.

Treatment includes rapid and aggressive cooling. The specific antidote is physostigmine. Benzodiazepines are also effective.

Other hyperthermia-induced drugs include:

- Topiramate is an anticonvulsant drug with a beneficial effect on various seizure disorders. Side-effects include hypohidrosis (or anhidrosis) causing hyperthermia, which is manifested as prolonged or intermittent elevated body temperature. The decreased production of sweat can be confirmed by pilocarpine iontophoresis sweat test.
- In a study of 277 children on topiramate, 161 (58%) developed adverse events, including nervousness, weight loss and hyperthermia [19]. These side-effects disappeared in most cases after reducing the dose. They are rare on monotherapy. The hyperthermia is probably due to inhibition of carbonic anhydrase in human eccrine sweat glands.
- Salicylate poisoning: see Chap. 10, Management of fever

2.4.3 Unclassified Hyperthermia

Sudden Infant Death Syndrome (SIDS)

This important subject is included because of its possible link to hyperthermia.

The accepted definition of SIDS is:

- An infant's sudden and unexpected death, which remains unexplained after thorough post-mortem examination.
- A thorough investigation of the death scene fails to find the cause of SIDS.
- A diagnosis of exclusion. Symptoms such as upper respiratory tract infection with possible fever, which do not have serious effects on the child's condition, do not exclude the diagnosis.

Although SIDS is still the leading cause of death in infants one to 12 months of age, its rate has declined since the start of the "Back to Sleep" campaign in 1991 (UK) and 1992 (USA).

- In the USA, the rate in 1992 was 1.2 death per 1000 live births, which decreased to 0.56 death per 1000 live births (a reduction of 53%) over 10 years [20]. During this period, the prevalence of prone positioning has decreased from 70 to 11.3%.
- In the UK, there has been a remarkable fall in incidence to 0.4 death per 1000 live births in the year 2000 and a further fall to 0.26 in the year 2003 [21].

Despite extensive research over the past decades, the cause of SIDS is unknown. The predominant hypothesis is that certain infants have maldevelopment or delayed maturation of the brainstem neural network, which is thought to be involved with arousal, chemosensitivity, respiratory drive, thermoregulation and blood pressure response. Long QT interval may also cause SIDS. A multifactorial cause, rather than a single one, appears likely. Risk factors associated with SIDS are shown in the

Table 2.9 Risk factors that contribute to SIDS

General factors	Hyperthermic factors
Maternal smoking	Prone position
Low birth weight	Bed-sharing with parents
IUGR	Overwrapping, bundling
Twins	High environmental temperature
Opiate addiction	Respiratory infections
Young maternal age	
Maternal alcohol consumption	
Deprived socio-economic status	
Polystyrene-filled cushions	
Sibling with a history of SIDS	
Prolonged QT-interval in the ECG	

Table 2.9. The risk peaks at 2–4 months of age and is low during the neonatal period (only about 4% of all SIDS cases). The two important factors are prone position and maternal smoking.

Although the vast majority of infants who sleep prone are not in danger of SIDS, up to 88% of SIDS victims were found in this position. A child in prone position may have limited head movement and thus limited access to fresh air. This factor may also explain the low incidence of SIDS in Asian children, who usually sleep in a supine position.

SIDS and Hyperthermia. Hyperthermia (e.g. in the form of heat stroke) has been implicated as a cause of SIDS. It may cause apnoea as a result of transient loss of respiratory chemoreceptor sensitivity. The most convincing evidence of the relationship between SIDS and hyperthermia was reported by Stanton [22], who found that 32 of 34 cases (94%) of SIDS victims were excessively clothed in an unusually warm environment or were hot and sweaty when found dead. In these cases, sweat and high rectal temperature suggested the presence of hyperthermia.

The mechanisms leading to hyperthermia in SIDS include:

- Excessive wrapping, thick bedding, high environmental temperature (such as proximity to a heat source) and a prone position, which may further limit heat loss through the face in the presence of overwrapping. Side sleeping is not as safe as supine sleeping
- Mild infection, commonly preceding SIDS, may produce fever, which in combination with excessive wrapping could produce heat stroke and SIDS.
- Bed-sharing infants experience warmer thermal environment than those sleeping in a cot.
- In addition, a period of thermoregulatory imbalance may exist during infancy where heat production in relation to surface area reaches a maximum by about 5 months of age, while dissipation of heat by sweating develops more slowly over the first year of life.

Factitious Hyperthermia (FF)

The creation of "fever" by manipulation (usually thermometer manipulation) is rare in children, particularly below the adolescent age. However, factitious hyperthermia is occasionally encountered in the differential diagnosis of PUO, occurring in about 2% of a large study of mainly adult cases [23]. It can be the most difficult diagnosis to establish. For example, an adolescent of 15 years of age from the USA with an 8-month history of fever was described [24]. It is true to say that the question as to whether a patient actually has a fever or not is rarely raised.

Many patients with FF appear to seek attention and feel protected in a hospital environment. Occasionally, it is an escape from intolerable conditions at home. Methods commonly used by these patients to induce FF include holding the thermometer next to a hot-water bottle, rubbing it against bedclothes, rinsing the mouth with a hot liquid before inserting a thermometer or switching thermometers.

Diagnostic clues include:

- Discrepancy between the generally well appearance of the child and the recorded "fever".
- The absence of warm skin, sweating, tachycardia and the usual diurnal variation of the fever.
- Normal laboratory findings, e.g. inflammatory markers: leukocytes, CRP.
- Normal body temperature when a nurse attends the temperature recording.

Induced Illness (Factitious Illness, Munchausen Syndrome)

This is the most extreme form of factitious disorder. In 1951, Asher described patients who fabricated illnesses and subjected themselves to medical investigations and treatment, including operation [25].Although principally an adult disease, the syndrome has also been reported in children [26] and is characterized by features shown in the Table 2.10.

In a review of literature over 30 years [27], 42 children (mean age 13.9 years) with falsified illness were identified. The most commonly falsified conditions were fevers (13%). The deception was carried out by warming thermometers with heating pads.

Induced Illness by Proxy (Factitious Illness by Proxy)

In 1977, Meadow reported two children whose parents by fabrication caused them to undergo innumerable, harmful medical procedures [28]. In a second report in 1982 [29], Meadow presented 19 children under the age of 7 years (above this age children are likely to reveal the deception) of which four had fever as the fabricated sign (incidence of fever generally is around 10%). Meadow considered epilepsy to be the most frequently fabricated illness. Mortality rate among children diagnosed is 9%.

The syndrome involves a parent (usually mother) or caregiver who tends to be young and articulate and who fabricates an illness in a child. The motivation for the perpetrator's behaviour is a psychological need to have the child assuming the sick role. The perpetrator often has a personality disorder and a significant family

Table 2.10 Main features of induced illness

Essential features
Pathologic lying
Simulation of a disease
Wondering
Minor features
Unusual or dramatic history
Previous treatment in hospital
Previous diagnostic procedures
Multiple scars
Experience in a medical field
Antisocial personality trait

dysfunction. Family history of unexplained child's death may be elicited. The syndrome is characterized by:

- Discrepancy between history, clinical findings and the child's healthy appearance.
- Mother appears less worried about the child's illness than medical staff. She usually welcomes even painful tests and procedures for her child.
- The child's "illness" is recurrent and cannot be explained medically.
- There is a history of multiple medical procedures.
- Symptoms and signs disappear in the mother's absence.
- Mother usually attentive and present in hospital.
- Once confronted, the perpetrator typically denies any knowledge.

Clinical presentations generally follow two patterns:

- Apnoea, feeding problems, seizures and cyanosis (seen during infancy).
- Diarrhoea, vomiting and fevers (seen in older children).

Although the majority of fabricated illnesses are not life-threatening, recurrent episodes of cardiorespiratory arrest induced by a mother have been reported, suggesting that Munchausen syndrome by proxy is a form of child abuse. A report of 56 children supported this view: a substantial proportion of the victims sustained failure to thrive, nonaccidental injury, inappropriate medication or neglect [30].

2.4.4 Therapeutic Effects of Hyperthermia

It has been known for thousands of years that hyperthermia helps the body against some diseases. In 1970s and 1980s, several trials have shown that hyperthermia combined with radiation or chemotherapy produced better anticancer treatment over radiation and chemotherapy alone. Therapeutic application of hyperthermia and the means to produce it are shown in the Table 2.11. Its potential use includes:

Table 2.11 Therapeutic application of hyperthermia (or fever) and means of producing it

Application of heat:	Local
	Deep (<3 cm under the skin)
	Superficial
	Regional
	Deep (<3 cm under the skin)
	Superficial
	Whole body
Externally produced heat	Microwave, thermal blanket, lasers, heating rods, infrared radiation, high frequency electrotherapy, ultrasound, extracorporeal
Internally produced heat	Pyrogens (bacterial substance producing fever; fever therapy)

Infectious diseases

Hyperthermia stimulates the immune system, including production of interferon (INF). Examples of diseases treated by hyperthermia are:

- During the nineteenth century, medical professionals observed that tumours regressed in size after an episode of a high fever due to infection. Wagner von Jauregg in 1917 treated neurosyphilis with malarial fever, for which he won the Nobel Prize (see Chap. 13). 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 for about 50 h administered in several sessions. *Borrelia* spirochaetes, the cause of Lyme disease, might also be susceptible to hyperthermia greater than 41 °C.
- Viral nasopharyngitis: Nasal insufflations of humidified air at 43 °C showed suppression of symptoms in 78% of patients [31].
- Human immunodeficiency virus (HIV) infection: Temperatures of ≥42 °C maintained for ≥25 min have been shown to inactivate approximately 25% of the HIV [32]. A daily use of such temperatures lowers the population of actively infected cells by 40%. A reduction of the virus by 40% would effectively reverse the depletion of T cells. HIV-infected cells are more sensitive to heat than healthy lymphocytes. This susceptibility increases when the cells are pretreated with tumour necrosis factor.

Musculoskeletal disorders

Local and regional hyperthermia have been used since ancient times to treat musculoskeletal disorders. Tissue heated at 44 °C increases extensibility of the tissue, decreases joint stiffness and muscle spasms. These effects occur mainly through increased blood flow. Whole body hyperthermia also induces soluble tumour necrosis factor receptors (TNF-R), which is an anti-inflammatory product.

Cancer

Hyperthermia is regarded as the fifth treatment of cancer after surgery, chemotherapy, radiotherapy and immunotherapy. Therapeutic hyperthermia as an adjunctive therapy has been used since 1970s to treat patients with cancer, yielding some positive results with complete or partial remission of the tumours. Hyperthermia has been shown to synergistically enhance the radiation response and cytotoxicity of chemotherapy. Heating can be achieved using microwaves, radio waves, laser and ultrasound waves. There is evidence that hyperthermia of 42 °C or greater for 30–60 min is tumouricidal. This effect of cell death is mainly caused by protein denaturation at hyperthermic range of 40–44 °C. Hyperthermia also causes cellular damage including apoptosis leading to cell death.

Hyperthermia in combination with chemotherapy has been shown to be effective in:

- Some patients with advanced malignancies, e.g. renal cell carcinoma [33].
- The management of retinoblastoma, which has gradually changed over the past 10–15 years: enucleation is preferable only for a large tumour that fills most of

the globe [34]. Over 95% of children with retinoblastoma are cured with modern techniques. These include the use of transpupillary thermotherapy alone or in combination with systemic chemotherapy (chemothermotherapy).
- Using regional hyperthermia (RHT) chiefly in children with sarcoma or germ cell tumours located in the abdomen, pelvic region, chest wall and extremities to improve operability [35].
- Treating malignant brain tumour such as glioblastoma [36] and malignant melanoma.

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Pathogenesis of Fever

3

Core Messages

- Although infection is the most common cause of fever, fever is also a common finding in hypersensitivity reaction, autoimmune diseases and malignancy.
- Febrile response is mediated by endogenous pyrogens (cytokines) in response to exogenous pyrogens, primarily micro-organisms or their direct products (toxins).
- These endogenous pyrogens act on thermo-sensitive neurons in the hypothalamus, which ultimately upgrade the set point via prostaglandins.
- The body reacts by increasing the heat production and decreasing the heat loss until the body temperature reaches this elevated set point.
- Fever, in contrast to hyperthermia, will not climb up relentlessly because of an effective central control of the hypothalamic centre.
- Cytokines play a pivotal role in the immune response by activation of the B cells and T-lymphocytes. The production of fever simultaneously with lymphocyte activation constitutes the clearest and strongest evidence in favour of the protective role of fever.
- The protective processes of the immune response are optimal at high temperature (around 39.5 °C).
- Not all effects resulting from fever generation benefit the host; some are harmful and even lethal. This occurs mainly by overproduction of the cytokines or imbalance between cytokines and their inhibitors, such as severe and fulminate infections and septic shock.

3.1 History of Research

Research in fever has been centred on the hypothesis that fever results from physiological processes that are set in motion by an external stimulus. Egyptian scholars recognized that local inflammation was responsible for fever. In 1868,

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_3

Billroth (1829–1894) attempted to confirm this ancient observation by injecting pus into animals, thereby producing a febrile response. In 1943, Menkin carried out similar experiments and isolated a product termed "pyrexin" [1]. Beeson in 1948 isolated a fever-inducing substance from a leukocyte, leukocyte pyrogens, which later became known as endogenous pyrogen (EP). Interleukin-1 (IL-1) was first identified as a cytokine by Gery and Waksman and proved to be identical with EP [2].

3.2 Definitions

- Fever (pyrexia) is a regulated body temperature above the normal range occurring as a result of IL-1-mediated elevation of the hypothalamic set point. Once fever is established, body temperature is regulated, as in health, by a net balance between heat production and loss.
- Hyperthermia is an unregulated elevated body temperature above the normal range due to imbalance between heat production and loss. Interleukins are not involved and therefore the hypothalamic set point is normal.
- A pyrogen is a substance (infectious organisms or their product toxins or cytokines) that provokes fever.
- Exogenous pyrogens are substances, which originate outside the body and which are capable of inducing interleukins.
- Endogenous pyrogens are substances, which originate inside the body and which are capable of inducing fever by acting on the hypothalamic thermoregulatory centre. IL-1, tumour necrosis factor (TNF) and interferon (INF) are endogenous of albumin and transferrin decreases. Characteristically there are a decreased concentration of iron and zinc and an increased copper concentration. The low iron is the result of reduced intestinal assimilation of iron and increased liver storage of iron. These changes contribute to host defence by depriving invading micro-organisms of essential nutrients, such as iron and zinc. The process is referred to as nutritional immunity.
- Cytokines are proteins produced throughout the body, mainly by activated macrophages, monocytes and T cells to regulate the immune responses within the body, control inflammatory and haematopoietic processes and may induce fever. As they enter the circulation and act on distant organs, they are considered as hormones. Pro-inflammatory cytokines (e.g. IL-1, IL-6, TNF-α, INF-γ, granulocytes-macrophages colony stimulating factor, GM-CSF) are responsible for initiating an effective defence against exogenous organisms (e.g. activating neutrophils). Their overproduction may be harmful by causing shock, multiple organ failure and death. Anti-inflammatory cytokines (e.g. IL-1 receptor antagonist, IL-4, IL-10) antagonize the pro-inflammatory cytokines and thus promoting healing and reducing inflammation.
- Monokines are cytokines that are produced by mononuclear phagocytic cells.

- Chemokines are cytokines that attract cells to the site of infection using chemical message (chemotaxis). Typical chemokine is CXCL-8 that attracts neutrophils.
- Interleukins are cytokines, acting specifically as mediators between leukocytes, hence their name. Their number known nowadays is enormous: at least 37 interleukins have been identified. If their amino acid sequence is known, they are assigned an interleukin number. If their sequence is not known, then they are named according to the biological property. IL-1 and IL-6 play a major part in the pathogenesis of fever.
- Lymphokines are cytokines that are secreted by lymphocytes to regulate the immune response. Important lymphokines are IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL-14 and TNF-gamma.
- Prostaglandins are lipids that are made at sites of infection and tissue damage to produce inflammation and fever as part of the healing process.
- Acute-phase response is the term used for haematological, endocrinological and metabolic changes that follow (within hours or days) the onset of fever in response to infections or local damage to a tissue. These changes are induced by several cytokines (IL-6 being the primary inducer), which are beneficial to the host. During the response, various acute-phase proteins, notably C-reactive protein (CRP) and serum amyloid A, are synthesized by hepatocytes and released into circulation in large amounts. CRP plays a role in complement activation, opsonization and increasing platelet aggregation. Although acute-phase response is closely associated with fever, CRP levels can be normal in viral infections and high in diseases without fever (e.g. tumours). Syntheses of albumin and transferrin and the concentration of iron and zinc decrease, while copper concentration increases. The low iron is the result of reduced intestinal assimilation of iron and increased liver storage of iron. These changes contribute to host defence by depriving invading micro-organisms of essential nutrients, such as iron and zinc. The process is referred to as nutritional immunity.

3.3 Exogenous Pyrogens (ExP) (Fig. 3.1)

Exogenous pyrogens (e.g. bacteria, viruses, toxins) initiate fever, usually within 2 h of exposure, by interacting with macrophages or monocytes, leading to cytokine induction. Other mechanisms to initiate fever include:

- Some endotoxins, produced by bacteria, act directly on the hypothalamus to alter the set point. IL-1 is not involved. Radiation of the hypothalamus, DDT (dichlorodiphenyltrichloroethane), poisoning and scorpion venom may also induce fever by a direct effect on hypothalamus.
- ExP may activate lymphocytes to secrete lymphokines, particularly INF-y, which in turn stimulate macrophages and monocytes to produce IL-1.

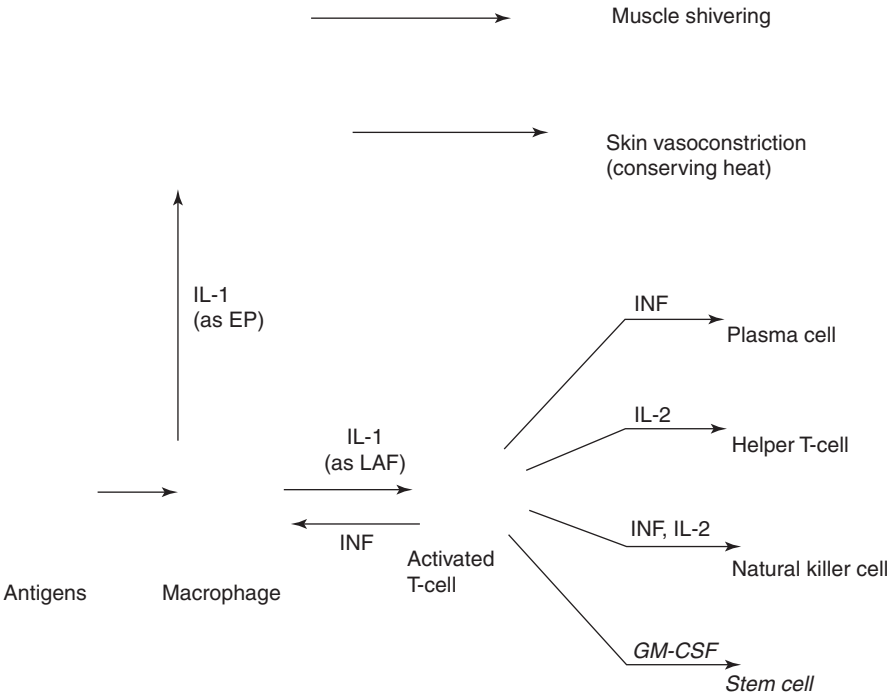

Fig. 3.1 The mechanisms of fever induction

- Some bacteria produce exotoxins, which stimulate macrophages and monocytes to release IL-1. This mechanism operates in scarlet fever and toxic shock syndrome. In toxic shock syndrome, the shock is due to the toxin. Diseases involving exotoxins produced by Gram-positive bacilli are less fever-inducing than those produced by pyrogenic Gram-positive cocci.
- Borrelia spirochetes (the cause of relapsing fever) do not contain endotoxin, and the attachment of these bacteria to the mononuclear cells induces IL-1.
- Other bacteria, such as pneumococci, have no endotoxin or other pyrogens, and the mechanisms responsible for fever are presumably immunological

3.3.1 Microbial Exogenous Pyrogens

- Gram-negative bacteria. The pyrogenicity of Gram-negative bacteria (e.g. *Escherichia coli*, *Salmonella*) is due to a heat-stable factor, endotoxin. The active components of endotoxin are lipid and carbohydrate (lipopolysaccharide, LPS), which are the major components of the outer membrane of these bacteria. Endotoxin causes a dose-related progressive increase in temperature. In severe

cases, it causes shock with vasodilatation, capillary leakage and hypotension. Septicaemia caused by Gram-negative endotoxin does not elicit fever in certain situations such as neonates, young infants or children with fulminating infection or with malnutrition. These children may present with normal temperature or even hypothermia in response to severe infection. Mortality is significantly higher in septic children [3] and adult [4] patients due to reduced capacity to release TNF-α and IL-β upon infection with LPS.

- Gram-positive bacteria. The main pyrogen of most bacteria is peptidoglycan that forms the cell wall. Penicillin works by inhibiting the biosynthesis of peptidoglycan, which results in cell lysis. This explains why penicillin is more effective against Gram-positive bacteria.
- Viruses. It is well known in clinical practice that viruses cause fever. Mechanisms by which viruses may produce fever include direct invasion of macrophages, immunological reaction to viral components involving antibody formation, induction by INF and necrosis of cells by viruses.
- Fungi. Live or killed fungal products are exogenous pyrogens that induce fever. The induction of fever mainly occurs when the fungi are in the bloodstream. Children with neoplastic diseases who develop fever associated with neutropenia are at high risk for developing invasive fungal infection.

3.3.2 Nonmicrobial Pyrogens

- Phagocytosis is largely responsible for fever in blood transfusion reactions (once an infection is excluded) and immune haemolytic anaemia.
- Antigen-antibody complexes. An exogenous antigen may react with circulating, sensitized antibodies to form a complex, which induces IL-1 production (immune fever). Examples of immunologically mediated fever include systemic lupus erythematosis and adverse drug reactions. Fever associated with penicillin hypersensitivity results from interaction of antigen-antibody complexes with leukocytes, which release IL-1.
- Most steroids are endogenous antipyretics, which suppress fever through their inhibitory effects on IL-1 and TNF-α production as well as inhibition of prostaglandin synthesis. Certain steroids, however, are pyrogenic in human such as etiocholanolone, a major metabolite of testosterone and 17-ketosteroid, which induce the release of interleukin-1. Etiocholanolone produces fever only when injected intramuscularly (not intravenously). Etiocholanolone fever is characterized by recurrent fever for few days, in association with arthralgia, abdominal pain, leukocytosis, high ESR and etiocholanolone level. Fever does not respond to antipyretics but to steroids, e.g. prednisolone. Etiocholanolone is responsible for fever in some patients with adrenogenital syndrome.
- Other nonmicrobial pyrogens include some hormones, drugs and intracranial lesions such as bleeding and thrombosis

3.4 Monocyte: Macrophage System (MMS) (Fig. 3.2)

Mononuclear cells are leukocytes (3–8% of the leukocytes) and are largely responsible for the production of IL-1 and fever induction. Polymorphonuclear granulocytes are no longer thought to be responsible for IL-1 production because fever may occur in their absence, e.g. agranulocytosis. The mononuclear cells are either circulating monocytes in the peripheral blood or tissue macrophages (histocytes) scattered in organs such as lung (alveolar macrophages), lymph nodes, placenta, peritoneal cavity and the subcutaneous tissue. The origin of both monocytes and macrophages is the granulocyte-monocyte colony-forming unit (GM-CFU) in the bone marrow. Monocytes enter the circulation either to remain there for a few days as circulating monocytes or to migrate to the tissue where they undergo functional and morphological transformation into macrophages, when their life span is several months. These cells play an important role in:

- Host defence, including engulfing and destroying the microbe (phagocytosis) recognition of antigen and presenting it to attached lymphocytes.
- Activation of T-lymphocytes and tumour cell destruction.

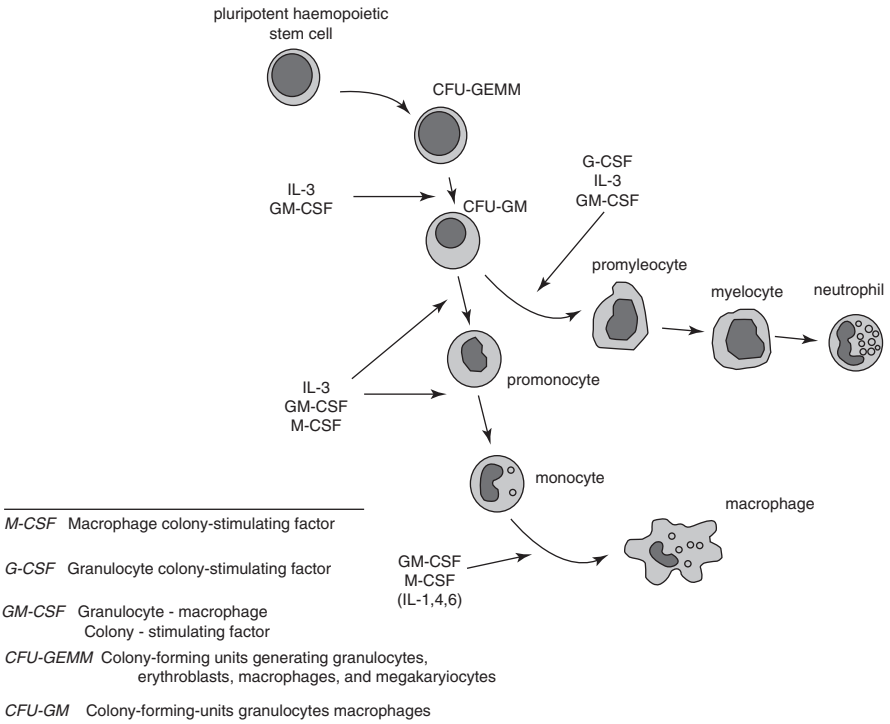

Fig. 3.2 Showing monocytes and macrophages

Situations associated with reduced function of the MMS include newborn infants, corticosteroid and other immunosuppressive therapy, systemic lupus erythematous, Wiskott-Aldrich syndrome (immune deficiency involving B and T cells, eczema and thrombocytopenia) and chronic granulomatous disease. The two major monocyte-macrophage products (cytokines) are IL-1 and TNF.

3.5 Endogenous Pyrogens (EP)

3.5.1 Interleukin-1 (IL-1)

IL-1 consists of three structurally related polypeptide, two agonists (IL-1α and IL-1β) and an antagonist (IL-1 receptor antagonist = IL-1ra), which inhibit the activities of the two powerful agonists. Anakinra is a naturally IL-1ra. IL-1α is produced in:

- Cells of healthy people including in all epithelial cells of mucosal membranes.
- Blood monocytes and tissue macrophages.
- Hepatic Kupffer cells, keratinocytes and pancreatic Langerhans cells.
- Astrocytes in the brain tissue, which may contribute to the immunological responses within the CNS and the fever secondary to CNS bleeding.
- Cells from certain malignant tumours (e.g. Hodgkin's disease, acute leukaemia and renal carcinoma). This explains the frequent association of fever in these conditions in the absence of infection.

IL-1β is not present in cells of healthy people and is mainly produced by monocytes, macrophages and dendritic cells.

Interleukin-1 has important roles in the following conditions (Fig. 3.3):

- Induction of fever by acting on the hypothalamus to raise its set point.
- Induction of hepatic acute-phase proteins (see above).
- Induction of inflammatory response and lymphocyte activation factor.
- Appetite suppression. IL-1 is a potent anorexic cytokine (more potent than the hunger inhibitor Leptin), which explains the reduction of food intake commonly

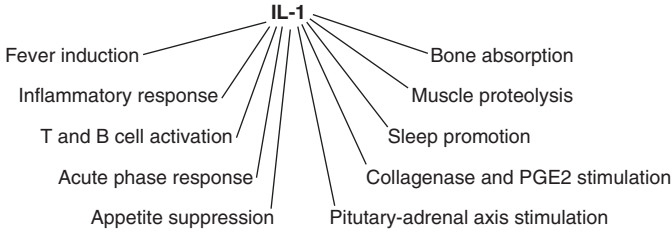

Fig. 3.3 Summary of the main functions of IL-1

seen in febrile illness. IL-1ra reverses the decrease in food intake. Circulating IL-1ra, along with IL-18, are increased in obese and type 2 diabetes [5].

- IL-1β (along with TNF-α) regulates sleep by promoting non-rapid eye movement sleep. This cytokine is produced in astrocytes of the brain. The action of IL-1β may explain the observation of increased sleep in febrile illnesses.
- Joint diseases such as rheumatoid arthritis (RA) and ankylosing spondylitis. RA is an autoimmune mediated by IL-1. Treatment with anakinra prevents the migration of inflammatory cells into the joint.
- Inflammation of the blood vessels (vasculitis).
- Stimulating the liver to produce acute-phase proteins (see above).
- Congenital deficiency of IL-1 receptor antagonist is associated with overwhelming inflammation of the skin, joints and bones and large infiltration of neutrophils. Infants with this condition die early in life unless anakinra is given that rapidly reverses the inflammation and prevents the death [6].
- Auto-inflammatory diseases are characterized by periodic fever due to recurrent episodes of systemic and local inflammation. Anakinra has been successful in treating conditions such as familial Mediterranean fever (see Chap. 6).
- IL-1-mediated inflammation is contributing to the acute ischaemic conditions such as myocardial infarction, stroke, liver and renal failure.
- HIV replication. IL-1ra has suppressive effects on the virus.
- Macrophage activation syndrome is a life-threatening disease in patients who suffer from EB-virus or cytomegalovirus. Anakinra causes rapid recovery.
- Diabetes (type 1 is an autoimmune disease mediated by T-lymphocytes; type 2 is associated with obesity and physical inactivity causing insulin resistance). Both types produce high glucose concentration that stimulates IL-1β causing destruction of the insulin-producing β-cells of the pancreas.

3.5.2 Tumour Necrosis Factor (TNF)

TNF-α, discovered in 1975, is a pro-inflammatory cytokine produced by immune cells, e.g. monocytes and macrophages (TNF-α), lymphocytes (TNF-β), natural killer cells, Kupffer cells, astrocytes and microglia of the CNS, in response to invasive or injurious insults. TNF-α is an endogenous pyrogen acting on the hypothalamus to induce fever. Unlike IL-1, TNF has no direct effect on stem cell and lymphocyte activation. TNF-α has diverse beneficial biological effects, including:

- Sharing many biological properties with IL-1, e.g. early enhancing host defence against infection, promoting normal tissue remoulding, including wound healing, enhancing chemotaxis of macrophages and neutrophils as well as increasing their phagocytic and cytotoxic activity.
- Stimulant (along with IL-6) for acute-phase response.
- Crucial physiological processes in the CNS such as learning and memory, sleep and water and food intake.

The initial enthusiasm to use TNF-α as a systemic antitumour treatment has waned because of its significant toxicity and lack of therapeutical benefit. However, TNF-α blockers (monoclonal antibodies, infliximab, adalimumab and etanercept) have altered the outcomes for children with inflammatory bowel disease, such as Crohn's disease and ulcerative colitis and rheumatoid arthritis. According to a systematic review of literature [7], the treatment has resulted in a variety of infections in the treated children including bacterial, fungal, viral and TB. Few children died.

3.6 Activated Lymphocytes

The antigen-specific cells of the immune system are lymphocytes, of which there are two main types:

- B cells are responsible for antibody production.
- T cells are the master regulators of the antigen-specific adaptive immune response. They regulate antibody synthesis and mediate cytotoxic function as well as inflammatory response of delayed-type hypersensitivity. T cells are either:
  - Th1 cells which produce INF-γ, IL-2 and TNF-β and promote cell- mediated immunity and phagocytic activity.
  - Th2 cells which produce Il-4, IL-5, IL-6, IL-9 and IL-10. These promote antibody production and play a crucial role in allergic responses (immediate-type hypersensitivity).

IL-1 has an essential role in the activation of lymphocytes. The T-lymphocyte recognizes antigen only after the antigens are processed and presented to them by macrophages; only then do T-lymphocytes become active.

3.6.1 Interferons (INF)

Interferons are known for their ability to "interfere" (hence the name) with viral replication in infected cells. In addition, these cytokines have pyrogenic effect, antitumour and immuno-regulatory functions. There are three types, type 1 (IFN-α, IFN-β), type II (IFN–γ) and type III (IFN-λ). Only type I is used as therapy. Type I and III are produced by a variety of cells (such as leukocytes, dendritic cells, fibroblasts and macrophages), whereas synthesis of type II is restricted to T-lymphocytes.

The functions of the interferons include:

- Key mediators of both innate and adaptive immune responses, stimulating B cells to increase antibody production, and increasing the efficiency of natural killer cells.
- Inhibition of viral replication including HIV-1 replication.

- Interferon-γ release assays (IGRA) serve as a useful blood test in patients with TB. The result cannot distinguish between latent and active TB, and it is not affected by BCG vaccination status.

Type I INF is used as a treatment for a variety of diseases, including:

- Various viral infections, in particular hepatitis B and C.
- Upper respiratory tract infection. INF-α in a nasal spray is capable of significantly reducing symptoms due to rhinoviruses, but not those due to influenza viruses, parainfluenza viruses or coronaviruses.
- Thrombocytosis associated with myeloproliferative disorders.
- Childhood angiomatous disease results from INF-anti-proliferative effect.
- Malignancy including non-Hodgkin's lymphoma, melanoma, multiple myeloma, basal cell carcinoma and chronic myelogenous leukaemia. Hairy cell leukaemia remains one of the most important indications for INF-α therapy, showing a response rate of more than 90%.

Toxic effects of INF preparations are numerous and include fever, chills, arthralgia, myalgia, severe headaches, somnolence and vomiting. Fever may occur in over 50% of the patients who receive INF and may reach 40.0 °C. These side-effects are responsive to paracetamol and prednisolone. Severe side-effects include hepatic and cardiac failure, neuropathy and pancytopenia. INF therapy is contraindicated in pregnancy owing to its anti-proliferative effect.

3.6.2 Interleukin-2 (IL-2)

IL-2 is probably the second most important lymphokine (after INF), which is released by activated T-lymphocytes (in particular $CD4^+$ and $CD8^+$) in response to exogenous pyrogen. It has a crucial effect on the growth and function of T cells, natural killer cells and B cells and for the development of $CD4^+$ T cells. Cases of severe congenital combined immunodeficiency due to a specific defect in the production of IL-2 have been reported. Effects of IL-2 include:

- Stimulating the release of other cytokines, including IL-1, TNF and INF-γ.
- As IL-2 is also produced by mast cells, it controls the severity of chronic allergic dermatitis.
- Antitumour cytotoxicity (e.g. melanoma, including metastatic melanoma, renal cell carcinoma, acute myelogenous leukaemia) as a result of proliferation and activation of activated cytotoxic T lymphocytes.

3.6.3 Interleukin-6 (IL-6)

IL-6 is the third most studied cytokines that has the following characteristics:

- A pro-inflammatory, multifunction cytokine, which is secreted by macrophages and T-lymphocytes to stimulate both B and T cell function and immune response against infection.
- Acting on hepatocytes to induce acute-phase proteins such as CRP, amyloid and haptoglobin.
- An early marker of infection (preceding the increase of CRP), responding within 3–4 h of bacterial infection, e.g. in early-onset neonatal bacterial infection.
- Increased in many diseases, e.g. sepsis, autoimmune diseases (e.g. systemic lupus erythematosus), Kawasaki disease, tumours (e.g. multiple myeloma, renal cell carcinoma), brain disorders (e.g. astrocytoma, glioma, psychosis), and auto-immune and chronic inflammatory diseases.

Table 3.1 Main lymphokines produced by T cells and their main effect/use

Interleukin	Effects
IL-3	Stimulatory effect on haematopoietic cells by controlling the production and function of granulocytes and macrophages. It plays an important role in myelomonocytic leukaemia
IL-4 (&IL-13, 14)	B-cell proliferation, regulating immune response
IL-5	Eosinophil differentiation factor, plays an important role in diseases associated with increased eosinophils, e.g. asthma
IL-7 (IL-27 &IL-36)	Regulates B and T cells, natural killer (NK) cells
IL-8	Pro-inflammatory cytokine, potent neutrophil activator and chemoattractant
IL-9	Stimulation of the growth of mast cells and erythroid, support growth of IL-2 and IL-4 growth of helper T cells
IL-10 (& IL-20)	Inhibition of Th1 cell production, including Th1-dependent IL-2, implicated in inflammatory process of JIA and development of haematopoietic cells. IL-20 helps proliferate keratinocytes
IL-11 (&IL-22)	Production of acute-phase proteins. IL-11 is effective for chemotherapy-induced thrombocytopenia
IL-12	Inhibition of IL-1 synthesis, plays a role in defence against mycobacteria, salmonella, toxoplasmosis, measles HIV virus
IL-13 (&IL-14, 17)	Stimulating activated B cells to proliferate and produce IgM, IgG and IgE. It plays an important role in ulcerative colitis
IL-15	Elevated and responsible for the pathogenesis in coeliac disease and may have a therapeutic value in this disease
IL-16	Chemoattracts immune cells
IL-17 (&IL-23)	Mediating the inflammatory, differentiation of T cells
IL-18	Pro-inflammatory, immuno-regulatory cytokine that induces IFN-γ from T-lymphocyte and natural killer cells; it does not induce fever. It is increased in obese and type 2 diabetes
IL-28 (& IL-29)	Playing a role in host defence against micro-organisms
IL-31 (&IL-32, 33)	Induction of cytokines (TNF, Il-8) and helper T cells

- Is markedly elevated in many rheumatic diseases including systemic juvenile rheumatoid arthritis (JRA) and ankylosing spondylitis. Anti-IL-6 receptor antibody, tocilizumab, has successfully been used to treat patients with JRA.

Other cytokines with their main effects are shown in Table 3.1.

3.6.4 Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

Of the four haematopoietic colony-stimulating factors (erythropoietin, granulocyte-colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF)), GM-CSF appears to have the most potential clinical benefits. It is a pro-inflammatory cytokine, which is produced mainly by lymphocytes, although monocytes, macrophages and mast cells are also capable of producing it. GM-CSF's principal functions and potential therapeutic uses are:

- To stimulate haematopoietic progenitor cells to proliferate and differentiate into granulocytes and macrophages, enhancing phagocytosis and promoting leukocyte chemotaxis and adhesion.
- As a treatment in sepsis-associated immunosuppression.
- It has a central role in the pathogenesis of autoimmune inflammatory diseases such as rheumatoid arthritis, multiple sclerosis and Crohn's disease [8].
- Approved to treat chemotherapy-induced neutropenia, myelodysplasia and aplastic anaemia associated with stem cell transplantation.
- GM-CSF alone or with IL-4 have been used in cancer treatment, including melanoma, renal cell carcinoma and glioma.

The administration of GM-CSF may be associated with the development of fever, which is blocked by non-steroidal anti-inflammatory drugs such as ibuprofen.

3.7 Thermoregulation

Thermoregulation requires intact peripheral mechanisms, which balance heat production and loss, and a functioning hypothalamic thermoregulatory centre regulating these mechanisms. This centre receives thermoreceptors from the temperature of the blood as it passes through the brain (the core temperature) and thermoreceptors from the skin via the dorsal horn of the spinal cord. Both thermoreceptors have cold and warm receptors. The activation of warm receptors causes inhibition of cold receptors. The aim of the thermoregulation is to maintain a relatively constant body temperature at 37 °C.

3.7.1 Heat Production

Heat production occurs by various mechanisms:

- At rest as many organs such as the brain, muscles, viscera, liver, heart, thyroid, pancreas and adrenal glands contribute to heat production at the cellular level involving adenosine triphosphate (ATP).
- The newborn infants have no shivering due to skeletal muscle immaturity, and they rely on non-shivering thermogenesis to produce heat to protect newborns against cold exposure. Brown adipose tissue (BAT), localized mainly in the neck and scapular area, is highly vascularized and contains a large quantity of mitochondria. Fatty acid oxidation in these mitochondria can increase heat production to twofold in response to cold.
- In older children and adults, the first response to cold is behavioural (e.g. curling up, putting more clothes). If this response is insufficient, then the hypothalamic centre is stimulated to conserve heat by vasoconstriction and generate heat by shivering. The predominant stimulus for shivering is the skin rather than the core temperature. The energy produced is released as heat.
- BAT was, until recently, thought to be only functional in neonates and some animals. BAT as a non-shivering thermogenesis has now emerged as a significant component of thermoregulation in elevating body temperature. This process induces and activates mitochondria, which uncouples protein to release chemical energy as heat. The BAT-metabolic thermogenesis is regulated by norepinephrine which is secreted by BAT-sympathetic nerve terminals.

Pathological uncontrollable increase of heat production occurs in malignant hyperthermia (see Chap. 2).

3.7.2 Heat Loss

In response to a rise in body temperature above 37 °C (or ambient temperature above 30–31 °C), heat is lost from the body via the four physical modalities: evaporation, radiation, convection and conduction. When the body core temperature rises (e.g. fever), heat loss through evaporation (causing sweating) becomes the primary mechanism of heat loss. This is associated with cutaneous vasodilatation via acetylcholine-mediated relaxation of the vascular smooth muscles. The following are the mechanisms by which heat loss occurs at rest:

- About one-quarter is lost by evaporation from the skin and lungs, which occurs as water is converted from liquid to gas (58 kcal is lost for every 100 mL of water).
- In general, 60% of the total heat is lost by radiation (transfer of heat from the skin surface to the external surroundings not in contact), through electromagnetic waves.

- Convection (12% of the heat loss) is increasing blood flow to body surfaces to maximize heat loss.
- Conduction (3% of the heat loss) is the heat transfer between two objects in direct contact and at different temperatures. This is the primary mode of heat loss from the core to the surface.

In a warm environment or when core temperature is elevated, the hypothalamic thermoregulatory centre activates efferent fibres of the automatic nervous system to produce vasodilatation. The increased blood flow to the skin causes heat loss from the core through the skin surface to the surroundings in the form of sweating. The hypothalamus stimulates vasodilatation to increase insensible loss (for every 1 °C elevation of body temperature, there is a 10% insensible loss) and activates the sweat glands to increase perspiration production.

Physical factors obviously affect the ability to respond to temperature changes. The greater heat loss in the newborn infant is mainly due to a greater surface area compared to that of an older child. Failure of heat loss occurs in anhidrotic ectodermal dysplasia and during anticholinergic drug overdose.

3.7.3 Temperature Regulation at the CNS Level

In the classical model of pathogenesis, fever induction includes the following stages:

- Pyrogenic endogenous cytokines (e.g. IL-1, TNF, IL-6 and interferons) are released into the bloodstream in response to exogenous pyrogens (e.g. viruses, bacteria, toxins).
- These endogenous pyrogens act on a specific preoptic area of the anterior hypothalamus, which contains clusters of thermo-sensitive neurons localized within the rostral wall of the third ventricle. The site is called organum vasculosum of the lamina terminalis (OVLT), which has emerged as an interface between circulation and brain. The firing rate of these thermo-sensitive neurons changes according to the temperature of the area's blood supply and the input from the skin and muscular thermoreceptors. Warm-sensitive neurons have firing rates that increase with warming and decrease with cooling, whereas the firing rates of cold-sensitive neurons increase with cooling or decrease with warming.
- Endogenous pyrogens enter the perivascular space of the OVLT through the fenestrated capillary wall to stimulate cells to produce prostaglandin E2 (PGE2), which diffuses into the adjacent preoptic area to upturn the temperature set point and cause fever.
- Another structure termed circumventricular organs (CVOs), which are situated in the anterior wall of the third ventricle. These organs are characterized by extensive vasculature and lack of blood-brain barrier allowing direct exchange between blood and nervous tissue. When circulating pyrogenic cytokines are detected by the CVOS, PGE2 is induced.

- The ultimate result of these complex mechanisms is an upward shift of the thermostatic set point to a febrile level that signals efferent nerves, especially sympathetic fibres innervating peripheral blood vessels, to initiate heat conservation (vasoconstriction) and heat production (shivering). This is aided by behavioural means aimed also to increase body temperature, such as seeking a warmer environment or covering up with a blanket. The resulting temperature increase continues until body temperature approximates to the temperature of the elevated set point.
- The raised set point is reset back to normal if the concentration of the cytokines falls or if antipyretics are administered that block prostaglandin synthesis. The normalization of temperature is initiated by vasodilatation and sweating through increased skin blood flow controlled by sympathetic fibres. Prostaglandin E2 has been found to exert a negative feedback on the release of the cytokines, thus terminating the mechanisms that initially induced the fever

The peptide angiotensin 11 has been shown to lower body temperature at the final step of fever. It is involved in maintaining body temperature at the set point. In addition, arginine vasopressin (AVP) acts within the CNS to reduce pyrogens-induced fevers. A decrease in hypothalamic calcium concentration or an increase in sodium concentration elevates body temperature.

3.8 Summary of Fever Induction

The generation of fever involves the following steps:

- Numerous substances from outside the body, exogenous pyrogens, initiate the fever cycle. Endotoxin of Gram-negative bacteria, with their pyrogenic component lipopolysaccharide, is the most potent exogenous pyrogen. Fever is also a common finding in children without obvious evidence of infection, for example hypersensitivity reaction, autoimmune diseases and malignancy.
- Exogenous pyrogens initiate fever by inducing host cells (primarily macrophages) to produce and release endogenous pyrogens such as interleukin-1, which has multiple biological functions essential for the immune response.
- Endogenous pyrogens are transmitted to the hypothalamic thermoregulatory centre, specifically organum vasculosum of the lamina terminalis (OVLT), where they induce synthesis of prostaglandins, of which PGE2 is the most important. These raise the thermostatic set point to initiate the febrile response.
- The hypothalamic thermoregulatory centre accomplishes heat production by inducing shivering and heat conservation through vasoconstriction. At an established degree, fever is regulated (even at a temperature of over 41.0 °C), and heat production approximates loss, as in health, though at a higher level of the set point. Therefore fever does not climb up relentlessly.
- In addition to the function as an endogenous pyrogen, IL-1 activates T-lymphocytes to produce various factors, such as INF and IL-2, which are vital

for immune response. The production of fever simultaneously with lymphocyte activation constitutes the clearest and strongest evidence in favour of the protective role of fever.

- The induction of fever results in inhibition of bacterial growth, increased bactericidal of neutrophils, production of acute-phase protein synthesis and other physiological changes such as anorexia and somnolence. These changes suggest that fever has an adaptive role in the host's survival during infection (see Chap. 9 for detail).

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Measurement of Body Temperature

4

Core Messages

- Body temperature measurement is mainly indicated to confirm the presence or absence of fever.
- There remains considerable controversy among professionals regarding the most appropriate thermometer and the best anatomical site for temperature measurement.
- Medical staff should be aware of those clinical conditions, which require accurate temperature measurement (e.g. febrile neutropenia) and those where screening for fever may be adequate (maternal intrapartum).
- Core temperature is generally defined as the temperature measured within the pulmonary area.
- In an environment where ambient temperatures are stable (e.g. neonatal units), temperature recorded from the axilla is nearly as accurate as that recorded from the rectal site.
- Although rectal temperature is a satisfactory reference standard for core temperature, it is reliable only if the body is in thermal balance and reacts slowly to changes in temperature.
- There is evidence to suggest that tympanic temperature accurately reflects pulmonary artery temperature even when body temperature is changing rapidly.

4.1 Introduction

Body temperature measurement is most commonly performed to confirm the presence or absence of fever. Many decisions concerning the investigation and treatment of children are based on the results of temperature measurement alone. An incorrect temperature measurement could result in the delayed detection of a serious illness or alternatively an unnecessary septic workout.

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_4

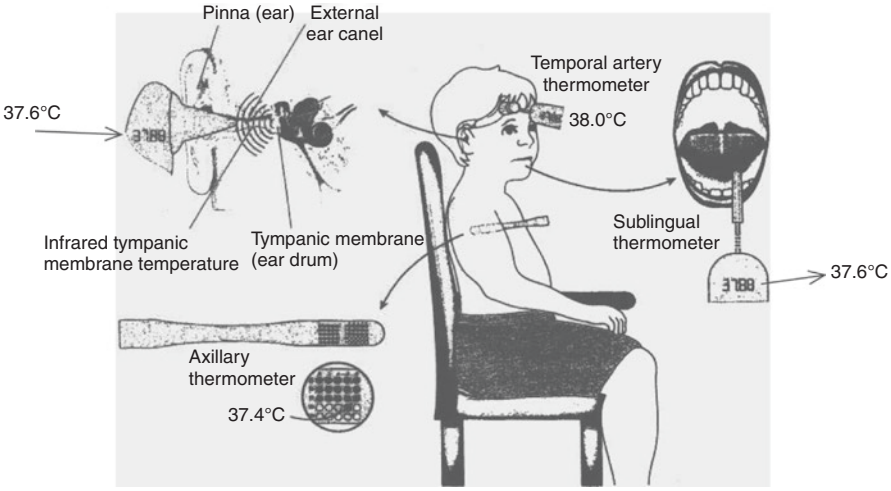

Fig. 4.1 Anatomical site of temperature readings showing febrile recordings from different sites

Despite the plethora of instruments that have become available in the last 40 years, there remains considerable controversy as to the most appropriate thermometer and the best anatomical site (Fig. 4.1).

This chapter discusses different sites for temperature measurement, includes advantages and disadvantages of currently available techniques and describes how the instruments work together with comment on their accuracy. It also makes recommendations based on available evidence and personal experience.

4.2 History of the Thermometer

The history of the thermometer began with the invention of the thermoscope by Heron of Alexandria century BC [1]. This instrument was a glass vessel with a water column that was displaced in proportion to the amount of heat applied. The instrument was reinvented by Galileo Galilei (1564–1642) at the end of the sixteenth century. Temperature was recorded by transmission of air through a tube from the mouth to a container of water.

In the eighteenth century, thermometry made significant advances (Fig. 4.2). Gabriel Fahrenheit, a Polish physicist, invented the mercury thermometer in 1714, using salt, water and ice. The freezing point of the system was 32 °F and the boiling point 212 °F. Anders Celsius of Sweden established the centigrade scale in 1742. A comparison between Celsius and Fahrenheit scales is shown in Fig. 4.3.

Carl Wunderlich, a professor of medicine in Leipzig, began in 1851 to collect data on one million measurements of body temperature. He used a foot-long thermometer, which had to be read in situ (under the axilla) and required 15–20 min to equilibrate. He noted that children react with higher temperature in response to

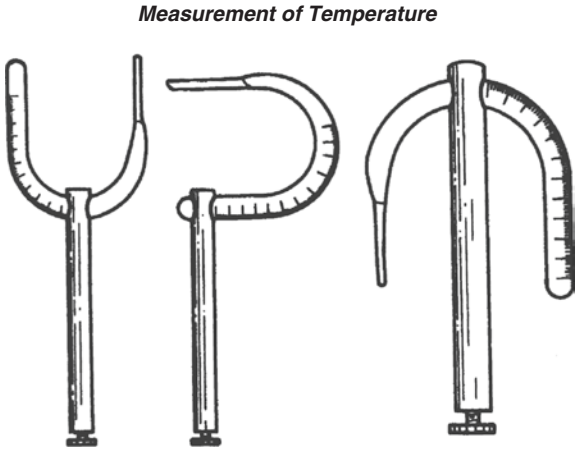

Fig. 4.2 The first thermometer was designed for insertion under the patient's tongue (From *Br Med J* 1912; 1:1137)

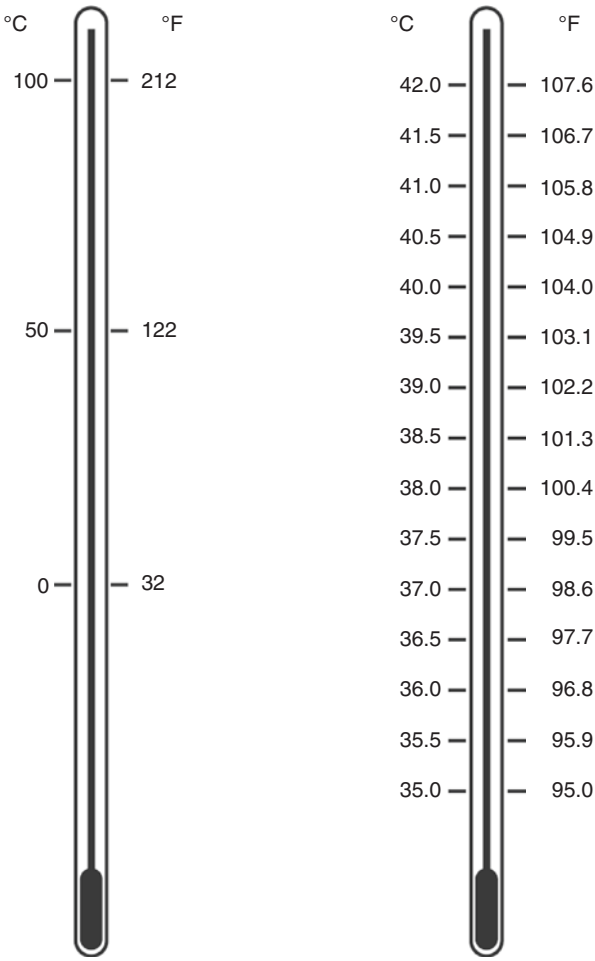

Fig. 4.3 A comparison of Celsius and Fahrenheit scales. NB:
°C = (°F − 32) × 5/9;
°F = (°C × 9/5) + 32

infection as compared to adults. His work greatly influenced medical practice, ushering in the routine use of the thermometer.

In 1867Allbutt of Leeds made a 6-in. glass thermometer that recorded temperature in 5 min. Two physicians in the USA, William Draper and Edouard Seguin, promoted the use of thermometer and designed the first bedside chart in the 1880s [2]. Since then temperature measurement belongs to the three vital signs, along with pulse and respiration.

4.3 Core Temperature

There is no uniform core temperature throughout the body. The hypothalamus is the site where body temperature is set and where the highest body temperature is recorded. Since the hypothalamus is inaccessible, core temperature is generally defined as the temperature measured within the pulmonary artery. Other standard core temperature monitoring sites (distal oesophagus, bladder and nasopharynx) are accurate within 0.1–0.2 °C of core temperature [3] and are useful surrogates for deep body temperature. During anaesthesia, bladder temperatures correlated well with oesophageal and pulmonary artery temperature. This correlation was maintained during rapid body rewarming, with an insignificant bias of 0.04 °C [4].

Since these deep-tissue measurement sites are clinically inaccessible, physicians have utilised the rectum as a practical site to monitor body temperature in the belief that this site most accurately reflects core temperature.

Any temperature measurement should take into consideration the normal diurnal temperature fluctuation of up to 1 °C (1.8 °F), with a peak at 5–7 p.m. and a minimum between 2 and 6 a.m. This diurnal variation, which begins to develop at the age of 4 months, can be so wide that a “normal” temperature in an individual is impossible to identify, but rather a range and a mean of body temperatures.

4.4 The Value of Temperature Measurement: Accurate or Screening

The presence of fever and its severity can be vital indicators of conditions that need careful investigation and prompt treatment. The accuracy of body temperature measurement is particularly important in the following situations:

- Fever in neutropenic children with cancer is frequently caused by bacterial infection, which is among the leading causes of death in these patients. Admission to hospital and administration of intravenous antibiotics are often based on the presence of fever alone. Children with sickle-cell anaemia are particularly susceptible to overwhelming bacterial infections, and detection of fever commonly has similar implications as with neutropenic febrile children.

- As epilepsy is defined by recurrent non-febrile seizures, the only outward difference between a febrile and an epileptic seizure at the onset of the seizure is the presence of fever in the febrile seizure (FS). Since the investigation, treatment and the prognosis of children with FS and epilepsy are different, measurement of body temperature at the onset of a seizure is of paramount importance.
- Critically ill children such as those in a paediatric intensive-care unit.
- Accurate temperature measurement is critical in infants younger than 3 months of age. In this age group, a temperature over 38 °C has been associated with serious bacterial infection in 3–15% of patients [5].
- Maternal intrapartum fever is a risk factor for neonatal sepsis, and therefore, it is essential to monitor maternal temperature during labour.
- During anaesthesia continuous body temperature monitoring is essential because of the common risk of perioperative hypothermia caused by inhibition of thermoregulation by the anaesthesia and the patient's exposure to a cool environment. Monitoring is also required to detect possible onset of malignant hyperthermia.
- A body temperature of >42 °C suggests hyperthermia. Whereas fever (interleukin-1 mediated elevation of the thermoregulatory set-point of the hypothalamic centre) does not climb relentlessly beyond 42 °C, hyperthermia may do so via peripheral heat production and loss.
- Drowning and near drowning can cause hypothermia. Cardiac arrhythmia and death may occur when the body temperature is <30 °C.
- Hypothermia (body temperature < 35 °C) is recognised as a significant contributor to neonatal mortality in developing countries, hence the importance of checking body temperature in neonates. Low body temperature of neonates on admission to neonatal ICU is associated with increased mortality [6].
- A difference between the core (central) and peripheral (skin) temperature of >4.0 °C is valuable in the diagnosis, management and prognosis of shock and correlates with clinical criteria of brain death in children [7].

The above situations requiring accurate temperature measurement are uncommon in clinical practice. It is often not possible or considered necessary to have accurate temperature measurements as paediatricians are usually only interested in the presence or absence of fever and its approximate degrees. For paediatricians small differences of body temperatures are less important parameter than how well or ill the child looks. In a busy emergency setting, GP practices, paediatric ward rounds or at-home screening for fever is what is often required.

4.5 Measurement of Body Temperature

Body temperature measurements vary depending on the temperature site. Table 4.1 shows the ranges and means of temperatures at various sites [8].

Table 4.1 Normal temperatures at different sites (revised from Ref. [8])

Body site	Type of thermometer	Normal range	Mean (°C)	Fever (°C)
Axilla	Electronic, Tempa-Dot	34.7–37.3	36.4	37.4
Sublingual	Electronic, Tempa-Dot	35.5–37.5	36.6	37.6
Rectal	Electronic, Tempa-Dot	36.6–37.9	37.0	38.0
Ear	Infrared emission	35.7–37.5	36.6	37.6

Where relevant the medical history should include questions as to how the temperature was taken at home and with which particular device. The recordings of temperature by the parents should be noted.

4.5.1 Tactile Assessment

Simple palpation has been used for thousands of years to assess body temperature. Even nowadays with the availability of electronic and infrared thermometers, tactile assessment is still the most widely used method of evaluating body temperature. Some physicians advocate its use on the grounds that the thermometer holds no advantage over tactile methods when evaluating children with fever.

This method of palpation is far from accurate mainly because of lowering of skin temperature during the early phase of fever due to vasoconstriction. When medical staff carried out palpation as a screening method, the presence of fever was accurately predicted in only 42% of cases [9]. Mothers, on the other hand, made the correct prediction in over 80% of cases [10]. Thus palpation by mothers was more sensitive than by medical personnel. The unreliability of touch to estimate body temperature was confirmed by an African study [11] that investigated the ability of medical students and mothers to use touch to determine whether 1090 children had fever. It was concluded that touch overestimated the incidence of fever and that a child who feels hot needs to have a temperature taken before fever is confirmed.

4.5.2 Instrumentation

An ideal thermometer should:

- Accurately reflect core body temperature in all age groups.
- Be convenient, easy and comfortable to use by patient and practitioner, without causing embarrassment.
- Give rapid results.
- Not result in cross infection.
- Not be influenced by ambient temperature.
- Be safe.
- Be cost-effective.
- Possess high reproducibility, i.e. how well several measurements of the same device agree with one another.

The ideal thermometer should include a combination of all these criteria or at least most of them. Despite advanced techniques, none of the temperature measurement devices meet all the above criteria. In practice, electronic and tympanic thermometers appear to be the closest to an ideal thermometer to screen for fever.

Electronic thermometers were introduced in the 1970s and are being increasingly used to measure rectal, axillary and oral temperatures. The technique is fast and safe, does not require the removal of clothing (when used orally) and is not influenced by environmental temperature (when used orally or rectally). Duration of temperature measurement takes up to 30 s. Although good accuracy is obtained when the device is used rectally or orally, inaccurate results are recorded when the electronic thermometer is used in the axilla (see later). Significant progress was achieved subsequently with the introduction of non-contact infrared ear thermometers. They measure the body temperature by detecting the thermal infrared energy that is naturally emitted from the tympanic membrane. Measurements are quick and convenient, particularly when used in a busy emergency setting where screening for fever is routine practice [12]. Chemical thermometers are used, including a single-use disposable Tempa-Dot that can measure oral temperature in 1 min and axillary temperature in 3 min.

4.6 Site of Temperature Measurement

Each site where body temperature is measured has numerous advantages and disadvantages as summarised in Table 4.2.

4.6.1 Axilla (AT)

This site has several advantages:

- It is safe, easily accessible and reasonably comfortable.
- In neonatal units, where ambient temperatures are stable, axillary temperature measurements were found to be as accurate as rectal measurements [13]. However, these studies involved afebrile neonates in a nursery where environmental temperatures and humidity were maintained at optimal levels.

There are several disadvantages:

- It requires supervision; otherwise, displacement may occur. AT measurement takes longer than rectal or sublingual measurement (takes 40–80 s with electronic thermometer) which is not cost-effective with regard to nursing time.
- Temperature measurement at this site is notoriously inaccurate. At the onset of fever when peripheral vasoconstriction is intense, the skin temperature may cool as the core temperature rises. In addition, the effects of sweating and evaporation cause the axillary temperature to be lower than the core body temperature.

Table 4.2 Summary of advantages and disadvantages of each thermometry

Measurement	Advantages	Disadvantages
Axillary (AT) measurement	Safe, easily accessible and comfortable. In neonatal units, AT measurements are as accurate as rectal measurements	Requires supervision, otherwise displacement may occur. Measurement takes longer than on other sites, e.g. 30–40s by electronic thermometer which is not cost-effective with regard to nursing time. Measurement is inaccurate. The effects of sweating and evaporation cause more inaccuracy
Skin, e.g. temporal artery	Convenient; easy to use, with safety; comfortable; and rapid results	Measurement is inaccurate and frequently records falsely normal temperature despite elevated core body temperature
Oral measurement (OT)	Not affected by ambient temperature. It is also easily accessible and accurate. Accurate with excellent correlation with pulmonary arterial temperature	Requires co-operation, therefore not suitable in children <5 years of age, with developmental delay, or in comatose or intubated patients. Hot baths, exercise, hot and cold drinks and mouth breathing influence the results. Accuracy relies on sealed mouth. The site should not be used in case of tachypnoea which causes cooling of the mouth. There is variation in temperature recorded depending on where the bulb is placed.
Rectal measurement (RT)	Widely viewed as the gold standard concerning accuracy The site is not influenced by ambient temperature and its use is not limited by age	Is frightening for small children and may be psychologically harmful for older children. Can cause discomfort and is painful for patients with perirectal infection or irritation. Site is not hygienic and presents an infectious hazard. The transmission of HIV through this route is a concern. RT should not be used in patients with neutropenia. Oncology centres routinely avoid this site. Measurement is time-consuming, requires privacy and has been reported to cause rectal perforation. RT varies depending on how deeply the thermometer is inserted into the rectum, local blood flow and the presence of stool and diarrhoea. It lags significantly behind a rapidly rising or falling core temperature. Therefore, RT should not be used for patient monitoring during anaesthesia
Tympanic measurement (TT)	Fast and easy to use without risk of cross infection, uninfluenced by environmental temperature, saves nursing time and is therefore cost-effective	The main reason why the TT has yet to be regarded as the gold standard for body temperature measurement is that some studies have reported inaccuracies, mainly in children younger than 2–3 years of age

Therefore, correlation between axillary temperature and core temperature is poor. The sensitivity of axillary temperature to detect fever has been reported to be only 27.8–33% [14, 15]. Rectal and axillary temperatures differed by up to 3 °C, and axillary temperature was occasionally very low.

In summary, the evidence suggests that AT with its low sensitivity should not be relied upon to detect fever in children and should be avoided if possible. AT is not a recommended method to screen for fever and certainly not where accurate temperature measurement is required (except on a neonatal unit). AT is recommended by the American Academy of Pediatrics to screen for fever in neonates because of the risk of rectal perforation with a rectal thermometer [15].

4.6.2 Skin

One device for temperature measurement is the temporal artery thermometer (TAT). It uses an infrared thermometer that scans the surface from the forehead to behind the ear with the highest temperature being over the temporal artery. Although this device was found to be easy to use (a gentle stroke across the forehead and then placement behind the earlobe), its accuracy remains a problem, with only 66% sensitivity to detect fever [16]. Comparison of TAT with pulmonary artery temperature measurements showed only modest agreement between the two sites [17]. A more recent systematic review and meta-analysis concluded that TAT is not sufficiently accurate to reflect one of the reference methods such as rectal, bladder or invasive temperature measurement methods [18].

Several companies have introduced re-usable or single-use disposable plastic-encased thermophototropic liquid crystals for forehead application. The substance changes colour as the temperature rises. They are most suitable for home use. Their advantages over conventional thermometers are obvious: convenient instruction, ease of use, safety, comfortable and rapid results. Measurement by these devices is inaccurate and frequently records a normal temperature despite presence of fever.

4.6.3 Sublingual (Oral Temperature = OT)

When measuring OT:

- Place the bulb (or the tip of Tempa-Dot) of the thermometer under the tongue at the mouth floor. As there is variation of temperature recorded from this site (Fig. 4.4), the bulb should be at the area of maximal temperature.
- Instruct the child to keep the mouth closed and to breathe through the nose.
- Hold the thermometer for about 40 sec (using electronic thermometer). Usually the thermometer will make a beeping noise signalling the end of reading.

This site is often used in children over 5 years of age. Its advantages:

- Less affected by ambient temperature and is more accurate than the axillary site.
- It is also easily accessible. The mean oral temperature measured by electronic thermometer or a chemical indicator is about 0.4 °C below simultaneously measured mean pulmonary arterial temperature.

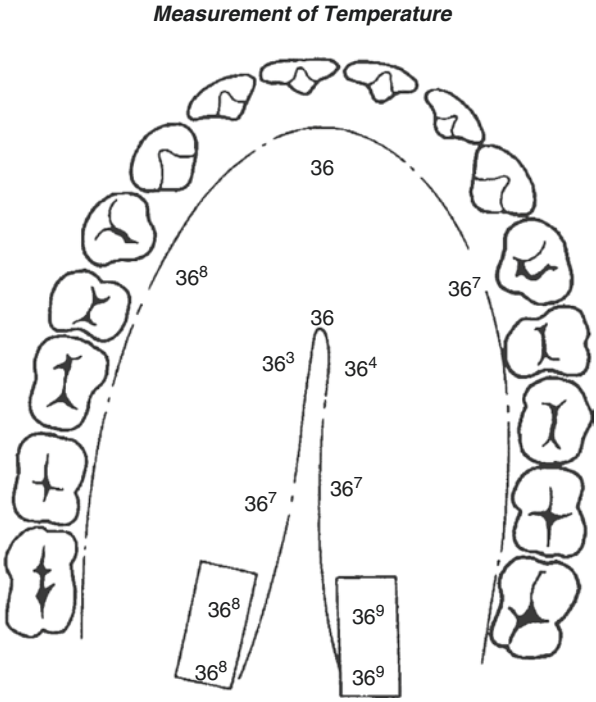

Fig. 4.4 Diagram of the floor of the mouth showing variations in temperature. The thermometer should be placed where the maximal temperature may be obtained

There are several disadvantages:

- The measurement requires the co-operation of the child. It is therefore not suitable for use in children less than 5 years of age, in some children with developmental delay or in comatose or intubated patients.
- Hot baths, exercise, hot and cold drinks and mouth breathing all influence the results. The site should not be used in the presence of tachypnoea which causes increased evaporative cooling of the oral cavity, and therefore results are misleadingly low.
- Oral laceration and mouth-to-mouth cross infection may occur.

4.6.4 Rectum (Rectal Temperature, RT)

The rectal route remained unchallenged for a century as the preferred site for the measurement of core temperature. In the 1960s, it began to be replaced by axillary and sublingual measurement. The method of measurement is as follows:

- Apply a sterile lubricant jelly on the bulb tip or, in case of electronic thermometer, on the disposable probe.
- Following proper positioning of the child, the buttocks are separated, and the thermometer is inserted without force a distance of 5 cm into the rectum.
- The duration of measurement is 40 s.

RT has the following advantages:

- It has been widely viewed as the gold standard for routine measurement of body temperature. RT measurement with a low reading thermometer is considered best clinical practice when dealing with potential hypothermia, e.g. near drowning and neonatal cold injury.
- It is not influenced by ambient temperature and its use is not limited by age.

There are numerous practical disadvantages to its routine use:

- It is frightening for small children and may be psychologically harmful for older children.
- The procedure may cause discomfort and is painful for patients with perirectal infection or irritation.
- The site is not hygienic and presents an infectious hazard. An outbreak of *Salmonella* cross infection has been reported in newborn infants [19]. The transmission of human immunodeficiency virus through this route remains a concern. For the same reason, this site should not be used in patients with neutropenia or other immunologic impairments. Oncology centres routinely avoid rectal temperature measurement.
- The measurement is time-consuming, requires privacy and has been reported to cause rectal perforation [20], calculated to occur in less than one in two million measurements [21].
- Rectal temperature varies depending on how deeply the thermometer is inserted into the rectum, local blood flow and the presence of stool and diarrhoea.
- RT may lag significantly behind a rapidly rising or falling core temperature because of relatively poor blood flow to the rectum. Even in a stable state, rectal temperature has been shown to differ significantly from pulmonary artery temperature. When the body temperature is changing, the temperature in the rectum takes twice as long to change as that in the pulmonary artery. Therefore, rectal temperatures should not be used for patient monitoring during anaesthesia. For the same reason, a misleadingly high temperature may be recorded after defervescence following antipyretic administration. In the presence of shock, perfusion of the bowel, including the rectum, may be markedly impaired, and rectal temperature will lag significantly behind a rapidly rising or falling core temperature.

In summary, it is questionable whether RT should be regarded as the gold standard for core temperature measurement.

4.6.5 Tympanic Thermometry (Tympanic Temperature, TT)

The method of temperature measurement is as follows:

- A tympanic infrared thermometer is used with a disposable probe.
- The pinna is first gently retracted, and the thermometer is inserted a few millimetres inside the left external ear canal until a beep indicates completion of the measurement.

- The measurement is repeated twice and the highest reading is recorded.

The basic principle of infrared ear thermometer (IRET) is this:

- Under normal conditions, 60% of total heat loss occurs via radiation in the form of infrared heat rays, a form of electromagnetic energy. This heat loss is increased during fever.
- As the tympanic membrane receives its blood supply from the carotid artery, its temperature may reflect that of blood flowing into the hypothalamus, thereby correlating closely with core body temperature.
- The thermometer measures the infrared rays emitted by the tympanic membrane.

There are many potential benefits to infrared ear thermometry:

- The technique is fast and easy to use without risk of cross infection and is not influenced by environmental temperature. Parents and nurses rated tympanic thermometers as being more favourable in terms of ease, speed, cleanliness and safety than oral or rectal thermometers. A reduction in the numbers involved in a nosocomial outbreak of vancomycin-resistant enterococcus and clostridium difficile infection has been achieved by replacing rectal and oral thermometers with tympanic membrane thermometers [22].
- TT is a practical method to measure body temperature in children in an emergency setting. It is more accurate than measurement taken by electronic axillary thermometer. It saves nursing time and is therefore cost-effective since the measurement is much faster than axillary measurements [23].

In recent years, tympanic thermometers have become very popular both with health professionals and at home. In the USA 65% of paediatricians and 64% of family practice physicians regularly use infrared ear-based thermometer, IRET [24]. As accuracy of body temperature measurement is particularly important in neutropenic children with cancer, IRET is suitable in providing high accuracy [25]. This group needs particular accuracy with regard to temperature measurement since intravenous antibiotics may be administered solely on the basis of a raised temperature.

The main reason why the tympanic thermometer has yet to be regarded as the gold standard for body temperature measurement is that some studies have reported inaccuracies, mainly in children younger than 3 years of age. These studies compared ear with rectal or oral temperature as the reference standard. There is no evidence that either of these sites represents the core body temperature.

It has been known for about 40 years that the tympanic membrane can provide accurate measurement of core body temperature. Recent studies (see next) have shown that tympanic temperature accurately reflects pulmonary artery temperature, even when body temperature is changing rapidly. For this reason infrared temperature has been found to be a reliable way of monitoring body temperature during anaesthesia when the patient might be at risk of developing malignant hyperthermia or hypothermia.

4.7 National Institute of Health and Care Excellence (NICE) Guideline [26]

In infants under the age of 4 weeks, body temperature should be measured with an electronic thermometer in the axilla. In children aged 4 weeks to 5 years, healthcare professionals should measure body temperature by one of the following methods:

- Electronic thermometer in the axilla
- Chemical dot thermometer in the axilla
- Infrared tympanic thermometer in the ear

Forehead chemical thermometers are unreliable and should not be used by healthcare professionals.

4.8 Evidence-Based Temperature Measurement

A search of all evidence-based medicine (EBM) reviews and systematic review studies (Cochrane DSR, ACP Journal Club, DARE and CCTR for systematic reviews 1991–2003: 39 articles; CINAHL 1982–2003: 83 articles; and PubMed 1980–2003: 582 articles on temperature measurements) was made for measurement of body temperature [27]. There is universal agreement that AT is inaccurate and insensitive when compared to any core temperature (i.e. from the pulmonary artery, oesophagus or bladder) with the exception of afebrile neonates in neonatal units where the environmental temperature and humidity were maintained at optimum levels for neonates. A systematic review of 20 studies comprising 3201 children confirmed the inaccuracy of AT [28]. A systematic review of 44 studies comprising 5935 patients comparing TT and RT concluded that infrared ear-based temperature is not a good approximation of rectal temperature although the mean differences between rectal and ear temperature measurements were small [29]. A third systematic review of the literature to determine optimal methods of temperature measurement in children concluded that RT is the optimal method until the child is old enough to co-operate with OT measurement [30]. Another review and meta-analysis comprising 75 studies (8682 patients) concluded that all peripheral temperature measurements (TT, OT, skin and AT) should not be used when accurate measurement will influence clinical decisions [31].

The question remains: is the RT the satisfactory reference standard for core temperature? RT is reliable only if the body is in thermal balance and reacts slowly to changes in temperature. As there is a consensus that the temperature of the pulmonary artery, oesophagus and bladder is representative of core temperature, a search of PubMed for all studies comparing TT with these sites was made, and the result is shown in Table 4.3. The majority of these studies (which included febrile patients or patients who underwent cooling and rewarming during cardiac surgery) show TT to be accurate, including the three studies with children. Accuracy was defined as an ear-based thermometer measurement within 0.1–0.6 °C or a high correlation ($r > 0.80$ of PA) [32, 33].

Table 4.3 Outcome of comparison studies between core temperature (PA = pulmonary artery, O = oesophageal, B = bladder temperatures) as a reference standard and ear-based temperature

No of Ref	No of patients	Core site	Other sites	Main outcome/conclusion
Group A				
40	15 C	PA/O	AT/RT	TT more accurate than RT
41	18 A	PA/O	AT/RT	TT 2nd to 0, TT is the reading of choice
42	27 A	PA	RT	TT tracks PA closely
43	30 C	B	AT/RT	TT correlated relatively well with PA
44	38 A	PA/B	AT/OT	TT is relatively close estimate of PA
45	50 A	B	AT/OT	TT has good correlation with B
46	96 A	O	AT	No difference between TT and O
47	51 A	PA	RT	Both TT and RT are accurate
48	128 A	PA	AT/RT	PA and TT were highly correlated
49	13 A	PA	AT/OT/ RT	If RT contraindicated, OT or TT is acceptable
50	9 A	PA	RT	PA and TT: not significantly different
51	20 C	PA	AT/RT	TT may be used instead of PA
52	32 A	PA	AT/RT	TT reflects PA > accurately than RT and AT
Group B				
53	15 A	PA/B	None	TT appears to give high readings
54	60 A	PA	AT	TT is clinically not reliable
55	102 A	PA	OT	OT is most accurate
56	72 A	PA	OT	OT is more accurate
57	32 A	PA	AT/OT	TT is not ideal
58	25 A	PA/B/O	AT/OT/FS	No non-invasive method is valid

Group A = studies found TT to be accurate/or close to accurate
Group B = studies found TT to be less or not accurate
CT core temperature, *TT* tympanic, *OT* oral, *AT* axillary, *FS* forehead skin temperature

4.9 Summary

Disagreement still exists as to the best anatomical site for temperature measurement. However, there is a consensus that:

- Axillary temperature measurement does not provide accurate measurements except in environments where the temperature is stable such as neonatal units and where the neonates are afebrile.
- Rectal temperature measurement is not favoured by parents and nurses and many hospitals have abandoned this method. The reluctance to take RT is cultural and is particularly widespread in Britain, Australia and New Zealand. In all other countries, hospitals and mothers usually take their babies' temperature rectally. RT is contraindicated in neutropenic oncology patients. This group needs particular accuracy with regard to temperature measurement since intravenous antibiotics may be administered solely on the basis of a raised temperature.

- The oral temperature measurement is not used in children less than 5 years of age and this is the group with the highest incidence of fever.
- The tympanic site using infrared thermometer appears to be the most suitable for use in hospitals, in GP surgeries and at home. Evidence confirming the accuracy of the infrared ear-based thermometer is incomplete; this is probably because ear measurements were compared with rectal or oral measurements. Neither site represents the true core temperature.

There remain a few unresolved issues. Error can potentially occur with tympanic thermometer if the probe is not directed towards the tympanic membrane. It is anticipated that in the future, tympanic thermometry will include a visible signal (e.g. a green light) once the probe of the tympanic thermometer is correctly directed towards the tympanic membrane. There are only a few small trials comparing tympanic temperature with core temperature in neonates. Efforts should continue to find a suitable IRET for this age group. Once these concerns are taken into consideration, the tympanic site is likely to become the gold standard for all children.

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Fever in Common Infectious Diseases

5

Core Messages

- Infection of the respiratory tract is the most common reason for seeking medical advice and hospital admission in children. A viral upper respiratory tract infection (URTI) is the most common infection of the respiratory tract.
- In developing countries, acute respiratory infection remains a leading cause of childhood mortality, causing an estimated 1.5–2 million deaths annually in children younger than 5 years of age.
- In developed countries viruses are responsible for most upper and lower respiratory tract infections, including pharyngitis and pneumonia.
- Although the degree of fever cannot differentiate between viral and bacterial diseases, high fever is associated with a greater incidence of serious bacterial diseases such as pneumonia or meningitis.
- Worldwide, diarrhoeal disease is the leading cause of childhood deaths under 5 years of age.
- If the fever does not have an evident source, urinary tract infection should be considered, particularly if the fever is greater than 39.0 °C and longer than 24–48 h.
- Widespread vaccinations against bacteria causing meningitis, such as Hib, and vaccines against meningococci and pneumococci have dramatically reduced the incidence of meningitis.
- A child with fever and non-blanching rash should be promptly evaluated to exclude meningococcal diseases.
- Young children with malaria may present with irregular fever and not with typical paroxysms of fever, occurring particularly in early falciparum infection or as a consequence of previous chemoprophylaxis, which modifies the typical pattern of fever.

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_5

5.1 Acute Upper Airway Infections

An upper airway infection is the most common infection in children, accounting for half to two-thirds of all childhood infections. This term includes viral upper respiratory tract infection, tonsillopharyngitis, otitis media and epiglottic diseases.

5.1.1 Viral Upper Respiratory Tract Infection (URTI)

An URTI (known as the common cold) is an exceedingly frequent infection characterized by nasal obstruction and discharge, cough, sore throat, with or without fever, decreased appetite and restless sleep. The initial watery nasal discharge is followed rapidly by mucopurulent nasal discharge, which does not necessarily indicate bacterial infection. It has been estimated that young children may have as many as 12 respiratory infections per year if he or she attends nursery, 9 infections per year if a sibling attends school, and 6 or 7 per year if the child and a sibling are not at school.

Well over 100 viruses are known to cause respiratory tract infection, such as rhinoviruses (most common virus), influenza A and B, coronaviruses, parainfluenza 1, 2 and 3, adenoviruses and respiratory syncytial viruses (RSV). Infection may result from inhalation, self-inoculation to the nasal mucosa or airborne inoculation to the conjunctival mucosa. Children tend to have greater concentrations of viruses in the nasal secretion and shed them for longer periods of time than adults. Viraemia is less common and the infection is usually restricted to the mucosa, including the sinuses and Eustachian tube. Viral URTI may be complicated by secondary bacterial infections including acute otitis media and sinusitis. Acute idiopathic pericarditis (presents as chest pain and pericardial rubs on auscultation) is a rare complication that is usually preceded by a recent URTI. Infection with influenza viruses occurs during annual winter epidemics and is usually a self-limited illness. However, it can cause severe illness and deaths, particularly in children with high-risk medical conditions and neurological, genetic and chromosomal disorders.

Inflammatory cytokines such as interferons (INF) IL-1, IL-6 and IL-4 and TNF are involved in the inflammatory changes of URTI. Symptoms occur as a result of the effects of these cytokines rather than the virus itself. Injection of IFN-alpha to volunteers causes fever, malaise, headache and myalgia.

Fever in URTI:

- Fever in URTI is present in about 50% of older children and in 90% of infants and young children.
- Although high degrees of fever occur in viral and bacterial infections, high fever may predict serious bacterial infection.
- High fever (>39.5 °C) is often associated with influenza A virus infections, occurring in more than 50% of children. Adenovirus infection causes fever exceeding 40 °C in about 20%, while fever in rhinovirus infection is usually absent or mild.

- Fever associated with respiratory virus infection may last for 3–5 days. A prolonged duration of fever is however common. Fever lasting 5 days or longer occurs in over 30% of children with this infection. The longest duration of fever (>7 days) may occur in association with adenovirus. The shortest duration of fever is associated with parainfluenza 2 viruses.
- Fever enhances body's immunity against infection, and antipyretics may negatively affect the outcome of the illness. Therefore antipyretics should only be given for symptomatic children, such as discomfort, and not for fever per se.
- Recurrent URTIs are mostly caused by viruses obtained from nursery attendance.

The knowledge that viruses can cause high and/or prolonged fever allows the physician to withhold antibiotic treatment and extensive investigations in children with prolonged fever who appear generally well, and common serious infections (e.g. UTI) have been excluded.

In the differential diagnosis, conditions mimicking URTI include:

- Allergic rhinitis. There is often a family history of atopy, a history of nasal symptoms with exposure to potential allergens and the symptoms tend to be persistent. Nasal eosinophilia, increased serum IgE level and the finding of possible allergens in skin prick tests or blood may confirm the diagnosis.
- Streptococcal throat infection. Children are usually >5 years. Fever tends to be higher than that in URTI. Nasal symptoms are usually absent.
- Sinusitis should be considered in a child with purulent nasal discharge and fever (usual range 38–39 °C), localized pain and tenderness, mucosal erythema and headache, whereas a higher fever with chills may suggest an extension of the infection beyond the sinuses.

Management of a febrile child with an URTI:

- No specific therapy is indicated for the majority of children, and the aim of treatment is to make the child comfortable.
- The most commonly prescribed analgesic-antipyretic is paracetamol (81%) followed by combination of ibuprofen and paracetamol [1], and URTIs are the most common reason for the administration of antipyretics.
- Symptomatic relief is obtained with antipyretics for pain, excessive myalgia and malaise. Paracetamol in a dose of 10–15 mg/kg, 4–6 h intervals may be given for children with fever ≥39.0 °C. Excessive paracetamol use can worsen asthma. The use of Ibuprofen is not recommended in children with dehydration. The practice of alternating antipyretics (paracetamol and ibuprofen) should be discouraged for there is no scientific evidence to support this practice.
- Antibiotics are not indicated in uncomplicated cases and should be avoided, as should antihistamines and cough suppressants. The effect of antibiotics on fever in children who recovered with or without antibiotics is shown in Fig. 5.1.

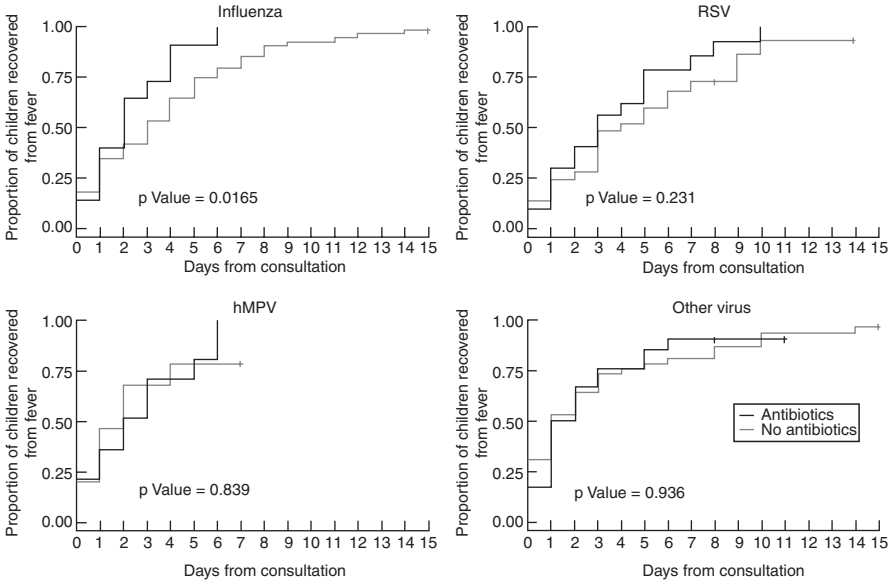

Fig. 5.1 Time to resolution of fever (days from consultation) according to virus detected and antibiotic prescribing. *hmpv* human metopneumovirus, *RSV* respiratory syncytial virus (obtained from *Arch. Dis. Child*. 2007; 92; 594–597; originally published online 16 Mar 2007; doi:10.1136/adc.2007. 116665)

- Nasal decongestants are rarely required, except perhaps for those infants with feeding or sleeping difficulty caused by the nasal obstruction.
- Vitamin C has been advocated for common cold, but its value is unproven. There is evidence that vitamin D can prevent acute viral URTI.
- Herbal preparations are often used. Ivy leaf extract (*Hedera helix*) is popular as an antitussive in many European countries. It contains saponins that have mucolytic, spasmolytic, bronchodilatory and antibacterial effects.
- Children, particularly those with high-risk medical conditions, may receive annual influenza vaccination to prevent the infection.
- Oseltamivir and zanamivir reduce replication of influenza A and B viruses and can reduce the duration of influenza by a median of 36 h. They are also effective for prevention of influenza complications such as pneumonia or myocarditis. Oseltamivir is not licensed for use in children aged less than 1 year. For further information on the treatment of influenza (NICE guidelines).
- The use of physical methods in reducing fever is discouraged.

5.1.2 Tonsillopharyngitis

The tonsils serve immune defence containing T-lymphocytes and macrophages. The main phase of immune acquisition continues until the age of 6 years, and

therefore enlarged tonsils (hyperplasia) are physiological at this age to be followed by regression in size until the age of 12 years. Although most cases of tonsillopharyngitis are caused by viral agents, group A beta-haemolytic streptococci (GABHS) are the most common bacterial cause, occurring in 20–30% of cases. Less common causes are pneumococci and other groups of beta-haemolytic streptococci.

Streptococcal tonsillopharyngitis is primarily a disease of children 5–15 years of age. It may begin abruptly with fever (in over 90%), malaise, sore throat, swallowing difficulty, headaches and abdominal pain. The tonsils are oedematous and hyperaemic. There may be purulent exudates confined to the enlarged tonsils. The pillars are not enlarged as it is the cases in peritonsillar abscess. The uvula is red and swollen and the upper, anterior cervical lymph nodes are enlarged (>2 cm) and tender. There is usually an absence of conjunctivitis, coryza or cough. Diagnosis is made by throat culture and a more than twofold rise in antistreptolysin O titres between two serum samples taken 2 weeks apart. Rapid antigen detection and PCR tests are useful for providing rapid results.

Mechanisms of fever induction: Pyrogenic exotoxins, such as streptococcal pyrogenic exotoxin A, induce human mononuclear cells to produce numerous cytokines, in particular TNF-α, IL-1β and IL-6, which play a leading role in the pathogenesis of the inflammatory process and fever. High fever correlates with high levels of these two cytokines.

The differential diagnoses of streptococcal tonsillitis are:

- Scarlet fever results from certain strains of haemolytic streptococci producing an erythrogenic toxin. The rash is an erythematous punctiform eruption that blanches on pressure and spares the area around the mouth. Initially the tongue has a thick white cover, which develops in a few days into typical strawberry tongue. Apart from the rash and the tongue, there is essentially no difference between streptococcal tonsillitis and scarlet fever. Fever in both conditions usually ranges from 39 to 40.5 °C peaking on the second day of illness. Without treatment, the temperature usually subsides on the fifth day, whereas penicillin therapy causes a rapid normalization of temperature within 12–24 h.
- Peritonsillar abscess is a rare suppurative complication of tonsillitis causing a toxic appearance of the child, fluctuant peritonsillar mass and asymmetric deviation of the uvula.
- Gingivostomatitis is usually caused by herpes simplex infection in infants and small children. It is characterized by irritability, anorexia and fever, which is usually in the range 38.5–39.5 °C (may also be as high as 40–40.5 °C). The child has painful oral vesicles that soon rupture. Submaxillary lymphadenitis may occur. The disease is self-limited and lasts about a week.
- Coxsackievirus A may cause herpangina. The initial temperature ranges from normal up to 41 °C; the temperature tends to be higher in younger children. Other features include headache and vomiting. Throat inspection reveals discrete punctuate vesicles, surrounded by erythematous rings on the soft palate, anterior pillars and uvula.

- Diphtheria, which develops insidiously, has a grey, thick membrane which bleeds easily if removed. The associated fever in diphtheria is typically low grade. Frequently, there is a pharyngeal erythematic and congestion (with or without tonsillar exudates). Anterior cervical adenitis is commonly present.

Treatment includes antipyretics (see above). Penicillin eradicates streptococci from the throat, bringing the symptoms, including fever, rapidly under control and effectively preventing suppurative and non-suppurative complications. Macrolides are used in case of penicillin allergy. Vitamin D is recommended to prevent recurrent tonsillopharyngitis.

5.1.3 Otitis Media (OM)

OM is one of the commonest infections in children, particularly during the first 2 years of life, affecting about 60% of all children. At risk are those who attend day-care centres and those whose parents smoke at home. The infection usually arises from an URTI, which spreads to the middle ear through the short and straight Eustachian tube. *Streptococcus pneumoniae* accounts for the majority of bacteria, followed by non-typeable *Haemophilus influenza* and *Moraxella catarrhalis*. Viruses (RSV, adenovirus, rhinovirus) are currently the most common cause of OM.

Bacterial OM often presents with a sudden febrile illness characterized by:

- History of or the presence of viral URTI and sudden rise of fever.
- High fever, irritability, ear pain and a prompt response to antibiotics. Fever of <39 °C occurs in about 25% and fever of >39 °C in about 75%. The highest fever is recorded in children less than 2 years of age. Only 4% of children persist with fever lasting longer than 48 h. Persistent fever suggests a viral cause, resistant bacteria, unsuitable antibiotic or a complication of OM.
- Findings include intense erythema and various degrees of bulging of the tympanic membranes, with or without otorrhoea.
- High cytokine levels, which correlate with the degrees of fever. In OM and middle ear effusion, high levels of cytokines exist, including IL-1β, Il-2, IL-4, IL-10 and TNF-α. High levels of IL-10 occur in infection by *S. pneumoniae*.

The absence of fever suggests a more insidious variety of OM characterized by mild lassitude and irritability. Conductive hearing loss is often present with this variety.

Complications include perforation of the drum, mastoiditis, chronic otitis, cholesteatoma, facial paresis, increased intracranial pressure (causing bulging of the fontanelle in infants), meningitis, brain abscess or lateral sinus thrombosis.

The introduction of pneumococcal vaccines has reduced the number of bacterial middle ear infections. The use of antibiotics is controversial except in cases with evidence of bacterial involvement. If antibiotics are prescribed, amoxicillin and a macrolide are sensible choices. The use of antihistamine, ear drops or decongestant

is controversial. Analgesics are often needed to reduce the pain. For a bulging tympanic membrane or if the response to antibiotics is not prompt, myringotomy may rarely be considered for aspiration of fluid.

5.1.4 Infectious Mononucleosis (IM)

IM is an acute viral infection caused by Epstein-Barr virus. Symptoms, laboratory findings and complications are shown on Table 5.1. The virus targets memory B-lymphocytes and T-lymphocytes; the latter release a multitude of cytokines (e.g. IL-1β, IL-6, TNF-γ and IFN-γ) that cause the IM symptoms.

A prodromal period of 3–5 days with malaise, fatigue and headache may precede the onset of fever. The majority (80%) of patients will have fever, pharyngitis and posterior cervical lymphadenopathy (pharyngeal form) and 20% present with fever alone (typhoidal form). Fever may last 4 days to 2 or 3 weeks (mean duration 2 week), peaking on the fifth day of illness. The pattern of fever is frequently intermittent, with a usual range between 38.5 and 39.5 °C, rarely higher.

IM commonly presents as:

- Asymptomatic infection occurring in about 90% during early childhood.
- Typical IM triad of abrupt onset of fever ranging from low-grade to high-grade fever, pharyngitis and cervical lymphadenopathy (especially posterior) occurring mainly in adolescents and young adults.
- A case of pyrexia of unknown origin with fever as the only sign of the disease.

Table 5.1 Features and complications of clinical data of infectious mononucleosis[a]

Physical signs	%	Laboratory findings	%	Complication	%
Fever	100	EB-IgM	100	Pneumonia	3
Lymphadenopathy	80	Monospot test	98	Haemolytic anaemia	3
Pharyngitis	80	High transaminases	90	Agranulocytosis	0.1
Splenomegaly	50	>50% lymphocytes	50	Thrombocytopenia	0.1
Rash				Neurological	1.5
Palatal petechiae	50			Guillain-Barre syndrome	
Exanthem	10			Meningoencephalitis	
				Transverse myelitis	
Hepatomegaly	20				
Jaundice	5			Other rare complications:	
				Ruptured spleen	
Airway obstruction	1–3.5			Myocarditis	
				Pericarditis	
				Arthritis	
				Nephritis	
				Pancreatitis	

[a]Revised from references [2, 3]

- A complication listed in Table 5.1, including, rarely, malignancies, e.g. Burkitt's lymphoma, Hodgkin's lymphoma and nasopharyngeal carcinoma.
- A cytomegalovirus mononucleosis characterized by prolonged fever, liver and haematological changes similar to those observed in Epstein-Barr infection. Heterophile antibodies are always absent. Pharyngitis is uncommon.
- Tonsillopharyngitis not responding to antibiotic administration or as an extensive rash following the use of ampicillin or amoxicillin.

Leukocytosis in the range of 15,000–20,000 is frequent. Absolute lymphocytosis (greater than 50%) and at least 10% of atypical lymphocytes are usual findings. Tests to demonstrate heterophile antibodies (positive in more than 80%) have been superseded by several rapid slide tests (monospot). IgM is positive in almost 100%. PCR for detection of EBV is now in routine use to aid diagnosis.

Therapy: IM is usually self-limiting requiring only symptomatic treatment. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce inflammatory features even at low doses. Paracetamol is used to reduce the fever and pain but should be used judiciously because of the liver status in IM. Aspirin should not be used because of bleeding risks and an association of IM with Reye's syndrome. Steroids do not influence the extent or the duration of fever, but they are mainly indicated for impending airway obstruction. Hyperplasia of the lymphoid tissue in Waldeyer's tonsillar ring may occasionally cause severe airway obstruction and will respond to steroids administered for 2 weeks. Antiviral and antibiotic treatment is not indicated. Close follow-up is recommended. Patients, particularly those with splenomegaly, should avoid excessive activity and trauma to minimize the risk of splenic rupture. Spontaneous splenic rupture and neurological complications are rare but account for the majority of fatalities.

5.1.5 Acute Upper Airway Obstruction

Croup (laryngotracheobronchitis) is a common cause of upper respiratory tract obstruction of the subglottic area. It is characterized by inspiratory stridor, fever, cough, hoarse voice and a variable degree of respiratory distress. Although symptoms often appear alarming, the infection is a benign self-limited illness, which usually persists for 2–6 days. Parainfluenza viruses account for about 75% of all isolates. Other pathogens include influenza A and B, adenovirus and mycoplasma pneumonia. The attack rate is highest in the second year of life (usually 3 months to 3 years), and male children are predominately affected. Onset is sudden (usually at night) with loud stridor and barking cough, preceded by 24–72 h of an URTI. The severity of croup is assessed by a scoring system (Table 5.2).

Fever is among the most common chief complaints in children presenting with upper respiratory infections. Variable degrees of fever are present in about 40% the patients with croup, ranging between 38 and 39 °C (mean 38.7 °C). Children with bacterial infection presenting with stridor (e.g. bacterial tracheitis) are mostly febrile with higher degrees of fever. Children with spasmodic croup are normally afebrile.

Table 5.2 Scoring system of severity for children with croup

	Mild-moderate	Severe
Barky cough	Occasional	Frequent
Stridor	Minimal	Severe
Retraction	None	Obvious
Air entry	Normal	Decreased
Distress/agitation	Absent	Present
Level of consciousness	Normal	Disorientated, drowsy

Management of a child with croup includes:

- Children with croup usually recover rapidly with minimal medical intervention. Children with mild croup and minimal or no respiratory distress can be managed at home. If hospitalization is required, the mother should whenever possible be with the child to minimize stress.
- Parental education on signs of respiratory distress and when to seek medical help is important.
- O_2 in case of hypoxia (O_2-saturation <94%) presenting as agitation or distress.
- Dexamethasone 0.6 mg/kg orally reduces respiratory distress within an hour of oral administration; the effect lasts about 10 h.
- Nebulized epinephrine (adrenalin) is effective in producing dramatic effects on airway obstruction and may be administered in severe croup before intubation.
- Although humidification is commonly used, trials have not shown this to greatly influence the clinical course of croup.
- Paracetamol 10–15 mg/kg is administered if the child is miserable with fever or sore throat.

Spasmodic croup is another entity of unknown aetiology. Onset is always at night. The characteristic presentation occurs in a child who previously has been well without associated upper respiratory infection and who awakens at night with sudden dyspnoea, croupy cough and inspiratory stridor. Fever is usually absent.

Bacterial tracheitis is an acute, potentially life-threatening bacterial infection caused mostly by *Staphylococcus aureus* of the tracheal mucosa, often producing thick purulent exudates. This infection usually begins as a viral-like illness or croup with stridor but progresses rapidly with high fever, toxicity and worsening respiratory distress. The diagnosis should be considered in any ill-looking child who does not respond to nebulised adrenaline.

Epiglottitis is an acute bacterial infection characterized by marked swelling of the glottis and arytenoids area. Septicaemia caused by *H. influenzae* type B is present in most cases. Epiglottitis is rarely seen nowadays following Hib vaccines. The infection has an abrupt onset with high fever, respiratory distress, dysphagia, drooling, irritability, restlessness, anxiety and a thick muffled voice. In a report of 100 consecutive admissions of children with epiglottitis, fever was noted in 88, with a range from 39 to 40.5 °C and a mean of 39.1 °C [1].

Differentiating epiglottitis from viral croup may be difficult. Epiglottitis is now very rare. Patients appear very unwell, with higher degrees of fever and respiratory distress, and there is usually leukocytosis and high CRP.

5.2 Acute Lower Airway Infection

5.2.1 Bronchiolitis

A clear distinction between bronchiolitis and bronchitis in the first 2 years of life is difficult and of no therapeutic significance. Both are preceded by URTI. About 20% of children develop bronchiolitis during their first year of life. The diagnosis of bronchiolitis is made in the presence of a history of an URTI followed by acute onset of respiratory distress with cough, breathlessness, wheezing, tachypnoea and clinical signs of chest inflation, occurring during a winter epidemic of bronchiolitis. RSV accounts for 60–80% of cases. Peak age is 4–6 months. Pre-existing chronic lung disease, congenital heart disease, immunodeficiency, prematurity and parental smoking are risk factors for severe presentation of bronchiolitis.

Fever in bronchiolitis: Information on the incidence of fever in bronchiolitis or on its relationship to clinical severity of bronchiolitis is limited. In a study of 90 children with bronchiolitis [2], fever (defined as a single recording of >38 °C or two successive recording >37.8 °C) was present in 28 infants (31%). Febrile children had a longer mean hospital stay and a more severe clinical course compared to those who were afebrile (Table 5.3). In infants with bronchiolitis, hypoxia is common and as many as 40–50% require oxygen supplementation. A rise of body temperature results in an increase in energy expenditure of about 10% for each 1 °C rise in temperature. These changes are accompanied by an increase in oxygen consumption of 10–12% for every 1 °C rise in temperature. The low incidence of fever in bronchiolitis may be due to low interferon production. Although interferon is known to be a potent endogenous pyrogen, this cytokine is significantly low during acute RSV bronchiolitis. RSV induces pro-inflammatory cytokines (IL-1β, IL-6, IL-8, IL-10 and TNF-α) that cause fever and attract inflammatory leukocytes.

The mainstay of treatment is:

- Adequate oxygenation and hydration. Hypoxia, as measured by pulse oximetry, requires oxygen administration.
- Nasogastric tube feeding or intravenous fluid is often required in moderate or severe cases to maintain fluid balance, to replace fluid loss from insensible sweating or tachypnoea and to minimize aspiration.

Table 5.3 Summary of clinical data of 90 children hospitalized with bronchiolitis

		Clinical severity	
Group	Mean length of stay in days	Severe	Mild
Febrile (n = 28)	4.2 (1–13)	20 (71%)	8 (28.6%)
Afebrile (n = 62)	2.7 (1–10)	18 (29%)	44 (71)
P value	<0.005	<0.005	

- Nebulized hypertonic saline (3%) may improve the clinical severity.
- Inhalation of beta-2 agonist (salbutamol) or anticholinergic agent (Ipratropium) is effective if there are signs of bronchospasm (wheezing).
- Antibiotics are of no value unless the disease is complicated by bacterial infection. Corticosteroids, antihistamine, cough suppressants and expectorants are also of unproven value. Ribavirin can be effective in reducing the shedding of virus and is used in immunocompromised patients. Palivizumab, an antibody directed against the virus, is recommended to prevent RSV in high-risk individuals such as immunocompromised children.

5.2.2 Asthma

Asthma is defined as reversible obstructive airway disease characterized by bronchospasm, mucosal oedema and mucosal plugging. The airway obstruction is unevenly distributed throughout the lungs, leading to ventilation-perfusion imbalance and hypoxia. There is increased airway responsiveness to various stimuli, including respiratory viruses (responsible for up to 90% in young children), house dusts, exercise, air pollutants, cigarette smoking and drugs. Cytokines enhance eosinophil differentiation and maturation as well as endothelial adherence and activation.

The clinical hallmarks of the disease are paroxysms of expiratory wheezing with prolonged expiratory phase, unproductive cough and dyspnoea. The predominant asthma type in school-age children (6–16 years) is the classic atopic variant that is associated with allergy problems as evidenced by strong correlation with serum IgE levels and with skin test reactivity to allergens. By contrast, asthma in children aged 1–5 years is characterized by recurrent, transient wheeze triggered by viral colds, a type previously termed as wheezy bronchitis and now as preschool viral wheeze. Physical examination reveals varying degrees of tachycardia, tachypnoea, use of accessory muscles of respiration and rhonchi on auscultation. Somnolence, fatigue, diminished wheezing and breath sounds usually signal respiratory failure.

Markers of asthma severity include an admission to hospital in the previous 12 months, less privileged social class, parental smoking and the frequency of prior and recent respiratory infections. Environmental factors such as climate and air pollution have been found to influence the prevalence and severity of asthma. Higher exposure rates to cockroaches and dust mites also correlated with asthma severity. There are three stages of asthma severity:

- During early stage, hypoxia causes increased minute ventilation, a fall in PCO_2 and normal or elevated pH (respiratory alkalosis).
- Moderate asthma is associated with increased hypoxia, normal PCO_2 and pH.
- In severe asthma, hypercarbia, low pH and respiratory/metabolic acidosis (respiratory failure) ensue as a result of respiratory muscle fatigue, hypoxia and anaerobic cellular metabolism producing lactic acidosis.

Relationship between asthma and fever: There is a lack of information about fever and its relation to asthma. A Medline/PubMed search identified 65,993

Table 5.4 Clinical data of 202 children with asthma

	Mean age in months (range)	Mean stay in days in hospital (range)	Asthma severity	
			Severe	Mild
<5 years				
Febrile = 27	24 (12–42)	1.7 (1–4)	1	26
Afebrile = 70	31 (12–58)	1.9 (1–9)	5	65
p-value	0.012	0.484	0.603	
95% CI	1.6–12.7	−0.3–0.7	n/a	
>5 years				
Febrile = 11	113 (78–172)	1.4 (1–2)	1	10
Afebrile = 94	118 (60–180)	2.2 (1–6)	18	76
p-value	0.700	0.065	0.688	
95% CI	19.1, 28.3	0.65, 15	n/a	

articles on the subject of asthma published since 1966 [3]. There were only three reports related to the occurrence of fever in asthma, but none on the incidence of fever in children with asthma or its relationship to the severity of the disease.

Fever is not a frequent finding in acute exacerbations of asthma. It was recorded in only 18.8% on admission of 202 patients, mostly younger than 5 years of age (Table 5.4) [3]. In this study, the severity of asthma was found to be inversely related to the degree of fever: children with severe asthma were usually afebrile and mildly asthmatic children were often febrile. Fever can therefore be seen as a marker of mild asthma. Similar observations were made at the turn of the last century when patients were noted to obtain a temporary relief of their asthma in association with fever. Subsequently various methods (diathermy) were used to treat asthma. It is possible that:

- Fever as a response to infection can limit the spread of infection by enhancing the host defence mechanisms to eliminate the viruses.
- As airway inflammation is a cardinal feature of asthma, cortisol, a potent glucocorticoid, is known to be elevated in febrile illness and could play a role as an endogenous anti-inflammatory agent.

The reasons why the majority of asthmatic children are afebrile may be due to:

- Tachypnoea, which accompanies asthma, increases heat loss through evaporation.
- Reduced interferon production has been reported in children with bronchiolitis and asthma. Interferon is known to be a potent endogenous pyrogen capable of inducing fever. Cytokines implicated in the pathogenesis of asthma, such as IL-5, IL-8, IL-4 and ECP, are not known to be potent pyrogens, and their presence is unlikely to induce fever in asthma [4].

Laboratory investigations such as full blood count, CRP and ESR are of little value in asthma. Leukocytosis is common in the absence of bacterial infection. A chest X-ray

is rarely indicated unless the diagnosis is uncertain, in patients with fever >39 °C and in case of severe asthma. Measurement of oxygen saturation is always indicated when a child is admitted to hospital. For older children measurement of the peak flow is important and should be repeatedly performed. Allergy skin tests (to detect IgE antibody in the skin to inhalants such as pollens and house dust mites) and the radioallergosorbent test (RAST, detecting IgE to various allergens in the serum) are often performed, but they do not seem to be of great diagnostic or therapeutic value.

Therapy aims at rapid reversal of the airway obstruction. Nebulised beta-2 agonists remain the first line of treatment. Corticosteroids are recommended for patients with acute severe asthma, but their effects are slow. Inhaled steroid (IS) therapy reduces symptoms and bronchial hyperresponsiveness and is currently widely used as an anti-inflammatory agent in asthma. For children taking steroid therapy who are still inadequately controlled, the use of long-acting inhaled beta-2 agonist or higher dose of IS is recommended. Children with mild asthma who are not taking adequate fluids by mouth and all children with severe asthma should have IV fluid therapy. Oxygen should be administered in all cases with hypoxia, that is, an oxygen saturation <92%.

Paracetamol and ibuprofen intake during pregnancy and during the first year of life has been reported to be associated with increased risk of asthma. Other reports found no evidence that paracetamol when used during febrile illness was associated with increased risk of asthma. Further studies are needed to ascertain this relationship between asthma and antipyretics.

5.3 Pneumonia

In 1900, pneumonia, called by Osler “the captain of the men of death”, is still the most common cause of deaths under the age of 5 years causing over a million deaths annually, mostly occurring in developing countries. In children, pneumonia is common, but its true incidence is not established owing to the lack of an accepted clinical definition of pneumonia. However, the bacterial incidence has significantly decreased after the introduction of *Haemophilus influenzae* type B and conjugate pneumonia vaccine PCV7. Peak incidence occurs between 6 months and 5 years. Factors that increase the risk of pneumonia include malnutrition, parental smoking, immunosuppression, low socio-economic status and prematurity. In recent years, HIV infection has contributed to increases in incidence and mortality.

The lungs are not only involved in gas exchange but also in mediating host defence. This includes non-immunological defence mechanisms (such as lysozyme secretion by macrophages) and immunological defence mechanisms (such as activation of macrophages and B- and T-lymphocytes). The alveolar macrophages respond to activation by exogenous pyrogens (such as endotoxin released by Gram-negative bacteria) by releasing potent inflammatory mediators, including interleukin-1 (IL-1), tumour necrosis factor (TNF) and IL-8. This leads to a febrile response, accumulation of neutrophils at the site of infection and inhibition and repair of tissue injury. IL-8 is particularly important for neutrophil chemotaxis.

Diagnosis of pneumonia is based on the following features:

- Community-acquired pneumonia is defined: fever, clinical signs (cough, dyspnoea, tachypnoea, grunting and nasal flaring and referred pain) and chest X-ray infiltrates in a previously well child. Lower lobe pneumonia may cause lower abdominal pain mimicking acute appendicitis. Upper lobe pneumonia may cause meningism (increased CSF pressure, but CSF is otherwise normal).
- Findings include inspiratory crepitations and bronchial breathing on auscultation. Tachypnoea (>40/min aged >1 year, >50/min aged 2–12 m and > 60/min aged <2 m) is the WHO-defined criterion to diagnose pneumonia.
- Wheezing, cough and fever may occur with mycoplasma infection.
- Chest X-ray is diagnostic, but it is often of limited value in distinguishing bacterial and viral. The presence of effusion and/or lobar consolidation suggests bacterial aetiology.

Isolation of the pathogens causing pneumonia is usually not possible in practice. Bacterial culture from the pharyngeal area or expectorated sputum is unreliable. However pathogens can be identified by:

- Blood culture (positive in 10% of cases with bacterial pneumonia).
- Serum or urine counter-immuno-electrophoresis is a rapid and more sensitive technique than blood culture for the detection of bacterial antigens.
- Culture of aspirated pleural effusion.
- High IgM, such as *Mycoplasma pneumoniae*.
- Respiratory secretion for rapid virus antigens (e.g. RSV, parainfluenza).
- Serological tests showing fourfold rise of antibody titres.
- Polymerase chain reaction (PCR) is increasingly being used.

Marked leukocytosis, sometimes exceeding 40,000/mm^3 (leukemoid reaction), is very suggestive of bacterial pneumonia, particularly pneumococcal or *H. influenzae* pneumonia. Although inflammatory markers (WBC, CRP) are usually normal in viral pneumonia, mild leukocytosis with a left shift in the differential count may occur, particularly in influenza pneumonia.

Fever in pneumonia: Fever is common in children with pneumonia older than 1 month of age. Reports [5] on fever and pneumonia indicated that:

- Of the 100 febrile children with pneumonia, a temperature of >40 °C occurred in 45, while the remaining 55 children had a fever of <40 °C.
- Fever was present in all children with *H. influenzae* pneumonia, with a mean temperature on admission of 39.9 °C (*H. influenzae* pneumonia is rarely seen nowadays).
- The onset of pneumococcal pneumonia was usually abrupt with a temperature of 39.5–40.5 °C. The highest fever however tended to be with staphylococcal infection (A temperature of 41 °C is not an unusual finding).

- The likelihood of pneumonia increased with increasing duration of fever longer than 3 days, e.g. during a febrile URTI. A study of 711 children with pneumonia from 13 hospitals in England found neither CRP, chest X-ray changes nor pyrexia was associated with increased severity of the disease.
- In children <3 years old, a combination of >38.5 °C, chest recession and a respiratory rate of >50/min indicates pneumonia. Dyspnoea is a more reliable sign of pneumonia in older children (The British Thoracic Society guidelines).

5.3.1 Pneumonia in Newborn Infants

During the neonatal period, pneumonia is usually caused by organisms acquired during or before delivery, mainly *E. coli* and group B streptococci. The amniotic fluid may be infected or the mother is an asymptomatic carrier of these organisms. Predisposing factors are prolonged rupture of membrane, prolonged labour or an infected, febrile mother. The infection by these bacteria is mainly due to low levels of opsonizing antibodies directed at the polysaccharides of the organism, impaired function of the lung macrophages and polymorphonuclear leukocytes. Pneumonia may also accompany a generalized intrauterine infection by cytomegalovirus toxoplasmosis, listeria or rubella virus. Chlamydia trachomatis is classically an afebrile pneumonia with a dry cough and increasing tachypnoea. Conjunctivitis is present in about 50% of cases.

The newborn infant with pneumonia usually presents with signs of respiratory distress with tachypnoea and grunting. Body temperature is usually normal. If the mother has been febrile before delivery, an increased temperature may be detected in the infant in the first few hours of life owing to the constant temperature gradient between mother and infant during pregnancy.

5.3.2 Pneumonia at the Age 1 Month to 4 Years

During this age, the rate of viral pneumonia is high, particularly in children around 6 months of age. Respiratory syncytial virus (RSV) remains the most common cause of pneumonia in industrialized countries. Febrile pneumonias are commonly caused by RSV, influenza A and B, parainfluenza type B and adenoviruses, while afebrile pneumonias are usually due to chlamydia trachomatis, cytomegalovirus or *Mycoplasma hominis*. Commonly an URTI precedes the onset of pneumonia.

In developing countries, the causes and patterns of pneumonias are affected by malnutrition, poor housing, lack of early medical attention and immunization. Pneumococci, streptococci, coliforms, *H. influenzae* and staphylococci are more common causes of pneumonia with high mortality.

Staphylococcal pneumonia is a rather rare cause of pneumonia, occurring sometimes as a complication of influenza virus infection. Its presentation is with shaking chills and high fever>40 °C, pallor, tachypnoea, abdominal distension and rarely

cyanosis. The diagnosis should be suspected in any child younger than 1 year of age who appears ill and does not respond rapidly to conventional antibiotics such as penicillin and ampicillin. Chest X-ray shows multiple nodules, which undergo cystic formation (pneumatocele) and empyema.

5.3.3 Pneumonia at the Age of >4 Years

Pneumococci and *Mycoplasma pneumoniae* are the most frequently identified organisms, while viruses are less common at this age. In pneumococcal pneumonia, patients have often flu-like symptoms for several days before the onset of pneumonia, which begins by an abrupt onset of rigor and high fever. The cough is not a feature initially but becomes intense later and is usually accompanied by chest pain. The sputum is classically rusty in colour due to alveolar haemorrhage, but this is seldom seen nowadays in children.

Mycoplasma pneumoniae is characterized by insidious onset of fever, headaches and abdominal pain, followed by cough. Transient skin rash is found in about 10% of cases. Mycoplasma pneumonia may also present with similar clinical and radiological features of pneumococcal and staphylococcal infection. In contrast to these infections, however, children with *M. pneumoniae* appear well despite the extent of the X-ray lesions. Fever is present in more than 90% of patients. In a study of 66 children with mycoplasma infection [11], the temperature distribution was as follows: temperature <38 °C was present in 22% of patients, 38.3–38.9 °C in 30%, 39.4–40 °C in 44% and >40.6 °C in 4%.

The diagnosis of *M. pneumoniae* is difficult, but it may be made by a combination of:

- History of unresponsiveness to penicillin or amoxicillin.
- A fourfold rise in antibody titre or a single titre of 128 or more.
- IgM antibodies.
- Serum cold agglutinins in 50–70% of the cases.
- Chest X-ray is not diagnostic but commonly shows peribronchial and perivascular interstitial infiltrates.
- A high CRP or ESR and a normal WBC count may be observed.

About 5% may develop neurological complications, such as encephalitis, meningitis, cerebellar ataxia, focal neuropathy or cerebral infarction. Other complications are haemolytic anaemia, arthritis, rash (popular, vesicular, erythema multiform) myocarditis, pericarditis and interstitial nephritis.

5.3.4 Pneumonia at any Age

Aspiration pneumonia may occur subsequent to aspiration of secretion from the oropharynx in weak or neurologically impaired children (e.g. in preterm infants,

cerebral palsy) and in children with tachypnoea (e.g. bronchiolitis) or following inhalation or accidental ingestion of kerosene or aspiration of gastric acid. The child presents with dyspnoea, tachypnoea, subcostal recession, cough, wheezing and cyanosis. Children are usually afebrile with aspiration pneumonia, with possible exception of kerosene pneumonia, which is often associated with fever of 38–39.5 °C. Chest X-ray shows infiltrates usually involving the right upper lobe in infants and right lower lobe in older children.

Pneumocystis jiroveci pneumonia = PJP (previously known as *Pneumocystis carinii*) occurs almost exclusively in patients who are immunocompromised, including those who are receiving immunosuppressive drugs for malignancy or organ transplantation or HIV infection. About 85% of patients with HIV develop PJP during the course of their illness. Unlike most infectious complications in cancer patients, PJP may occur while the patient is in remission from the primary cause. Clinical manifestations include fever, cough, cyanosis, marked tachypnoea with intercostal retraction and a paucity of physical signs of pneumonia. Among 1251 children with malignancies, PJP was identified in 51 (4.1%) [12]. Fever was the first sign of abnormality and occurred in almost all patients with, or shortly preceding, tachypnoea. The extent of the fever varies from mild to severe.

The diagnosis is suggested by a chest X-ray showing a hazy, bilateral alveolar infiltration. Sputum examination and bronchoalveolar lavage (BAL) can identify PJP in the majority of cases. The diagnosis is confirmed by detecting PJP by histological or cytological demonstration of thick-walled cysts, as obtained by BAL or from percutaneous transthoracic needle aspiration of the lung.

Antibiotic therapy of pneumonia depends on the age of the child and likelihood of the causative agent. Neonates are treated with penicillin and gentamicin. Older children respond to amoxicillin and second- or third-generation cephalosporins or co-amoxiclav. Suspected cases of staphylococcal pneumonia should receive anti-staphylococcal agent such as flucloxacillin. Patients with mycoplasma pneumonia usually respond well to macrolides. The treatment of choice for patients with PJP is trimethoprim-sulfamethoxazole 20 mg/kg/day.

5.4 Gastroenteritis

Worldwide, diarrhoeal disease is the leading cause of death under 5 years of age. More than two million children die every year from gastroenteritis, almost all living in resource-constrained countries. In the absence of diarrhoeal diseases, the total infant and child mortality in the Third World would not differ significantly from that of developed countries. Data collected from 276 surveys on diarrhoea in 60 countries have shown that one-third of all deaths in children below 5 years of age were caused by diarrhoea. Approximately 1.5 billion diarrhoeal episodes and 4.6 million deaths in children occur per year (or 12,600 deaths/day), accounting for 21–29.3% of all childhood deaths [6].

In developing countries, bacterial (*Escherichia coli*, *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia enterocolitica*) and parasitic (*Entamoeba histolytica*,

Table 5.5 Major enteropathogenic agents in children with gastroenteritis

Bacteria	Virus	Parasites
Salmonella	Rotavirus	*Giardia lamblia*
Shigella	Adenovirus	*Entamoeba histolytica*
E. coli	Other viruses	
Campylobacter jejuni		
Yersinia		
Vibrio cholerae		
Other bacteria		

Table 5.6 Febrile non-enteritis conditions that cause diarrhoea

Conditions	Diagnostic clue
Intussusception	Intermittent, colicky abdominal pain
HUS	Bloody diarrhoea, abdominal pain, vomiting
Appendicitis	Young age of 1–3, predominately diffuse abdominal pain
Neuroblastoma	Abdominal mass
Primary immunodeficiency	Associated recurrent infections
HIV infection	Commonly associated with thrush, recurrent infections, weight loss
Kawasaki disease	Lymphadenopathy, conjunctivitis, rash
Addison's disease	Diarrhoea occurs in chronic adrenal insufficiency, abnormal electrolytes, pigmentation, adynamy
Crohn's disease	Associated weight loss, anaemia, high CRP

HUS Haemolytic uremic syndrome

Giardia lamblia, *Cryptosporidium* species) pathogens are the major causes of gastroenteritis, particularly in summer months (Table 5.5). In developed countries, viruses are responsible for approximately 70% of the gastroenteritis. Viral GE causes shorter illness than bacterial GE and is associated with increased risk of vomiting and dehydration compared to bacterial GE. Rotavirus is the most common causative pathogen followed by norovirus and adenovirus. Enteric adenovirus is associated with longer-lasting diarrhoea.

Fever is common in both bacterial and viral gastroenteritis. High fever is commonly present in many bacterial causes (e.g. *Shigella*, *Salmonella*, Shiga toxin-producing *E. coli*). Fever is often absent or low-grade in other diseases (e.g. enteropathogenic *E. coli*, cholera). Other febrile conditions that cause diarrhoea and need to be differentiated from GE are shown in Table 5.6.

Bacteria or viruses acting as exogenous pyrogens can cause fever by inducing endogenous pyrogens which raises the hypothalamic thermoregulatory set-point. Clinical and laboratory findings, which can differentiate bacterial from viral aetiology of acute gastroenteritis, are shown in Table 5.7.

Dehydration, the most common cause of hyperthermia, leads to cutaneous vasoconstriction and decreased sweating, causing an increase in body temperature. In hypernatraemic dehydration, an increase in sodium pump activity needed to offset

Table 5.7 Factors likely to predict the aetiology of acute gastroenteritis

Bacterial aetiology	Viral aetiology
Fever >39 °C	No fever or low-grade fever
Presence of bloody stools	No bloody stools
Summer months	Winter months
High CRP, WBC, IL-6	Normal or mildly elevated CRP, WBC, IL-6
Hyponatraemia is common	Hyponatraemia is uncommon
Increased WBC in stool	None to few WBC in stool
High-serum TNF-alpha	Low serum TNF-alpha

Table 5.8 Typical water losses per 100 kcal of energy expended for a healthy 10 kg child

Source of water loss	Approximate water loss (mL/kg/day)
Insensible	
Skin	30
Respiratory	15–20
Sensible	
Stool	10
Urine	50–60
Total	105–120[a]

[a]The above average calculation. The sum of insensible water loss (average 50 mL/kg/day) with 16 mL/kg/day subtracted for endogenous water for oxidation produces 34 mL/kg/day. The addition of 66 mL/kg/day urinary loss would produce 100 mL/kg/day fluid requirement

the high extracellular sodium concentration may further raise the body temperature. High sodium levels may also act directly upon the hypothalamus to increase the set-point. For every 1 °C increase of body temperature, there is an increase in insensible water loss of 10%. Table 5.8 shows typical water losses based on caloric expenditure of 100 kcal/kg/day for an infant weighing 10 kg body weight.

5.4.1 Bacterial Gastroenteritis

Bacterial gastroenteritis is caused either by secretory pathogens (such as cholera, which causes watery diarrhoea through colonization and adherence to the small bowel mucosa) or invasive pathogens (such as *Shigella*, which cause inflammatory cell exudates in the distal bowel and/or colon). Secretory pathogens are likely to cause severe diarrhoea. Invasive organisms may cause watery or grossly bloody diarrhoea with cramps and tenesmus, but severe diarrhoea is infrequent.

Salmonellae are Gram-negative rods with over 1400 known species. The most common serotypes are *S. typhimurium*, *S. enteritidis* and *S. infantis*. In industrialized countries non-typhoidal salmonellae (NTS) infection is more common. This is usually a self-limiting and benign disease, and invasion beyond the gastrointestinal tract occurs in only about 5% of patients. In many African countries,

bacteraemia is a major cause of death, and NTS account for 20–50% of cases, ranking second only to pneumococcal pneumonia as the leading bacterial cause of child mortality. Most human infections occur in late summer and early autumn and are caused by the ingestion of contaminated food (meat, poultry products, eggs) or water. Increased susceptibility to the infection occurs in children with sickle cell anaemia, impaired cellular immunity and achlorhydria. About 12–48 h following ingestion of contaminated ingestion of contaminated food, the onset is abrupt with nausea, fever, and crampy abdominal pain, followed by loose, watery diarrhoea, occasionally containing mucus, blood or both. The illness is indistinguishable from *Shigella* infection. Vomiting is a not a striking feature in salmonellosis. While salmonellosis in older children is usually self-limited disease requiring no antibiotic therapy, there is a significant incidence of bacteraemia (range 15–45%) and meningitis in infants younger than 3 months. Bacteraemia may occur in the absence of fever in this age group. The absence of fever usually excludes bacteraemia in older children.

Fever in Gastroenteritis

- Endotoxin is a complex lipopolysaccharide structure that constitutes the outside portion of the cell wall of *Salmonella*. Endotoxin releases IL-1 from macrophage into the circulation, accounting for the fever and other systemic manifestations of the disease. Cytokines are responsible for the symptoms and development of the protective mechanisms in the disease. Mean serum concentrations of TNF-alpha, TNF-gamma and IL-12 are increased during the acute phase of the disease. IL-8 and IL-10 are involved in the pathogenesis of rotavirus GE.
- Diarrhoea is usually more frequent in afebrile than in febrile cases.
- Children with bacterial GE are more likely to develop high fever than those with viral GE, and there is a significant relation higher fever and shigella GE.
- In a study from Finland [7] comprising 102 children salmonella gastroenteritis, 15 had a fever >40 °C, 66 had a fever of 38–39.9 °C and 21 had a temperature of <37.9 °C. There was a significant correlation between the degree of fever and the duration of organism excretion: a fever of >40 °C had the shortest and no fever the longest duration of excretion (Table 5.9). Fever therefore appears to have a favourable prognostic influenza on the duration of salmonella excretion. The gastrointestinal tract acts as a major barrier against the potentially noxious substances, such as microbes. Immunological defences include secretory IgA, mac-

Table 5.9 Fever on admission and duration of bacterial excretion after salmonella gastroenteritis in 102 children (Ref [7])

		Duration of salmonella excretion (weeks)		
Degree of fever (°C)	No of children	Range	Mean	Mean (SD)
(A) > 40 0	15	0–10	0	1.9 (2.9)
(B) 38–38.9	66	0–18	3	4.1 (4.0)
(C) <37.9	21	2–60	7	11.7 (15.1)

P value: (A) vs. (B), $p = 0.160$; (B) vs. (C), $p = 0.0011$; (A) vs. (C), $p = 0.0001$

rophage and activated T-lymphocytes in the Peyer patches and lamina propria. Fever is beneficial to the infected host by enhancing macrophage and T- and B-cell activity.

- Convulsion may occur during the diarrhoeal disease. About 10% develop febrile or afebrile seizures. Febrile seizures (FS) are particularly common with shigella infection. Occasionally, afebrile seizure may occur in association with dehydration, electrolyte imbalance, hypoglycaemia or hypocalcaemia. A third form of seizure is an afebrile seizure, particularly during viral GE, without dehydration of electrolyte imbalance. This type of seizure is usually benign. CSF and EEG are normal. Paracetamol has not been shown to prevent FS.
- Ibuprofen is an antipyretic that is frequently administered for febrile children with GE. Acute renal insufficiency may occur in association with ibuprofen and should therefore be avoided.

Typhoid fever includes infection with *S. typhi* and *S. paratyphi* A, B and C, rarely *S. choleraesuis*, *S. heidelberg* and *S. typhimurium*. The incidence of typhoid fever in the USA is 0.2 cases per 100,000 population, with a case fatality rate of 1.3% [8].

Elevated pro-inflammatory pyrogenic cytokines, particularly tumour necrosis factor-α and IL-6, are responsible for the prolonged fever, which is characteristic of the disease. High serum levels of these cytokines have been linked to disease severity. High level of IL-6 suggests poorer response to antibiotic therapy and its decline correlates with successful therapy. Vigorous antipyretic use may lead to shock.

In older children, presentation of a typical case follows the following steps:

Onset is insidious with fever (without shaking chills), which is present in all patients, and is associated with headache, cough and abdominal pain. Symptoms then gradually increase over 2–3 days. The child is often constipated, nauseated and anorexic. The temperature continues to rise in a stepwise fashion to reach 40–41 °C. In young children the onset of fever is more often abrupt, then becoming sustained or intermittent. The stepwise pattern of fever is less common. In all ages, fever may continue for many days despite successful antibiotic therapy, and the child does not become afebrile until the end of the therapy. At the end of the first week, patients remain febrile with hot, dry skin, abdominal tenderness, hepatosplenomegaly and relative bradycardia. Roseate spots may be detected in about 20–40%, characterized by a few discrete popular erythematous lesions confined to the anterior chest and abdomen. Delirium, convulsion, meningeal irritation, psychosis and ataxia may be noted. If untreated with antibiotics, fever remains continuous at 39–40.5 °C for 2–3 weeks before abating slowly. By the end of 2 weeks, perforation or haemorrhage (in about 5%) may occur due to typhoid ulceration and defects in coagulation. This serious complication is associated with 50% mortality. Typhoid bacilli persist indefinitely in the bile passage in about 3–5% who recover from the infection.

Laboratory findings include leucopenia, anaemia, thrombocytopenia and increased serum aspartate transaminase (SGOT). Elevated agglutination titres of O and H antigens at 1:160 are significant. The diagnosis is based on isolation of *S. typhi* or other salmonella strains from blood or bone marrow culture.

Shigellae are Gram-negative rods with worldwide distribution. Humans are the principal host for shigellosis (bacillary dysentery). The majority of patients are under 5 years of age; the infection is rarely seen in infants under 6 months of age.

Four serotypes are known: *Shigella flexneri*, *S. dysenteriae*, *S. sonnei* and *S. boydii*. The first two species are more common in developing countries, whereas *S. boydii* and *S. sonnei* usually cause a self-limiting febrile illness in developed countries. *Shigella* must penetrate the mucosa in order to cause dysentery.

The disease onset is usually acute with fever and malaise, often progressing to dysentery consisting of cramps, tenesmus and frequent stools composed largely of blood and mucosa. Severe dehydration is not a typical feature of the infection. High fever is common. Of 57 children with *Shigella* gastroenteritis, 27 (47%) had a fever greater than 40 °C at presentation, 21 (37%) had a fever between 38 and 40 °C and the remaining 9 (16%) were afebrile [9].

Complications include toxic megacolon, protein-losing enteropathy, hyponatraemia due to inappropriate antidiuretic hormone secretion, disseminated intravascular coagulation, renal failure, haemolytic uraemic syndrome and bacteraemia. *Shigella* bacteraemia occurs in 4.0% of patients. Neurological symptoms, particularly convulsion are among the most frequent extra-intestinal manifestations of shigellosis occurring with or without evidence of the production of Shiga toxin (neurotoxin). Death can occur in children with poor nutritional state.

Amoebic dysentery, caused by *Entamoeba histolytica*, may cause colitis simulating shigellosis. Virulence of *E. histolytica* depends on the trophozoites being able to bind to colonic epithelium. The infection tends to run a more chronic course with intermittent watery or semiformed diarrhoea (containing blood and mucosa) without or with a low-grade fever. Young children tend to present with acute symptoms similar to cases with *Shigella* infection. Liver abscess may occur a few months after the intestinal infection, causing discomfort over the liver, intermittent fever with chills and sweats and weight loss. Findings suggestive of amoebic liver abscess include an elevated right diaphragm, hepatomegaly and a history of colitis. The diagnosis of amoebiasis is confirmed by demonstration of *E. histolytica* in a stool (motile trophozoites during the diarrhoea, cyst if the diarrhoea is not present) or in tissues. The indirect haemagglutination (HA) test and enzyme-linked immunosorbent assays (ELISA) are positive in almost all patients with amoebic liver abscess and in majority of those with intestinal infection.

Escherichia coli cause either non-bloody diarrhoea (e.g. enterotoxigenic *E. coli*, ETEC; enteropathogenic *E. coli*, EPEC) or bloody diarrhoea (e.g. Shiga toxin-producing *E. coli*, STEC; enteroinvasive *E. coli*, EIEC). *E. coli* cause significant fluid loss and dehydration, but bloody stools are relatively infrequent.

- ETEC produce enterotoxins that cause copious, watery diarrhoea in developing countries. In severe form, the illness resembles cholera and is responsible for high mortality among young children. It is an uncommon cause of diarrhoea in industrial countries, but it is the most common cause of traveller's diarrhoea.

EPEC infection was in the past a common cause of outbreaks of infantile diarrhoea in industrialized countries, usually occurring in neonates and young children <2 years of age. Since the 1970s the infection has been reported less frequently, and the severity of the illness has lessened in children of these countries. It can cause protracted diarrhoea.

- EIEC and STEC produce Shiga toxins, causing a dysentery-like diarrhoea and haemolytic uraemic syndrome (HUS) by the strain 0157:H7.

Fever occurs frequently in the range of 38–40 °C. Fever, very often low-grade, is reported in only one third of patients in children infected with EIEC and STEC. EPEC usually does not cause systemic manifestations because the organisms remain confined to the bowel lumen. Fever was found in only 5 of the infected 49 children from Addis Ababa [10].

Campylobacter enteritis is an important cause of enteritis in both developed and developing countries. *C. jejuni* is the most important species. The enteritis is a zoonosis and a man-to-man transmission is unusual. Raw cow's milk and incompletely cooked poultry meat have caused most of outbreaks in the UK. Contaminated water is another cause of outbreaks in developing countries.

Infection is usually self-limited in industrialized countries, lasting 2–4 days, following an incubation time that averages 5 days. Children present with an acute illness accompanied by fever, diarrhoea and bloody stools in about 90% of cases. Abdominal pain occurs almost universally, but vomiting is mild and occurs in about 30%. In a study from Canada, all 32 children with this infection who were older than 12 weeks develop fever up to 40.5 °C, whereas all five children who were younger than 12 weeks remained afebrile. In a study from Iraq, 202 children with diarrhoea, *C. Jejuni* was found in 13.86% and fever was detected in 82.14% [11].

Yersinia enterocolitica is an anaerobic, Gram-negative bacillus that causes an infection mostly in cooler climates such as Scandinavia and Canada. Serotype O:3 is the most common isolate. Transmission of *Y. enterocolitica* to humans occurs from ingestion of contaminated foods (particularly contaminated pork), water and milk.

Presentation is characterized by bloody diarrhoea in about one third of patients. The fever is usually mild, ranging between 38 and 39 °C. The associated abdominal pain sometimes mimics appendicitis (pseudo-appendicitis). The disease is usually mild although it can be prolonged (1 day to 3 weeks). A Canadian study of 181 children with *Yersinia* infection (45) reported that diarrhoea occurred in 98%, fever in 88%, abdominal pain in 64.5% and vomiting in 38% [12].

Rare complications are arthritis and erythema nodosum. Other rare complications include intestinal perforation, diffuse ulceration, ileocolic intussusception, peritonitis, glomerulonephritis, meningitis and peri-myocarditis. The infection can occur as septicaemia and patients then have high fever, toxic appearance and confusion.

5.4.2 Viral Gastroenteritis

Rotavirus infection is responsible for 30–60% of all cases of dehydration and diarrhoea in young children (peak age 3–15 months) in both developed and developing countries. The infection is prevalent in winter months. Approximately 125 million cases of rotavirus diarrhoea occur annually in developing countries, leading to an estimated 800,000–900,000 deaths a year [13]. Although viraemia is rare in healthy individuals, this was reported in 67% of immunocompetent children with rotavirus diarrhoea.

Nosocomial acquired outbreaks of rotavirus have occurred in newborn nurseries and paediatric hospital wards. The virus can be detected in oropharyngeal aspirates with or without diarrhoea. Spread occurs via the faecal-oral route. The virus is shed in faeces in high concentration, which allows its easy identification by electron microscopy.

There is often a preceding or accompanying upper respiratory tract infection or otitis media. Within 2 days of exposure, there is fever and vomiting, which last 1–3 days, and usually preceding the onset of watery diarrhoea, which lasts 4–7 days. Dehydration occurs as a result of marked faecal fluid loss.

Most children with rotavirus diarrhoea have fever. A study from Finland [14] reported that 14% of 336 infants had fever of 39–40.2 °C and 65% had less than 39 °C. Many cytokines, particularly IL-6, IL-10 and INF-γ, play an important role in the pathogenesis of as well as protection against rotavirus reinfection. IL-6 is elevated in children with fever.

Enteric adenovirus: Several studies have shown that adenovirus is second to rotavirus as the most common cause of viral gastroenteritis, occurring commonly during the first year of life. The infection was identified in 8.6% of 900 paediatric inpatients with diarrhoea, serotypes 40 and 41 being the most common isolates [15]. In contrast to enteric adenoviruses, other respiratory adenoviruses are not associated with diarrhoea. Watery diarrhoea is the most common presentation, usually followed by 1–2 days of vomiting. Illness typically lasts 5–12 days (mean 9 days). The duration of the diarrhoea usually lasts longer compared to that caused by rotavirus. Severe dehydration is less common compared to rotavirus infection.

A low-grade fever for 1–3 days is commonly recorded with adenovirus enteritis. A Canadian study [16] of 127 children with adenovirus enteritis found that 41% of them had a rectal temperature of >38 °C. The range of body temperature was 36.2–40.8 °C (mean 38 °C). The average duration of fever was 1.6 days (range 1–30 days).

The outcome of adenovirus gastroenteritis is generally good. Adenovirus is now more frequently diagnosed (due to PCR) in immunocompromised patients and is an important cause of mortality.

Other viruses: Norfolk virus and Norwalk-like viruses are major causes of small and large outbreaks of winter vomiting in older children and adults with or without diarrhoea. These outbreaks occur commonly in recreational camps, communities or schools in the USA. Presentation is similar to that of other types of viral gastroenteritis and includes anorexia, malaise, fever and abdominal cramps, followed within

48 h by vomiting and watery diarrhoea. Symptoms usually last 2–3 days and full recovery is the usual outcome. Astrovirus can also cause gastroenteritis. The infection is frequently asymptomatic in the newborn infants.

Treatment: Breast milk is the best prophylaxis against gastroenteritis, and exclusively breast-fed children remain remarkably free of severe diarrhoea in developed and developing countries.

The standard treatment of all diarrhoeal diseases is the replacement of fluid and electrolyte loss. This is best accomplished by oral rehydration solution (ORS) which has revolutionized the management of diarrhoeal diseases in developing countries. This is safe, cheap, convenient to use and superior to IV fluids because it can be started early at home. The sugar-electrolyte mixture recommended by the WHO contains (mmol/L water) sodium 90, chloride 80, potassium 20, sodium bicarbonate 30 and glucose 111, with an osmolality of 331 mosmol/L. A hypotonic solution with a sodium concentration of as low as 50–60 mmol/L and an osmolality of 224 mosmol/L has been shown in Finland to have clinical advantages over the standard ORS. Rice-based ORS compared with standard ORS reduced the 24 h stool volume. Intravenous electrolyte-glucose solution should be used for children with moderate to severe dehydration and persist vomiting.

Antibiotic therapy is usually not required for patients with gastroenteritis because it does not affect the clinical course of the majority of cases. Severe systemic manifestations associated with bacterial gastroenteritis (notably *Shigella*, *Campylobacter*, *Yersinia* and cholera) probably require antibiotics. Infants with salmonella gastroenteritis less than 3 months of age should be treated with an antibiotic, such as third-generation cephalosporin or a quinolone depending on the regional resistance pattern. Patients with typhoid fever and *E. histolytica* should also receive antibiotic treatment.

5.5 Viral Hepatitis

Hepatitis occurs as a result of a variety of causes, including viruses (hepatitis viruses, Epstein-Barr viruses, cytomegalovirus), bacteria (leptospirosis), parasitic infection (amoebiasis) and drugs.

5.5.1 Hepatitis A Virus (HAV)

HAV is a highly contagious infection, spreading mostly by faecal-oral contact from person to person.

The clinical features are usually mild, and most infected children have an anicteric illness with flu-like symptoms or gastroenteritis with lethargy, nausea, vomiting, abdominal pain and anorexia. Clinical findings often reveal a tender and enlarged liver. Splenomegaly is present in about 20% of cases. About 99% of children recover

completely from the infection. Fulminant hepatic failure may occur in the remaining 1%. Chronic hepatitis or cirrhosis is not part of the HAV infection.

Fever, usually low-grade between 38 and 39 °C, is found in about 40% of cases. The low incidence of fever in hepatitis is probably due to impaired production of IL-1β, which increases slightly during the first week of illness, reaching a peak during the second and third week and thereafter decreasing to a normal level. IL-1, IL-6 and TNF-α are mediating the inflammatory process, while IL-10 suppresses it.

Diagnosis rests on detection of the specific IgM, which is a marker of recent infection. It is usually positive before the onset of jaundice, peaking at 1 week and is undetectable 4–8 weeks later. IgG anti-HAV indicates previous exposure and is detectable approximately 1 week later than IgM and persists for years as a sign of immunity. High transaminases enzymes are characteristic of the disease. These enzymes are elevated during the anicteric phase of the illness and usually persist for a few weeks. Serum bilirubin and alkaline phosphatase are mildly or moderately elevated. Prothrombin time is usually normal.

Standard immunoglobulin preparations administered within 2 weeks of exposure have proved effective in preventing hepatitis A. Vaccine against HAV is effective.

5.5.2 Hepatitis B Virus (HBV)

Approximately 350 million people are chronically infected with HBV worldwide. Transmission of this virus usually occurs via vertically from mother-to-child at birth or any bodily secretion or fluid. Children exposed to multiple blood transfusions are at high risk of contracting the virus. The incubation period for HBV infection ranges from 6 weeks to 6 months (mean 90 days). The HB surface antigen (HBsAg) appears during the incubation period several weeks before clinical or biochemical illness develops and is usually undetectable after 6 months. The core antigen (HBcAg) and e antigen (HBeAg) are other antigens of HBV associated with greater infectivity. HBeAg is the only HBV virus that crosses the placenta.

Neonates are at high risk if the mother has acute hepatitis or carries HBsAg (chronic carrier) at delivery. Viral acquisition may follow swallowing of maternal blood during delivery, rarely via the transplacental route or through ingestion of breast milk. Most infants born to HBsAg-positive mothers remain asymptomatic for months and years.

Clinical manifestations are usually absent or mild without evidence of fever. The vast majority of children (>90%) infected with this virus develop a chronic carrier state, and less than 5% develop hepatitis. Children are at risk of developing hepatocellular carcinoma and should therefore be regularly monitored with serial ultrasound scan and serum alpha-fetoprotein. Patients have substantial abnormalities of cell-mediated immunity and cytokine production, including a decreased production of TNF-alpha.

In HBV infection in older children, prodromal symptoms may include urticaria and arthralgia, which precedes a spectrum of clinical presentations ranging from acute viral hepatitis, severe or fulminant hepatitis, chronic persistent hepatitis, chronic active hepatitis to the asymptomatic chronic carrier state.

5.6 Urinary Tract Infection (UTI)

UTI is a common cause of an acutely febrile illness in children affecting 7% of girls and 2% of boys. The infection is mainly caused by ascending faecal bacteria from the perineum to the bladder. UTI is frequently the result of sepsis during the first 3 months of age, occurring more commonly in males. Known predisposing factors for UTI include maternal febrile UTI, congenital malformation of the urinary tract, urolithiasis, indwelling urinary catheter, constipation and uncircumcised males. The principal sequence of UTI is vesicoureteric reflux found in 30% of acute cases, which may lead to chronic renal failure and/or hypertension in adults.

The most common organisms are:

- Uropathogenic *E. coli*, which contain lipopolysaccharide, lipoprotein and proteoglycan. By attachment of the bacteria to the urinary tract, these substances are capable of inducing an inflammatory response and fever.
- Less common aetiological agents include *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterococci* and *Staphylococcus epidermidis*.

The pro-inflammatory cytokines IL-6 and IL-8 play an important role in the inflammatory process of UTI. Serum and urine IL-6 and urine IL-1β positively correlate with fever in UTI. The cytokines sequester the bacteria in the bladder and reduce ascent to the kidneys.

UTI presents in one of the following ways:

- High fever, rigor, vomiting, meningism and abdominal discomfort, loin pain and tenderness, usually affecting infants and young children.
- As sepsis with or without fever, occurring in about 30% of neonates, 20% of infants aged 1–2 months and 5.0% of infants >3 months of age.
- Febrile seizure as the first symptom of an underlying UTI.
- As lower UTI (cystitis) with dysuria, frequency, urgency or dribbling, occurring in older children, particularly in girls who are usually afebrile.
- Asymptomatic (without fever) bacteriuria is common in school girls (1–2%), but the infection is of little clinical or prognostic significance.

Diagnosis of UTI rests on the following findings:

- A febrile child without a focus whose urine showed positive nitrite and leukocytes in the urine dipsticks, which are very suggestive of the diagnosis. Negative result of these two indicators virtually excludes it. A positive urinalysis is defined as five or more WBC per high-power field.
- Urine culture as the ultimate tool to confirm or refute the diagnosis. UTI is diagnosed if the urine shows a colony count of 100,000 colonies/mL of a single bacterial species. Suprapubic puncture is important for accurate diagnosis during infancy, and a culture of 50,000 colonies is diagnostic. In older children midstream urine sample is sufficient.

- Laboratory tests: Leukocytosis >15,000, high CRP (>40 mg/L to support the diagnosis. CRP is particularly valuable when fever has been present >12 h. IL-6 is a useful diagnostic tool for early recognition of UTI. Procalcitonin (PCT) > 0.5 ng/mL is a major predictor (compared to WBC count and CRP) for identifying children with acute upper urinary tract infection (pyelonephritis) during early stages of UTI.
- Once UTI is confirmed, recent NICE guidelines recommend a renal ultrasound scan for all children <6 months of age within 6 months of the infection and no ultrasound scan in children >6 months with uncomplicated febrile UTI. Ultrasound should be arranged early in case of severe or recurrent infections. Micturating cystourography (MCUG) is currently less commonly performed than previously and should be reserved (along with DMSA isotope scan) for atypical presentation or recurrent infections occurring in infancy.

Fever in UTI has the following significance:

- About 5% of highly febrile infant and young children have UTI (pyelonephritis), and 20% of children without a focus of infection have UTI.
- About 95% of children with UTI are feverish, usually >39.0 °C.
- The diagnosis of UTI should be considered in every febrile child, particularly when the fever is without a focus and of duration longer than 24–48 h. A delay in diagnosis and treatment increases the risk of renal scarring.
- Resolution of fever after initiating antibiotic therapy indicates adequate therapy.
- Persistent fever of >48 h is an indication to admit the child to hospital (if he/she was treated as an outpatient), arranging an ultrasound scan and commencing IV antibiotic treatment.
- Afebrile status is a criterion for discharge from hospital.

Therapy: There are no significant differences in persistent renal damage or duration of fever between oral antibiotics (a second-generation cephalosporin or co-amoxiclav) for 7–10 and short courses (2–4 days) of IV therapy followed by oral therapy for the same period. Dysfunctional voiding (e.g. ineffective bladder emptying) should be eliminated. Circumcision should be considered for recurrent UTIs in boys. Probiotics may be useful.

5.7 HIV Infection

Over three million children <15 years are estimated to be HIV-infected. This accounts for more than 10% of the total HIV-infected population. Some 50–60,000 HIV-infected infants are born every year. The fast majority of children (90–95%) are infected through vertical transmission mother-to-child (in utero, intrapartum and breast milk). Typical presenting symptoms are fever, asthenia, failure to thrive, prolonged diarrhoea, recurrent infections and lymphadenopathy.

Fever in HIV infection: Fever occurs in 85% and is caused by:

- Common viral or bacterial infections, similar to children without HIV infection. Fever >7 days is more likely to be due to bacterial or parasitic infections rather than viral infections. More prolonged fever could be due to TB, connective tissue disease or malignancies.
- The HIV infection itself. Acute retroviral syndrome may occur 2–4 weeks after the infection, mainly in teens, as a febrile illness resembling glandular fever.
- Immune reconstitution syndrome (IRS). This is a transient deterioration or emergence of new manifestations (such as high fever, worsening of CNS lymphadenitis lesions) of an opportunistic infection occurring after the initiation of antiretroviral therapy (ART). The syndrome also occurs after initiating anti-TB treatment in patients already on ART.
- Secondary infections (such as tuberculosis).
- Drug fever, commonly associated with ART.
- Unknown causes of fever, which may present as a case of pyrexia of unknown origin (PUO).

The incidence of fever is higher with a coinfection such as TB. Children with fever >39.0 °C are at high risk of bacteraemia with S. pneumonia. Unexplained persistent and/or recurrent fever (>37.5 °C intermittent or constant) for >1 month is considered as a moderate severe HIV.

In a study [17] of 316 febrile children with advanced HIV disease, the diagnoses were disseminated mycobacteria avium complex (MAC) infection in 36%, tuberculosis in 16%, B lymphoma (6%), disseminated CMV infection (4%), extrapulmonary cryptococcus (3.5%) and 17% of cases presented as PUO. Other less frequent diagnoses were drug fever, endocarditis, HIV primary infection, pancreatic abscess, pseudomonas aeruginosa bacteraemia and visceral leishmaniasis.

The majority of these patients (about 75%) were receiving co-trimoxazole prophylaxis with or without antiretroviral treatment.

Children with HIV infection often present with:

1. Fever without focal signs and duration <14 days in HIV (Table 5.10)
2. Fever without focal signs and duration >14 days (Table 5.11)

Evaluation of fever among patients with HIV infection requires a detailed history, focusing on:

- Duration of fever
- Recent travel to an area of malaria or dengue disease
- Skin rash, cough, pain during swallowing, headache, diarrhoea, dysuria
- Weight loss
- The last CD4 cell count? (normal CD count: 600–1000)
- Current treatment (e.g. ART) and adherence

Table 5.10 Differential diagnosis of fever without focal signs and duration <14 days in HIV infected children

Differential diagnosis	Diagnostic clues
Malaria	• Living or a history of visiting malaria area • Blood film/dipstick positive • The presence of anaemia, low platelets
Typhoid fever	• Seriously ill without apparent cause • Abdominal tenderness • Relative bradycardia in relation to body temperature • Maculopapular rash, often sparing palms
Urinary tract infection	• Dysuria, frequency, pyuria, tenderness in renal angles • Positive nitrate and WBC dipstick
Dengue	• Patient from areas at risk • Sudden onset of high fever with headache, pain behind eyes, joint and muscle pain • Macular rash in 50% (centrifugal, itching) (In dengue haemorrhagic fever, there is in addition bleeding tendency, e.g. from the nose, bowel, fingers)
Septicaemia	• Seriously ill with no apparent cause
Immune reconstitution inflammatory syndrome	• Recent start of HAART • CD4% < 10% at start of HAART • Rise in $CD4^+$ lymphocyte count
Drug-induced fever	• Nevirapine, cotrimoxazole, dapsone, ß-lactams, isoniazid, anticonvulsants, abacavir, efavirenz

HAART highly active antiretroviral treatment

Examination should include routine physical examination focusing on areas likely to be involved in the infection, such as thorough palpation of the lymph nodes, neurological examination and fundoscopy for cytomegalovirus (CMV) and TB.

Laboratory investigations should include the following:

- Blood tests: complete blood count with differential counts; blood chemistry (transaminases, alkaline phosphatase, LDH); blood smear for malaria; serum cryptococcal antigen test (SCrAg); dipstick for malaria (rapid tests), if in endemic zone; viral load, CD4 count; dengue serology (if patient is living or have travelled to endemic areas)
- Urinalysis
- Chest X-ray, abdominal ultrasound
- Stool examination for bacterial culture and AFB
- Lumbar puncture
- Mantoux Test or INF gamma assay

Management of newly diagnosed children who present with PUO entails:

- A thorough search and adequate treatment of the secondary infections should be carried out prior to starting the antiretroviral therapy.
- The above investigations should be initiated prior to any treatment.

Table 5.11 Differential diagnosis of fever without focal signs and duration >14 days in HIV infected children

Differential diagnosis	Diagnostic clues
Disseminated TB	• Advanced HIV/AIDS, with anaemia • AFB seen on sputum, gastric aspirate, CSF, pleural fluid and/or fine needle aspirate of lymph nodes • Enlarged mediastinal or hilar lymph nodes, pulmonary infiltrates or miliary lesions on chest X-ray. Enlarged liver or spleen or enlarged lymph nodes on abdominal ultrasound
Mycobacterium Avium Complex (MAC)	• Severe immunosuppression or WHO stage 4 disease • Symptoms compatible with disseminated TB but failing to respond to TB medicines • Absence of peripheral lymphadenopathy • Severe anaemia and neutropenia
Cytomegalovirus (CMV)	• Very low CD4 count (CD4 < 50 cells/mm^3 in children >5 years) or WHO stage 4 disease. Blind spots in one or both eyes, with signs of retinitis
Disseminated cryptococcal infection	• Very low CD4 count (CD4 < 50 cells/mm^3 in children >5 years) or WHO stage 4 disease • Headache, molluscum-like skin lesions • Positive serum cryptococcal antigen tests • Isolation of the pathogen from CSF, lymph nodes, sputum or skin ulcers (Indian ink)
Visceral leishmaniasis	• Splenomegaly, lymphadenopathy. Pancytopenia • Amastigotes seen in samples of tissue or body fluid under the microscope (Giemsa stain)
Bacterial endocarditis	• Enlarged spleen, heart murmur • Petechiae on skin and mucosa, anaemia • Splinter haemorrhages in nail bed
Relapsing fever	• Exposure to ticks or body lice • Recurrent pattern of fever. Headache, muscle pain, enlarged liver and spleen, red eyes and photophobia
Abscesses	• Tender or fluctuant mass, often detected by ultrasound
Trypanosomiasis	• Travel to or living in region with tsetse flies • History of painful trypanosomal chancre at site of inoculation of the parasite • Bouts of high fever lasting several days are separated by afebrile periods, lymphadenopathy, itching and maculopapular rashes

- Antibiotics to cover the likely infections, particularly *Streptococcus pneumoniae* while waiting for results may be required.
- Patients with confirmed or probable TB (abnormal chest X-ray, positive gastric aspirate/ sputum AFB, abdominal lymphadenopathy, positive IFN gamma release assay) should start on antituberculous treatment. This treatment is also indicated as an empirical therapy in cases of unexplained weight loss and fever in advanced AIDS.
- If a patient is not improving on anti-TB treatment, alternative diagnoses such as MAC should be considered.

- Patients responding to mycobacteria avium complex (MAC) therapy should continue until CD4 cells have adequately recovered. This may takes months/years.
- During the whole period of treatment, patients should repeatedly be re-evaluated for the appearance of new symptoms and signs, which may indicate additional infections.

Management of HIV patients with PUO while taking antiretroviral therapy:

- An associated skin rash should arouse the suspicion of drug fever. Nevirapine is a frequent cause of this. Abacavir is also a cause of hypersensitivity reactions.
- Patients who initially responded to treatment for opportunistic infections (OI) prior to the start of antiretroviral therapy, and then developed a worsening of the OI after the start of antiretroviral therapy (e.g. reappearing of fever), should be considered as having IRS (if other obvious causes of fever are excluded). Patients should continue OI and ART, but steroids treatment should be considered.

5.8 Infections of the CNS

5.8.1 Meningitis

Meningitis remains one of the most important infectious causes of neurodisability and death in childhood. Newborn infants and children between 6 and 12 months of age are at greater risk of meningitis than older children; 90% of reported cases occur below 5 years of age. Congenital and acquired T- and B-cell defects, sickle-cell anaemia, splenectomy and malnutrition all predispose to meningitis.

Definitions of the clinical variations of the CNS (central nervous system) infections are provided in the Table 5.12.

Meningitis occurs most commonly in the individual who bears the organisms as an asymptomatic carrier. Organisms enter the CNS through vulnerable sites in the blood-brain barrier (choroid plexus or cerebral microvasculature). The cell wall

Table 5.12 Definitions of meningitis, meningococcal disease and encephalitis

• Confirmed meningitis: isolation of bacteria from CSF, blood or DNA detection through PCR from a patient with a CSF pleocytosis of white cells >10 cells/mm^3. In neonates a pleocytosis of >20 white cells is accepted. Diagnosis is also accepted in case of postmortem diagnosis.
• Probable meningitis: the presence of clinical symptoms and signs of bacterial meningitis in the absence of laboratory confirmation.
• Meningococcal disease: a clinical condition caused by *Neisseria meningitidis* with purulent conjunctivitis, septic arthritis and septicaemia with or without meningitis.
• Aseptic meningitis: the presence of CSF white cell count >10 cells/mm^3; CSF is negative for bacterial culture, occurring usually in summer months. Viruses are most common causes.
• Encephalitis: an inflammation of the parenchymal tissue of the brain caused by an infection producing varying degrees of impaired consciousness.

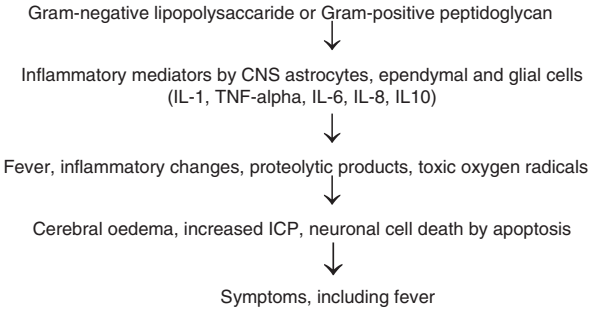

Fig. 5.2 Pathogenesis of meningitis and fever

components of these organisms stimulate macrophage-equivalent brain cells (astrocytes, microglia). Once bacteria reach the CSF, they are likely to survive because humoral defences, including immunoglobulin, complement and opsonic activities, are virtually absent. Meningitis may also result from haematogenous dissemination or rarely by direct invasion from ear or sinus infection. Several cytokines, particularly IL-1 beta, IL-2, IL-4, IL-6 TNF-alpha and INF-gamma, increased the blood and CSF in almost all children with meningitis (Fig. 5.2).

Meningitis accounts for an estimated 180,000 deaths every year worldwide. The widespread use of vaccines against *Neisseria meningitidis*, *H. influenzae* type B (Hib) and pneumococci have dramatically decreased the incidence of these forms of meningitis and their complications in well-immunized populations by approximately three quarters. This has led to an increase of the median age of patients with bacterial meningitis to nearly 40 years of age. In developing world with low immunization rates, however, these types of bacterial meningitis still occur.

Bacterial Meningitis

Neonatal meningitis is most common during the first week of life (early onset). Beyond the first week of life, it is termed late-onset. The susceptibility of neonates to meningitis, particularly premature infants, is mainly due to immaturity of cell- and antibody-mediated immune mechanisms. The neonate is infected by bacteria from the maternal genital tract, the risk being higher after membrane rupture.

A study of 274 neonates from England and Wales established an annual incidence of bacterial meningitis at 0.21/1000 births [18]. The overall case fatality rate was 6.6%. Group B streptococcus was the leading pathogen (about 50% of cases, Table 5.13). Currently, *E. coli* is the predominant bacteria isolated. In contrast to older children, the onset of neonatal meningitis is usually insidious. Infants present with:

- Symptoms such as failure to feed, lethargy alternating with irritability, seizures, vomiting, thermal instability (fever or hypothermia), cyanosis, apnoea, jaundice and respiratory distress.
- Signs such as an ill appearance, a tense or bulging fontanelle, pallor and reduced capillary refill time. Neck stiffness and head retraction are not parts of the symptomatology.

Table 5.13 Causes of bacterial meningitis

Neonate	
• Early-onset	(Caused by vertical transmission) Group B streptococcus (GBS) *Escherichia coli* (*E. coli*) *Listeria monocytogenes* Coagulase-negative staphylococci *H. influenzae*
• Late-onset	(Caused by nosocomial or community spread) Gram-negative enteric bacteria: *E. coli*, *Klebsiella*, *Enterobacter*, *Salmonella*, *Proteus*, *Pseudomonas*
Older children	*Neisseria meningitidis* *Streptococcus pneumoniae* *H. influenzae*

Complications include hydrocephalus, ventriculitis, neurodisability and seizures.

Meningitis in older children is mostly meningococcal (in combination with sepsis called meningococcal disease, MCD) or pneumococcal. Less common causes are *E. coli*, group B streptococci, staphylococci *Listeria*, *Borrelia burgdorferi* (Lyme disease), TB and fungi. Factors that increase the risk for bacterial meningitis include immunoglobulin deficiency (e.g. HIV infection), asplenia, neurosurgical procedures (e.g. ventriculoperitoneal shunt), penetrating head injury and cochlear implants (particularly for pneumococcal meningitis).

Meningitis has a variety of presentations:

- In MCD, the nonspecific early symptoms (in the first 4–6 h) are fever, irritability and decreased appetite. This is followed (at a median time of 8 h) by early symptoms of sepsis: leg pain, abnormal skin colour and cold hands and feet. Classic meningitis symptoms appear later (13–22 h): purpuric rash, impaired consciousness and meningism.
- Fever, vomiting, irritability or drowsiness, headache and photophobia.
- Convulsive status epilepticus with fever.

Tuberculous meningitis compromises about 5–10% of extrapulmonary cases of TB. It often occurs within 6 months of the initial Tb infection following haematogenous dissemination or a rupture of a subependymal focus into subarachnoid space. Fever is the most common presenting symptom, and meningism (e.g. neck stiffness) is the most common finding at presentation. The incidence is highest in children aged 1–5 years. The three recognized stages are:

- Conscious, with nonspecific symptoms (fever, night sweats, anorexia, weight loss, fatigue) and no neurological signs
- Onset of neurological signs: headache, confusion, drowsiness, neck stiffness
- Stupor, deepening coma, focal neurological signs

Relationship Between Meningitis and Fever
Fever in bacterial meningitis is:

- The most common presenting symptom in children beyond the neonatal age owing to the presence of inflammatory mediators, particularly IL-1 and TNF in blood or within the CNS. In MCD, fever was the first symptom in children younger than 5 years and 94% developed fever at some point.
- Uncommon in neonatal meningitis. It occurs in 30% of neonates with *E. coli* meningitis. Neonates have a reduced capacity to produce cytokines, which may explain their frequent afebrile presentation.
- Usually very high in older children. Temperatures between 40 and 41 °C are common, with a mean degree of 39.2 °C. The degree of fever varies depending on the age of the patient and the causative organisms. The incidence of fever was 71% with meningococcal infection, 88% with staphylococcal infection and 90% with *H. influenzae* type B. Children with TB meningitis have the highest incidence of fever with 97% [19].
- Absent in rare cases of severe infection. Hypothermia carries a bad prognosis.
- May present as febrile seizures with meningitis as the underlying cause. These children are usually symptomatic (e.g. impaired consciousness) prior to the seizures. Features such as complex type of seizure (e.g. prolonged or focal) are suggestive of possible meningitis.
- An important sign when monitoring the effect of treatment in bacterial meningitis, i.e. normalization of fever, is very suggestive of a good response and improvement. Nonresponders may produce the following fever patterns:
  - Persistent for 4–7 days
  - Prolonged >7 days
  - Secondary fever (fever reappearing after at least one afebrile day)

The following considerations should be made in persistent or prolonged fever:

- The antibiotics or the doses used for meningitis therapy are inappropriate
- (e.g. penicillin administered for staphylococcal meningitis).
- The meningitis may be aseptic or TB meningitis.
- There are complications listed in Table 5.14.
- The child needs thorough re-evaluation to find out the cause of the fever.
- Morbidity and mortality are higher than in those cases who have responded to treatment.

Animal models of meningitis have provided substantial information on the pathophysiology of fever in the disease. Fever on experimental meningitis in rabbits concluded that high body temperature had a direct inhibiting effect on the growth rate of bacteria in the CSF. On the other hand, the lower the temperature, the faster was the rate of bacterial growth. Thus fever is likely to be a host defence in this disease. Similar results are available in human studies. The reported overall case

Table 5.14 Causes of persistent, prolonged and secondary fevers in meningitis

Persistent
• Causative organisms *S. pneumonia* or *H. influenzae*, fungi
• Foci of the infection
• Nosocomial infection
• Subdural effusion
• Drug fever
• Phlebitis
Prolonged
• Subdural effusion
• Drug fever
• Arthritis
Secondary
• Causative organisms *S. pneumonia* or *H. influenzae*, fungi
• Nosocomial infection
• Subdural effusion
• Drug fever

fatality rate in 100 children with meningococcal infection (55 had meningitis) did not indicate a poor prognosis, but all children with hypothermia died [19].

In a study of 476 children with meningitis, 90% of patients with *S. pneumoniae* and *N. meningitidis* became afebrile within 5 days of the antibiotic therapy, compared to 72% of those with *H. influenzae* meningitis. The rate of persistent fever, prolonged fever and secondary fever was 13, 13 and 16%, respectively [20]. Complications from meningitis have decreased following decreased incidence of meningitis due to the routine *H. influenzae* vaccination in 1992 and recently pneumococcal vaccine but still occur with other types of bacterial meningitis, including persistent and prolonged fever.

Laboratory findings include:

- Characteristic CSF findings (Table 5.15) and identification of the pathogens in CSF and/or blood cultures and/or PCR. In TB meningitis, additional positive findings are microscopy for acid-fast bacilli from CSF, gastric aspirate, sputum (ZN stain), tuberculin test >5 or 10 induration, history of TB contact and radiological evidence in the CNS of tuberculoma and/or other changes, such as hydrocephalus.
- A polymorphonuclear leukocytosis and high CRP in the blood.
- High procalcitonin (PCT) level (>0.5 ng/mL). PCT is a precursor of calcitonin, which is more valuable than CRP and IL-6 in early differentiating bacterial from viral meningitis. PCT is also higher in severe compared to mild disease.
- Other abnormalities: Inappropriate secretion of ADH with hyponatraemia, water retention, increased intracranial pressure, DIC (manifesting as thrombocytopenia, increased fibrin degradation products and prolonged prothrombin, PT, and partial thromboplastin time, PTT).

Table 5.15 Usual CSF findings in normal and in various central nervous system (CNS) infections

Normal	Cell-mm^3	protein Mg/dl	CSF/serum glucose ratio %
Normal	0–5 (lymphocytes)	20–40	>50
Bacterial meningitis	100 to 1000 (PMN)	100–500	<0.5
Tuberculosis	30–600 (lymphocytes)[a]	>100 up to 3 g	<0.5
Viral meningitis	100–2000 (lymphocytes)[a]	Normal to 200	Normal
Encephalitis	Normal to few hundreds	50–100	Normal
Abscess	10–100 (PMN/ lymphocytes	30–200	Normal

PMN polymorphonuclear cells
[a]PMN predominate initially with lymphocytes predominating after 48 h

Table 5.16 Treatment recommended for children with tuberculosis

Drugs	Daily dose mg	Maximal daily mg/kg/day	Major side-effects
INH	10	300	Peripheral neuropathy
Rifampicin	10–20	600	Hepatitis
Pyrazinamide	25–35	2 g	Hepatotoxicity
Ethambutol	15–20	2 g	Optic neuritis
Streptomycin	40	1 g	Ototoxicity

Complications include seizures, neurodisability, paralysis of the cranial nerves, subdural collection, blindness, hydrocephalus, cerebral herniation and deafness.

Therapy consists of prompt IV administration of antibiotics. Neonates are treated with cefotaxime, penicillin (or ampicillin) and gentamicin for a duration of 2 (GBS and Listeria) or 3 weeks (Gram-negative bacteria). Older children are treated with third-generation cephalosporin cefotaxime or ceftriaxone. Treatment of TB meningitis is shown in Table 5.16. Dexamethasone has been advocated for the treatment of bacterial meningitis. Early dexamethasone has been shown to reduce the duration of fever, levels of cytokine concentration and the incidence of hearing impairment. It is mainly beneficial for *H. influenzae* and *S. pneumoniae* meningitis if it is given with or before antibiotics.

Intravenous fluid should be restricted to minimize the effect of inappropriate ADH effect and the cerebral oedema. Monitoring the electrolytes and body weight is important for the management of the fluid and electrolyte balance.

The presence of coma, shock, seizures and hypothermia are associated with poor prognosis. Children with TB meningitis usually make full recovery if they are fully conscious at presentation, while those in coma have high rate of neurodisability and deaths. The younger the child, the worse the prognosis.

Viral Meningitis

The true incidence of viral meningitis is unknown mainly because CSF with aseptic meningitis is often not examined for viruses. The incidence of proven viral meningitis is 0.05/1000 live births. As there has been substantial reduction in bacterial meningitis following routine vaccination, most childhood meningitis in developed countries is now caused by viruses. The most frequent aetiological agents remain non-polio enteroviruses (echovirus and coxsackievirus). Mumps meningitis, which used to be the most common form of viral meningitis prior to the combined measles, mumps and rubella (MMR) vaccination in 1988, has declined dramatically. Symptoms are similar to those of bacterial meningitis, but they are usually mild and the children appear generally well. This infection affects mainly older children.

Fever varies usually between 38.5 and 39.5 °C, rarely higher. Fever along with drowsiness and irritability are the major presenting symptoms. The incidence of fever is around 70%.

Of the various cytokines capable of inducing fever, INF-gamma produced in the intrathecal space appears to be associated with the pathogenesis of viral meningitis and the production of fever. CSF INF-gamma levels correlate well with the severity of febrile episodes.

Laboratory findings include clear or rarely opalescent CSF. CRP and WBC are usually normal. Procalcitonin is a useful marker to differentiate bacterial and aseptic meningitis.

Diagnosis requires isolation of the specific virus from the CSF and/or a fourfold rise in antibody titre to the virus. Rapid identification of the virus by immunofluorescent examination of the CSF is possible for many viruses. The prognosis is very good.

5.8.2 Acute Viral Encephalitis

This is an illness with an acute onset and rapid progression caused commonly by herpes simplex virus (HSV). Other viruses include varicella, cytomegalovirus, EB-virus, coxsackievirus, echovirus, poliovirus, mumps, measles and adenovirus. The annual incidence is 8.8/100000 children younger than 16 years of age [21].

Clinical features vary depending on the nature of the causative virus, the age of the patient and the severity of the infection. Commonly the disease begins with an acute onset of fever, headache and vomiting. Evidence of meningeal irritation and stiff neck is often lacking. Encephalitis is suggested by drowsiness, paralysis, coma, seizure (febrile seizure), ataxia, tremor, mental confusion or hyperexcitability. Ataxia is common, particularly following varicella encephalitis.

Fever is common in viral encephalitis irrespective of the causative agent. It was present in 30% patients with mumps encephalitis, in 85% with coxsackievirus B encephalitis and in 90% of patients (A third had a fever greater than 39 °C) with herpes encephalitis [22]. Fever, lethargy and headaches may last 4–5 days before other symptoms (such as behavioural abnormalities) occur.

Laboratory diagnosis of herpes encephalitis mainly depends on PCR (polymerase chain reaction) detection from the CSF, which is highly sensitive and specific. EEG commonly shows paroxysmal focal abnormalities (such as slow complexes every 2–3 s) over the involved temporal areas. A CT scan of the head may show characteristic low-density lesions in these areas, in addition to diffuse brain oedema. An MRI is a superior investigation for showing lesions in the temporal areas, uni- or bilateral.

Therapy with acyclovir should be initiated to all cases with suspected encephalitis while awaiting laboratory confirmation.

Subacute sclerosing panencephalitis (SPPE) is a progressive inflammatory disease of the CNS caused by persistent, aberrant measles virus infection, characterized by progressive loss of intellectual function, with behaviour and learning difficulty, often associated with abnormal myoclonic movements. High anti-measles antibody titres in serum and CSF confirm the diagnosis. The mean interval between measles and the onset of SPPE is about 10 years. The MMR vaccine has resulted in virtual elimination of SSPE. Fever is not part of SPPE.

5.8.3 Brain Abscess

Brain abscess is uncommon in children. It may occur as a complication of otitis media, mastoiditis, sinusitis or meningitis or ventriculoperitoneal shunt infection, following trauma or surgery to the skull or as a result of haematogenous dissemination in children with acyanotic congenital heart disease.

Fever was the most common clinical finding in a study [23]of 101 children with brain abscess, occurring in 80% of the children, followed by vomiting, headache, seizure, focal neurological abnormalities and lethargy. Papilloedema and meningeal signs were also common. Overall mortality was 30%. High fever, age less than 1 year, multiple brain foci and the presence of meningism or coma have a poorer prognosis.

The most frequently encountered pathogens are *S. aureus*, streptococci and Gram-negative aerobic bacilli.

Laboratory findings in the CSF reveal that the CSF culture is usually negative unless there is rupture of the abscess into ventricles. A CT scan shows the characteristic finding of a ring-enhancing lesion.

Therapy consists of antimicrobial treatment (third-generation cephalosporin, vancomycin and metronidazole) with or without surgical excision or aspiration.

5.9 Osteomyelitis and Septic Arthritis (See Also Chap. 12: Differential Diagnosis: Arthritis)

Infection of the bone may occur as a complication of septicaemia or due to local trauma (e.g. wound, abrasion). Acute haematogenous osteomyelitis involves most commonly the rapidly growing metaphysis of the long bones. The femur and tibia are most commonly affected bones. Septic arthritis is usually haematogenously

acquired or the result of an extension from an osteomyelitic lesion. The knee is most commonly involved. *Staphylococcal aureus* is the most frequent bacteria causing the infection (accounts for 90%), followed by *Kingella kingae*, *S. pneumonia*, *S. pyogenes* and *P. aeruginosa* as less common causes. Children with sickle-cell anaemia and other haemoglobulinopathy are at high risk of osteomyelitis caused by non-typhi salmonella.

This infection presents:

- In neonates with irritability and tenderness when the affected area is touched. There is limited movement of the affected extremities (Pseudoparalysis). Fever is either mild or absent.
- In older children with high fever, refusal to walk, bone pain and limping (if the lower extremities are affected). Examination reveals localized pain, tenderness, warmth and erythema of the affected area.

The diagnosis is based on the following criteria:

- The isolation of bacterial pathogens or positive PCR from blood (positive in 30–60%), bone or joint. Needle aspiration of the soft tissue or incision and drainage of the bone may yield the organism. In septic arthritis, joint fluid aspiration usually reveals purulent exudates with >50,000 leukocytes/mm^3, Gram-positive cocci and a positive culture. Leukocytosis and elevated CRP are usually present. CRP is a very reliable parameter to assess the effectiveness of the treatment and recovery.
- Radiological findings (soft tissue swelling, bone rarefaction, periosteal elevation, bone necrosis) may not appear during the first 2 weeks of the infection. A nuclear bone scan (showing increased uptake of the isotope) is a valuable adjunct to the diagnosis and is often positive before the appearance of the lesion in the X-ray.

Fever is the most common presenting symptom of bone infection, occurring in 90% on admission with a mean temperature of 39.1 °C [24]. The majority of those who were afebrile on admission became febrile during the ensuing 48 h after admission. Normalization of fever is not usually achieved during the first week despite antibiotic treatment. High fever usually continues for 4–5 days after the treatment. Therefore the presence of persistent and high during treatment does not necessarily signify failure of antibiotic treatment.

Initial antibiotics are likely to include IV ceftriaxone with clindamycin, flucloxacillin or fucidin for 3–6 weeks.

5.10 Viral Exanthems

Viral exanthems are common causes of febrile illness in children. More than 50 viral agents are known to cause a rash. Historically, exanthems were numbered in the order in which they were differentiated from other exanthems. Thus the first was measles; second, scarlet fever; third, rubella; forth, so-called Filatov-Dukes disease (no longer

recognized as an entity); fifth, erythema infectiosum; and sixth, exanthema subitum. As more exanthems were described, numerical assignment became impractical.

5.10.1 Measles

The first written record of measles is credited to Razes, a Persian physician of the tenth century; before that measles was thought to be a mild form of smallpox. Sydenham in the seventeenth century drew an accurate clinical picture of the disease, including recognition of its complications. When the USA was swept by measles during the seventeenth and eighteenth centuries, the infection was still believed to be a sequel to smallpox. Measles virus was cultivated in 1938.

Prior to the present vaccine, the attack rate of measles worldwide was close to 100% and measles was an important cause of mortality. Measles vaccine resulted in about 80% decease in measles deaths, preventing an estimated 20.3 million deaths between 2000 and 2015 [25]. In developing countries without immunization, measles affects virtually all children by the age of 4 years, the highest incidence being in the second half of the second year. Mortality in the past has ranged between 15 and 25%. More recently this mortality has decreased progressively in developing countries. The single most important factor affecting mortality is poor nutritional status, leading to deficiencies in cell-mediated immunity and often death due to giant-cell pneumonia, diarrhoea or inclusion body encephalitis.

Measles is caused by paramyxovirus, which spreads by droplets from person to person. The incubation period is about 11 days. The spreads of the virus occur through the following steps:

- Virus entry to the epithelium of the conjunctiva and upper respiratory tract.
- Viral antigens activate macrophages and T cells to produce pro-inflammatory cytokines TNF, IL-1β, IL-6 and IL-17. The IFN production is inhibited.
- High affinity IL-2 receptors rise before the onset of the rash and remain elevated for several weeks.
- Following its spread by day 5 to the mononuclear phagocytes of the liver and spleen, the virus continues its spread by day 8 via the blood to its target tissue (eye, lung and gut epithelial cells). During these stages, viral spread is limited by natural killer cells and cytotoxic T cells. B cells are primed to produce antibody.
- Complications occur in about 30% and include pneumonia (viral or bacterial), otitis media, gastroenteritis, laryngitis, encephalitis, bronchiectasis, reactivation of tuberculosis and SSPE.

Fever in measles: Clinically, the infection progresses through the following steps:

- The pre-exanthem stage expresses like a common cold, with abrupt high fever, sneezing, dry cough and conjunctivitis. The temperature increases gradually to

reach a level ranging from 39 to 40.5 °C that lasts 4 to 7 days. About 24 h prior to the appearance of exanthem, Koplik's spots can be detected in about 80% of cases as tiny (about 1 mm) whitish spots in the buccal mucosa opposite the lower morals.

- The exanthem appears at the peak of symptoms with a temperature of about 39.5 °C. The rash appears first behind the ears and spreads to the face, neck, trunk and extremities. The rash begins to clear on the third day. During the exanthem period, the fever usually peaks on the second or third day and then falls by lysis over a 24-h period. Fever which persists after the third day may signify bacterial complication. There are signs of pharyngitis, cervical lymphadenopathy and occasionally a mild splenomegaly. Shortly after the rash appears, the child becomes anergic, with suppression of the delayed hypersensitivity to skin test antigens and reduced lymphoproliferation and lymphokine production in response to mitogenic stimuli. The infectivity decreases considerably with the onset of the rash.

Laboratory findings: Blood counts often show leucopenia and lymphopenia. Suppression of immune function is manifested in vivo by the loss of response to tuberculin skin test. The diagnosis of measles can be confirmed by measles complement fixation or haemagglutination antibody test. Blood or saliva can be utilized to demonstrate measles-specific IgA.

Therapy: Paracetamol or ibuprofen may be administered to reduce fever and pain Aspirin should be avoided because of Reye's syndrome. Gamma globulin (0.25 mg/kg) within 5 days of exposure to measles virus prevents the disease. Treatment is symptomatic. Oral vitamin A (400,000 U) can decrease mortality in children in developing countries.

5.10.2 Varicella

Varicella zoster virus is a member of the herpesvirus family. The eruption is often the first sign of the onset of varicella, particularly in young children. Older children and adults may have prodromal symptoms preceding the characteristic eruption by 1–2 days, which include fever usually in the range of 38–38.5 °C (temperature up to 40.5 °C may rarely occur during the first 3 days), malaise, headache and abdominal pain. The characteristic eruption of macules and papules appears first on the back and then on the rest of the trunk, spreading within hours to the face and scalp. The lesions progress from macules to papules to vesicles and begin crusting within 8–10 h. Characteristically, these lesions are found simultaneously.

When maternal varicella develops within 4 days of delivery, neonates develop severe varicella within 5–10 days postpartum. The disease is associated with a mortality of around 20% due to disseminated chickenpox, usually with severe pneumonitis. When maternal varicella develops 10–20 days before delivery, transfer of maternal antibodies causes a more benign illness.

Varicella is usually a benign disease. Complications include pneumonia in about 1% (affecting primarily adults and newborn) with a chest X-ray showing nodular infiltrates, secondary staphylococcal skin infection, thrombocytopenic purpura, cerebellar ataxia and encephalitis. Secondary bacterial infection from staphylococci and streptococci can be fatal and needs urgent treatment. Varicella is severe and may be fatal in patients with impaired cellular immunity, such as those receiving cytotoxic drugs. Children with hypogammaglobulinaemia recover normally from varicella.

Therapy: The majority of patients require no special treatment. Aspirin should not be administered because of the risk of Reye's syndrome. Itching can be relieved by simple soothing lotions such as calamine and oral antihistamine. Patients with severe varicella or with complication should receive acyclovir. This antiviral drug promotes the cutaneous healing and reduces the duration of fever. A vaccine is now available and is increasingly being used to prevent this disease. Vaccination is associated with increased risk of febrile seizures (FS), and the use of antipyretics prophylactically prior to vaccination does not prevent FS.

5.10.3 Rubella

Rubella virus may cause inapparent or severe infection. The infection is usually mild, and children usually present with sore throat, rash, lymphadenopathy and low-grade fever (rarely exceeding 39 °C) for several days. Fever may persist for 1–2, rarely 3 days. In older children, particularly in females after puberty, the infection is more severe and prolonged. There are usually painful and visibly enlarged lymph nodes, involving postauricular, occipital and posterior cervical nodes, with polyarthralgia or arthritis.

The infection with rubella virus is particularly important to paediatricians because of possible foetal-maternal transmission. Congenital infection (rubella syndrome) is highest in the early weeks of pregnancy, manifesting as eye disease (cataract, retinopathy, glaucoma), sensorineural deafness, heart lesions (patent ductus arteriosus, pulmonary artery stenosis, aortic stenosis, coarctation of the aorta or ventricular septal defect), neurological abnormalities or thrombocytopenic purpura. Prevention of maternal rubella used to be through routine immunization of all girls of 11–14 years of age and women of child-bearing age, but the use of the MMR has been more successful in reducing rubella syndrome by preventing transmission of the virus from children to pregnant mothers. Rubella, as measles, could be eliminated worldwide if comprehensive vaccination was achieved.

5.10.4 Erythema Infectiosum (EI)

EI or the fifth disease is an acute benign, communicable disease with a characteristic eruption that usually affects children aged 5–15 years. The infection is caused by

parvovirus B19, which also can cause a transient aplastic crisis in patients with haemolytic anaemia, bone marrow failure, anaemia and hydrops during pregnancy and arthritis similar to rheumatoid arthritis.

Fever in EI: During 5–10-day incubation, children may be asymptomatic or have mild influenza-like symptoms with fevers. The eruption is generally the first and only diagnostic clinical manifestation of the disease, occurring in 100% of cases. It starts on the face with a "slapped cheeks" appearance, with nasal sparing, resembling scarlet fever. The rash spreads to the trunk and extremities in 1–4 days after the onset of the facial rash. The rash is erythematous maculopapular and tends to assume a reticular or lacy pattern, which last for 4–6 days. Fever is observed in about 23% of cases. Common associated clinical findings are pruritis, arthralgia/or arthritis (mainly in adults) and headache. Encephalitis is a very rare complication.

5.10.5 Exanthema Subitum (ES)

ES is a common self-limiting illness caused by human herpes virus 6 (HHV-6) that was identified in 1988. HHV-7 can also cause ES. The virus is a major cause of febrile illness with viraemia and a high temperature (mean 39.7 °C). Sometimes the virus can cause febrile seizures, an inapparent infection without fever or a rash without fever or fever without any focus. HHV-6 is implicated in drug-induced hypersensitivity syndrome, multiple sclerosis, chronic lymphocytic thyroiditis and chronic fatigue syndrome.

ES is the most common febrile exanthem in children under the age of 3 years causing up to 20% of all febrile illnesses. Approximately 30% of children develop this disease eventually. Ninety percent of all cases occur in children aged 6–24 months. HHV-6 stimulates the secretion of pro-inflammatory cytokines including IL-1β, IL-15, TNF-α and interferon.

Before the onset, children may have a short period of irritability and malaise. Onset of fever is abrupt (sometimes triggering a febrile seizure) and characteristically continuous (or less commonly intermittent), often as high as 40–41 °C. The fever persists for 3–4 days in about 75% and for 5–6 days in the remaining 25%. There is usually no focus to explain the presence of fever except often a mild pharyngitis, suboccipital or posterior cervical lymphadenopathy. The temperature usually drops by crisis over a period of a few hours, coinciding with the appearance of the rash (Fig. 5.3). The rash appears predominately on the neck and trunk, lasting 24–36 h. Characteristically, the child becomes well and afebrile when the rash erupts.

When fever is intermittent, the temperature is normal or slightly elevated in the morning, only to rise to 40–40.5 °C by early evening. Fever may fall by lysis over a period of 24–36 h.

Laboratory findings commonly show leukocytosis of 12,000–20,000 with a slight increase in neutrophils.

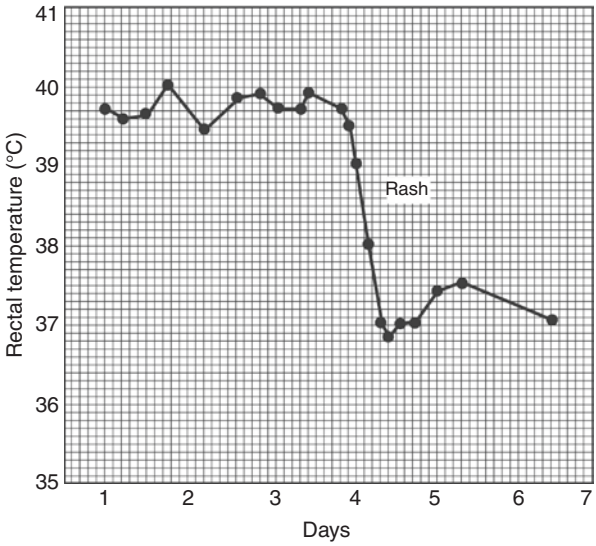

Fig. 5.3 Continuous fever pattern seen in erythema subitum, with a drop in temperature by crisis

5.11 Tropical Diseases

5.11.1 Tuberculosis

Tuberculosis is a major cause of morbidity and mortality throughout the world. Although reported cases have declined, particularly in developed countries, about one million children still develop TB each year, and about 210,000 die because of its complications [26]. Children acquire the infection from adults who have active disease and are expectorating tubercle bacilli. Children themselves are non-contagious. Therefore every effort should be made to identify the adult source for eradicating the source.

Neonatal TB occurs through transmission of infection from mother to infant via the placenta or amniotic fluid. Neonates present with feeding difficulty, failure to thrive, jaundice, respiratory distress or hepatosplenomegaly. Fever is usually absent. Chest X-ray shows bronchopneumonia. The disease often runs a fulminant course with rapid multiplication of tubercle bacilli and minimal giant cell formation.

Older children often experience typical reactivation tuberculosis with classical symptoms of low-grade fever (38–38.5 °C), night sweats and cough. Radiologically, a parenchymal lesion is usually not visible, but hilar adenitis is prominent and may cause compression of the adjacent soft bronchus, causing wheezing and non-productive cough. With increased compression, or following perforation of an infected lymph node into the bronchus, segmental atelectasis may ensue. Other presentations are erythema nodosum, phlyctenular conjunctivitis (as a result of hypersensitivity reaction) or TB pneumonia, which resembles radiologically bacterial

pneumonia with high fever, cough and dyspnoea. Haematogenous disseminated TB may cause miliary TB in children <3 years and within 2–6 months of infection. The illness can be either acute or more often indolent and prolonged with spiking fever found in about 75% of cases. Associated symptoms include anorexia, weight loss, night sweats and dyspnoea. Ophthalmoscopy may detect typical choroidal tubercles in the retina.

Extrapulmonary manifestations account for about 30% of cases, of which two thirds present with lymphadenitis of cervical lymphadenitis, followed by TB meningitis.

The diagnosis of TB is established by:

- History of contact with an infectious case.
- Symptoms: persistent, unremitting cough, persistent fever and fatigue, night sweating, chest pain and weight loss.
- Identification of the mycobacteria (positive in about 30–40% of cases), from sputum, early morning gastric fluid, pleural fluid, CSF or other tissues or by PCR. Acid-fast smear is positive in 10–20%.
- X-ray findings, often in the form of "unresolved pneumonia", with enlarged mediastinal lymphadenopathy.
- Positive tuberculin test, performed by using 5 tuberculin units of purified protein derivative (PPD). A positive reaction is 5 mm or more induration present after 48–72 h.
- Detection of *Mycobacterium tuberculosis*-specific antigens (IFN-γ release assays).

Fever in TB may occur in the following situations:

- In pulmonary TB, disseminated TB, e.g. miliary TB, and in extrapulmonary TB. Children with combined intrapulmonary and extrapulmonary TB have a higher peak and a longer duration of fever than those with intrapulmonary TB alone.
- As a persistent fever without focus for several weeks and sometimes for several months presenting as pyrexia of unknown origin (PUO).
- In HIV as a coinfection, often present as unresolving pneumonia. This carries a high mortality despite adequate anti-TB and HIV therapy.
- In hypersensitivity to antituberculous drugs (usually appearing between the third and fifth day of treatment). This should be considered in any patient with persistent fever after initiation of therapy. Such a drug reaction should be suspected if the fever becomes higher than it was prior to therapy and when other manifestations of hypersensitivity such as rash or eosinophilia appear.

Drugs used for treatment of TB are shown in the Table 5.16. A 6-month regimen for drug-susceptible TB with isoniazid (INH) and rifampicin and pyrazinamide for the first 2 months followed by INH and rifampicin for the remaining 4 months is recommended. This regimen cures 99% of cases. If drug resistance is possible,

initial treatment should include ethambutol, streptomycin, amikacin or ciprofloxacin. Shorter regimes using four drugs in the initial phase are increasingly being adopted. After commencing anti-TB therapy, fever usually subsides within 1 week and occasionally within 2 weeks of commencing medications. Adverse reactions to drugs include hepatotoxicity (due to INH and rifampicin) and fever mainly linked to pyrazinamide.

5.11.2 Malaria

Malaria is caused by a protozoan of the genus *Plasmodium* transmitted by *Anopheles* mosquitoes. The four species that commonly infect man are *P. malariae* (benign quartan malaria), *P. vivax*, *P. ovale* (benign tertian malaria) and *P. falciparum* (malignant tertian malaria). Whereas *P. vivax* invades mostly the youngest erythroblast and *P. malariae* invades primarily the older erythrocytes in both no more than 1–2% of erythrocytes are infected at a time. *Plasmodium falciparum*, on the other hand, invades all ages of erythrocytes indiscriminately, resulting in a very high infection rate and death. The number of malaria cases and deaths has decreased globally since 2000. In 2013 there were 584,000 deaths and 198 million malaria cases. Over 50% of childhood deaths in many parts of Africa are attributed to malaria [27].

Patients with *P. falciparum* infection have elevated tumour necrosis factor-alpha (TNF-α), soluble interleuin-2 (IL-2) receptors and natural killer cell activity but a decrease in the CD4:CD8 lymphocyte ratio. The level of TNF correlates with the severity and mortality rate in patients with this infection. Changes in the TNF also correlate with the rise and fall in temperature during *P. vivax* paroxysms.

Infected children present with fever, lethargy headache, cough anorexia, nausea, vomiting, diarrhoea, abdominal pain and dehydration. Physical examination reveals splenomegaly (detected in almost 100%) and commonly hepatomegaly. Nephrotic syndrome may occur with *P. malariae* infection. The presenting clinical signs of cerebral malaria are severe headache, irritability, delirium, coma, hyperpyrexia, convulsion and meningism.

Relationship between malaria and fever: There is a strong positive correlation between malaria and fever. Malaria is a major cause of fever, occurring in virtually 100% of cases. Out of 11,480 febrile children younger than 5 years of age from Nairobi, Kenya, 22% had malaria [28]. Classical periodicity of fever may not occur in children during the first few years of life, rather intermittent, continuous or remittent patterns may all occur. In endemic areas, malaria is often diagnosed and empirically treated based on the presence of fever alone.

A child with fever caused by malaria may present with:

- A typical tertian paroxysm (*P. vivax* and *P. ovale*) in a nonimmune child with shivering and rigor (usually in the afternoon or evening), lasting 1–2 h. The skin is cold and pale. The next stage is marked by high fever, up to 41 °C, lasting 2–4 h. The skin is dry and warm and the patient feels hot and has usually head-

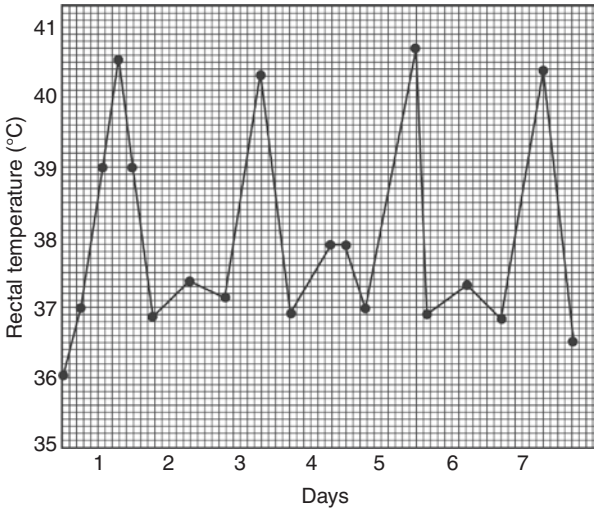

Fig. 5.4 Febrile cycle seen in tertian malaria caused by *Plasmodium vivax* infection

ache. The last 2–4 h are characterized by a drop in body temperature to normal with sweating. In tertian infection, the paroxysm recurs at 48 h intervals (Figs. 5.3 and 5.4), while in quartan infection the paroxysm recurs at 72 h intervals (Fig. 5.4). Early in the infection with P. falciparum the fever may be irregular or continuous. A significant correlation exists between heavy parasitaemia of 2% or greater and high-grade temperature.

- Febrile seizure (FS). Malaria is the most common cause of FS worldwide.
- Blackwater fever, a state of acute intravascular haemolysis accompanied by haemoglobulinuria, as a complication of P. falciparum.
- Human parvovirus B19 infection, adding to the severity of anaemia. The virus is highly erythrotropic, infecting erythroid progenitor cells.
- Complication of malaria, e.g. pneumonia or anaemia.
- PUO, with fever as the only sign of malaria without anaemia or splenomegaly.
- Recurrent fever months after treatment of falciparum malaria due to relapse.

Diagnosis is easy when children present with typical paroxysms of fever. Definite diagnosis is made by a Giemsa-stained blood smear (thick smear increases the yield). A rapid diagnostic tests (RDTs) can be obtained by utilizing ribosomal ribonucleic acid (rRNA) of the parasite. Laboratory findings include anaemia (Hb: 5–11 g/dL), leukopenia, thrombocytopenia, hyponatraemia and hypoglycaemia.

Therapy: Hospitalization for any child with suspected or confirmed malaria is always indicated to assess severity and extent of severity. Paracetamol is commonly used for fever management. Paracetamol has been reported to prolong parasitaemia although the evidence for that was found to be insufficient. Chemoprophylaxis and therapy are shown in the Table 5.17. Chloroquine remains the treatment for choice for benign malarias while quinine is given for falciparum malaria. Children receiving iron therapy may be at increased risk of fever associated with severe parasitaemia (see the section of anaemia Chap. 6).

Table 5.17 Drugs used for prophylaxis and therapy of malaria[a]

	Dose	Adverse reaction
Prophylaxis		
Chloroquine	5 mg base/kg/weekly	Retinal damage
Fansidar	125–750 mg (according to the age)	Severe mucocutaneous reaction
Therapy		
Chloroquine	10 mg/kg; followed by 5 mg/kg in 6 h, then 5 mg/kg twice daily for 2 days	Gastrointestinal upset, visual disturbance, rash
Quinine	25 mg/kg/day three times for 10–14 days	Tinnitus
Primaquine	0.3 mg base/kg once daily for 14 days	Methaemoglobulinaemia, haemolytic anaemia (in G6PD)

[a]Treatment of malaria varies considerably around the world and advice about antimalarial drugs will depend upon the location and expert advice

5.11.3 Brucellosis

Brucellosis is primarily a zoonotic infection caused by small, nonmotile, Gram-negative coccobacilli of the genus *Brucella*. There are four important species pathogenic to humans: *B. melitensis* (Malta fever, found primarily in goats and sheep), *B. abortus* (abortus fever, in cattle), *B. suis* (swine) and *B. canis* (dogs). The infection is transmitted to humans through direct contact with infected animals or their products and through consumption of infected milk, milk products or meat. More than half a million cases per year occur worldwide.

The clinical features of brucellosis depend largely upon the infected species of organism. Infection with *B. melitensis* produces more severe symptoms and signs than other species. Fever is usually present with nonspecific symptoms of migratory arthralgia, myalgia, anorexia and sweats at night. Hepatosplenomegaly and cervical adenopathy are common findings.

Fever manifests in almost every patient (90–100% of cases) as:

- Undulant fever rising insidiously over the course of 1–3 weeks with temperature rising to reach 39–40 °C then falling like a wave (Fig. 5.5) to remain normal for 10 days before rising again.
- A remittent pattern, suddenly with chills, rising to a peak of 40.5 °C in the afternoon and falling to a normal level at night.
- Pyrexia of unknown origin (PUO), particularly in endemic areas.

Complications include spondylitis, osteomyelitis, granulomatous reaction of the eye, meningitis or meningoencephalitis. *Brucella endocarditis* is rare and may be responsible for the majority of death due to the disease.

Laboratory findings include anaemia, leucopenia, lymphopenia and raised liver enzymes. The diagnosis is established by positive culture of brucella organisms from blood or bone marrow aspirate or positive serological tests (agglutination titre of >1:80), IgM by ELISA or PCR.

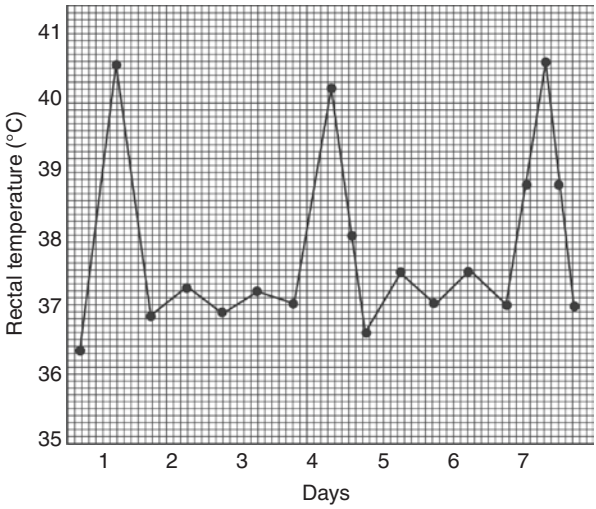

Fig. 5.5 Febrile cycle seen in quartan malaria caused by *Plasmodium malariae* infection

Therapy: The best option is a combination of doxycycline and rifampicin for 3 weeks with or without gentamicin. Rifampicin has also been used successfully in combination with streptomycin in the treatment of *Brucella endocarditis*.

5.11.4 Lyme Disease

Borreliosis includes both relapsing fever and Lyme disease (LD). LD is a multisystem inflammatory disease caused by the spirochete *Borrelia burgdorferi*. It is transmitted by the deer tick (*Ixodes dammini*). LD is the most common vector-borne illness in the USA. *B. burgdorferi* is a potent inducer of IL-1 from peripheral blood mononuclear cells. Lyme disease has been divided into three stages:

- The first one consists of a flu-like illness with a characteristic annular skin rash (*Erythema migrans*), which develops at the site of the tick bite in approximately in two thirds of patients. Antibiotics at this stage may prevent subsequent stages.
- The second stage follows 2–12 weeks after the tick bite and is characterized by disseminated infection causing aseptic meningitis and cranial neuritis (most commonly presenting as facial palsy) and carditis (most commonly presenting as atrioventricular block or myocarditis).
- The third stage is characterized by oligoarticular arthritis and acrodermatitis chronica atrophicans from 6 weeks to 2 years after the tick bite in 50–80% of patients.

Macrophages and B cells produce both pro-inflammatory and anti-inflammatory cytokines, particularly IL-1 and IL-6. Interleukin-1 and IL-1 receptor antagonist, both produced by monocytes and macrophages, may influence the course of arthritis. High concentration of IL-1 receptor antagonist and low concentration of IL-1

may indicate rapid resolution of arthritis, whereas the reverse pattern of cytokine concentration may indicate recovery.

Fever is often an early sign of the disease, appearing within 18 h of the bite. It occurs with other flu-like manifestations. Fever is usually intermittent and low-grade and has been reported in about 50% of children. Fever, however, can be as high as 40 °C and persistent, which can cause pyrexia of unknown origin (PUO). Approximately 1:80 patients present with PUO defined as fever that lasts at least a week during which fever is present in most days and the diagnosis is not clear after 1 week of intense investigation (Chap. 1). There is no pattern of fever in LD but it can be recurrent.

Diagnosis of LD depends on characteristic clinical features, in particular the appearance of erythema migrans. PCR may detect *B. burgdorferi*. Specific IgM antibodies against *B. burgdorferi* appear 3–4 weeks after the infection and peak after 6–8 weeks. Specific IgG antibodies usually become detectable in the second month of the illness. Both IgM and IgG can be detected by ELISA test.

Therapy: Uncomplicated cases of LD are treated with oral penicillin or amoxicillin divided into three doses for 21 days. For children older than 12 years, doxycycline twice daily for 21 days or tetracycline for the same duration is effective. For arthritis, antibiotic therapy should continue for 4 weeks and often includes a third-generation cephalosporin. For meningitis, penicillin G/cephalosporin is given IV for 2–3 weeks.

5.11.5 Leptospirosis

Leptospirosis is a zoonosis, which is probably the most common zoonosis worldwide. It is caused by spirochaetal bacteria of the genus *Leptospira*. Human infections occur through contact with water (e.g. flood water) or soil contaminated with infected animal's urine. The incubation period is usually between 6 and 12 days. The common presentation is characteristically biphasic:

- The primary phase manifests as an influenza-like illness lasting 5–7 days with abrupt onset of chills and fever 39.5–40.5 °C lasting 3–7 days. This phase reflects the presence of leptospiraemia (the septicaemic phase). Fever lasts longer than 5 days in two thirds of cases.
- In the second phase, lasting 4–30 days (the immune phase), specific antibodies begin to appear and fever starts to subside. Leptospira are excreted in the urine. Fever is not prominent in this phase but may occur as a result of aseptic meningitis mediated by antigen-antibody reaction.

A small proportion of patients develop a severe and potentially fatal form (Weil's disease), and patients present with jaundice, haemorrhage, anaemia and multi-organ failure (e.g. acute renal failure). Cases with PUO may occur in about 10% of cases.

Concentrations of various cytokines, such as IL-1β, IL-2, IL-8, IL-10 and TNF-α, are significantly higher in severe and fatal cases compared to those in mild cases.

Laboratory findings include leukocytosis, hyperbilirubinaemia and intravascular haemolysis. *Leptospira* may be cultured from the blood (dark field microscopy), urine and CSF. IgM-Elisa test and PCR confirm the diagnosis.

Doxycycline and penicillin are the treatment of choice. Initiation of antibiotic therapy may precipitate a febrile inflammatory reaction known as Jarisch-Herxheimer reaction, which was originally described in patients treated for syphilis.

5.11.6 Leishmaniasis

Of the three clinical forms of leishmaniasis, cutaneous, mucocutaneous and visceral, only the latter form is associated with febrile episodes. The infection is defined as a person from an endemic area with fever for more than 2 weeks and splenomegaly and confirmed by either rapid diagnostic test (based on rk39 antigen) or bone marrow or splenic aspirate. The disease is transmitted to humans by a bite of infected sand fly *Phlebotomus*. It is the second most fatal parasitic disease after malaria. Coinfection with HIV is not uncommon.

The visceral form (also known as kala-azar, black fever) is caused by the protozoan *Leishmania donovani*. The infection produces the following clinical course:

- Following the invasion of the blood stream, the organisms settle in the reticuloendothelial system and viscera, where they multiply within the cell's cytoplasm despite being engulfed by mononuclear cells. Eventually, the mononuclear cells rupture and release many organisms, which are subsequently engulfed by other phagocytic cells.
- A few months after the initial bite, the patients develop symptoms manifested by varying degree and patterns of fever (see below), emaciation, massive hepatosplenomegaly, lymphadenopathy, profound weakness and pancytopenia. The weakness is mainly caused by anaemia and chronic infection. The pancytopenia is caused by a combination of invading the bone marrow by Leishmania, hypersplenism and autoimmune process. Thrombocytopenia may be severe enough to produce bleeding. Leukopenia causes secondary bacterial infections, such as pneumonia.
- Death occurs within 1–2 years in 80–90% of untreated patients.

All infected children have fever (Table 5.18), which manifests in protean patterns:

- In young children, it increases gradually to a peak within 2 weeks from the onset (40–41.1 °C), becoming then intermittent (temperature returning to a normal level within the same day) or continuous (fever fluctuates by less than 1 °C) and resolving usually by lysis.
- In older children, with more chronic presentation, fever may be continuous initially but is usually low grade.

Table 5.18 symptoms and signs of kala-azar in 100 children, admitted to Baghdad's University Hospital

Clinical findings %	
Fever	100
Splenomegaly	96
Hepatomegaly	91
Abdominal distention	89
Respiratory distress	50
Diarrhoea	13
Jaundice	3
Associated septicaemia	2
Haemorrhage	1

- Classically fever is double quotidian (two spikes within 24-h or a 12-h cycle).
- PUO may occur with a duration between 1 and 18 months, with a median duration of fever of 4–5 weeks.

Pathogenesis and fever are related to the interaction of T-helper cells and various cytokines. INF-gamma, IL-6 and IL-4 are involved during active disease. Dysfunctions of macrophages and T cells lead to severe immunosuppression.

Treatment is presently with miltefosine, orally 2.5 mg/kg/day for 4 weeks. Pentavalent antimony compounds and liposomal amphotericin B are also used. Defervescence usually occurs after a median of 6 days of treatment.

5.11.7 Fever and Malnutrition

It has been estimated that 10.6 million children are still dying yearly, mostly due to pneumonia, diarrhoea, neonatal causes and malaria in sub-Saharan Africa. Malnutrition was an underlying cause in over 50% of the deaths. These children are particularly susceptible to measles and tuberculosis.

Protein-calorie malnutrition (PCM) has been divided into severe (kwashiorkor, marasmus and intermediate cases), moderate severe (nutritional, dwarfing or stunting and wasting) and early (clinically detectable only by anthropometric measurement). In developing countries, the severe form of malnutrition is common as a result of several factors, including severe dietary imbalance. Marasmus results from deficiency of all nutrients, whereas kwashiorkor is due primarily to protein deficiency. In developed countries, PCM may result from debilitating chronic diseases.

Patients with PCM are susceptible to infection and fever for a variety of reasons:

- Delayed mononuclear cell release from the bone marrow.
- Impaired T-cell-mediated immunity, deficiency in circulating levels of the complement system and interferon.
- Reduced secretary IgA (while B-cells and circulating immunoglobulins are normal).
- Impaired acute-phase response.

Fever in a malnourished child is usually the result of infection. Respiratory infections, e.g. pneumonia, TB and intestinal infection, are most common. In severe malnutrition, fever may be absent, and instead hypothermia may occur in response to infection signifying a poor prognosis for survival.

Malnourished children who are febrile are at increased risk of paracetamol-induced hepatotoxicity. Reduction in calorie or protein intake in association with multiple doses of paracetamol may have profound effects on sulphate and glucuronide. The combination of malnutrition and HIV is particularly devastating.

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Fever in Non-infectious Diseases

6

Core Messages

- Fever is commonly found in children with haematological disorders, of which sickle-cell anaemia is the most common.
- An important cause of febrile illnesses in children with haemolytic disorders is infection with human parvovirus B19 (HPV B19).
- Children with cancer are often neutropenic, and any associated fever needs urgent medical attention because of underlying serious bacterial infections, which may be responsible for 50% of deaths.
- Fever in children with cancer may be due either to the disease (neoplastic fever) or to infection. The diagnosis of neoplastic fever should only be considered after exclusion of infection.
- Early administration of antibiotics to children with febrile neutropenia prior to confirming the infection has improved the survival in these children.
- In rheumatology, children with juvenile idiopathic arthritis have the highest incidence of fever. Children may present with persistent fever of unknown origin and are often subjected to intensive investigations, including many trials of antibiotics and occasionally laparotomy.
- In Kawasaki disease, fever has diagnostic and prognostic importance: higher temperature during days 10–13 of the disease and its continuation for more than 14 days are a risk factor associated with coronary involvement.
- Fever following vaccination is common and usually trivial. It is not a contraindication to further doses of vaccines.

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_6

6.1 Haematology

6.1.1 Haemolytic Anaemia

Sickle-Cell Anaemia (SCA)

Children with haemolytic anaemia have the highest number of febrile reactions among all patients with anaemias. SCA is by far the most common single type of anaemia associated with fever.

SCA is an autosomal recessive defect in haemoglobin characterized by:

- Substitution of valine for glutamic acid at position 6 of the beta-chain, leading to production of a defective form of haemoglobin known as HbS.
- HbS that is less soluble than the normal HbA causing RBC to sickle at low O_2.
- RBCs that are too fragile to withstand the mechanical trauma of circulation, leading to haemolysis. Life span of SCA RBCs is 10–20 days; normal RBC life span is 120 days.
- An electrophoresis demonstrating mostly HbS with a variable amount of HbF.

The disease mostly affects those of African ancestry and people of Mediterranean and Middle Eastern descent. About 0.3% of blacks in the USA are affected. Anaemia and crisis do not occur in the heterozygous state (SC trait).

Clinically the disease is characterized by recurrent episodes of painful, vasoocclusive crisis, occurring either spontaneously or precipitated by infection. Clinical manifestations include fever, vomiting, headache, bone pain, splenomegaly, pallor and jaundice. Episodes of fever, symmetrical swelling of the hands and feet (hand-foot syndrome or dactylitis) or abdominal pain is often the first symptoms.

Complications are numerous and life-threatening (Table 6.1):

- Susceptibility to overwhelming bacterial infections, e.g. septicaemia and meningitis, caused primarily by *streptococcus pneumoniae* (400–600-fold increased risk compared to normal children) [1], *H. influenzae* type B (invasive Hib infections have greatly decreased through vaccination) and *Salmonella* osteomyelitis, which presents insidiously with multiple and symmetrical bone involvement. This enhanced susceptibility results from deficient opsonizing and complement activities and defective splenic phagocytic function (functional asplenia), beginning as early as 3 months of age. Without prompt administration of antibiotics, these infections are associated with high mortality.
- Acute splenic sequestration (ASS) may cause circulatory collapse and rapid death as a result of pooling of blood in the liver and spleen.
- Acute chest syndrome (ACS) is a combination of fever, clinical and radiological evidence of pneumonia. It is the most common reason for hospitalization and perhaps mortality. Infection is predominately due to *S. pneumonia*, *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*.

Table 6.1 Summary of the complications of SCA

Complication	Presentation
Infection	Sepsis, pneumonia, osteomyelitis, meningitis
ASS	Enlargement of spleen, drop of haematocrit
Dactylitis	Swelling of the hands and feet, symmetric
Aplastic crisis	Parvovirus B 19 infection, drop of Hb
ACS	Gram- and + bacteria, atypical bacteria, viruses fat emboli
Stroke	Infarct of internal carotid/cerebral arteries
Hepatic	Cholelithiasis, cholecystitis, cholestasis, pancreatitis
Renal	Reduced urine concentration, enuresis, haematuria, chronic renal failure
Priapism	Painful penile erection; its persistence leads to ischaemia and impotence
Leg ulcers	Deep venous thrombosis
Heart/lung	Myocardial ischaemia, pulmonary emboli

ASS acute splenic sequestration
ACS acute chest syndrome
GBD gallbladder diseases

- Recurrent UTIs and vasoocclusive episodes causing medullary ischaemia, with a loss of renal concentrating ability and acidification that may lead to chronic polyuria manifesting as enuresis and renal failure.
- Infection with plasmodium falciparum remains the commonest cause of sickle-cell crisis and a leading cause of death in Africa (although HbS tends to protect against malaria).
- Human parvovirus B19 (HPV B19). This virus selectively infects erythroblasts leading to an arrest of erythropoiesis in bone marrow for 7–10 days. In immunocompetent individuals, this virus is the cause of erythema infectiosum, acute symmetric polyarthritis or hydrops fetalis. In patients with chronic haemolytic anaemia, the virus causes transient erythroblastopenia that manifests clinically as a further drop of Hb. In patients with SCA, HPV B19 is the leading cause of acute erythroblastopenia as well as a cause of mortality. Fever was found in 90% of patients with the infection, followed by pain and ASS [2].
- Priapism, a prolonged and painful penile erection, is often precipitated by sexual activity, with fever and/or dehydration being the next most common precipitating factors.

The majority of febrile episodes in SCA show no evidence of bacterial infection, and the fever is assumed to be caused by vasoocclusive crisis, atypical or viral organisms. Fever caused by vasoocclusive crisis is probably related to an inflammatory response resulting from avascular necrosis of the bone. The elevated temperature in children with only vasoocclusive crisis is:

- Commonly less than 39 °C
- Subsides within 1–2 days following rehydration and analgesia

These episodes tend to increase in number until patients reach their third decades and then the episodes decline. Their frequency was found to correlate with clinical severity of the anaemia and early death in 3578 patients followed at multiple centres in the USA [3]. In contrast, fever caused by infections is:

- Usually greater than 39 °C (especially fever greater than 40.0 °C)
- Unresponsive to rehydration and analgesics
- Associated with a more ill appearance than without infection
- Associated with a higher risk of deaths in children younger than 2 years
- Usually associated with leukocytosis >20,000 and high CRP

Bacterial infections in children with SCA occurred in 38% of febrile children [4]. If the cause of the fever is unclear (vasoocclusive or infection), it is imperative to commence prompt antibiotic therapy. Patients should be informed of the high risk of serious infections and urge them to visit medical facilities promptly for any illnesses associated with fever greater than 38.5 °C (101.3 °F).

Laboratory findings during vasoocclusive crisis are characterized by normocytic, hypochromic anaemia (usual Hb 6–10 g, RBC 2–3 million), leukocytosis, thrombocytosis, hyperbilirubinaemia and hyperplastic bone marrow. The marrow may become aplastic during sickling crisis or severe infection.

Management includes:

- Fluid therapy in the form of glucose-saline solution.
- Medications: analgesics (paracetamol and narcotics) are used to control the pain. Aspirin should not be given because of its adverse reactions, including the acidifying tendency. Children with high fever and children who appear seriously ill irrespective of the degree of fever should be promptly treated with IV antibiotics (such as ceftriaxone). Prophylactic penicillin reduces morbidity and mortality. Hydroxyurea, daily orally, reduces the painful crises by 50%. Deferasirox is an effective oral iron chelator to treat transfusional iron overload.
- Transfusion for anaemia. Regular transfusion reduces the risk of stroke and ACS.
- The combined use of polyvalent pneumococcal vaccine and blood transfusions, which are required for serious complications such as acute sequestration syndrome and aplastic crisis. Regular blood transfusion for only anaemia is generally discouraged. Splenectomy may be indicated in sequestration crisis and hypersplenism.
- Allogeneic stem cell transplantation and gene therapy. However, these are not available for the majority of patients.

Homozygous Beta-Thalassaemia (Thalassaemia Major)

Homozygous beta-thalassaemia, the most severe form of the thalassaemia syndrome, is a chronic haemolytic anaemia characterized by a defective production rate of the beta chain of haemoglobin, which leads to hypochromic, microcytic anaemia, with HbF as the predominant Hb.

Clinical features are the consequence of:

- Anaemia with pallor, jaundice, splenomegaly and decreased growth
- Expanded bone marrow, causing thickening of the cranial bones and maxillary hyperplasia
- Transfusional and absorptive iron load, causing cardiomyopathy and liver cirrhosis

Characteristic laboratory findings include hypochromic microcytic anaemia, with a large number of nucleated erythroblasts, target cells and basophilia.

Fever may occur subsequently to complications, including:

- Cardiac, such as pericarditis, lasting a few weeks with a tendency to recur. Patients present with fever, cough, chest pain and dyspnoea. Occasionally, fever is the only presenting sign. There is usually either a friction rub detected clinically or pericardial effusion found by an ultrasound.
- Unexplained fever (range 39–40 °C), associated with severe anaemia. This is often caused by HPV B19. The fever responds to antipyretics and blood transfusion.
- Infections in splenectomized children. Patients are highly susceptible to fulminating bacterial infection, particularly meningitis and bacteraemia, caused by *S. pneumoniae* and *H. influenzae* type B (very rare in immunized children). These infections are more frequent during the first 5 years of life, and therefore splenectomy should be deferred beyond this age. Oral penicillin, pneumococcal and *H. influenzae* vaccines have led to marked reduction in these infections. Bone marrow transplantation after the first year of life is curative and is recommended for children with this disease.

Other Haemolytic Anaemias

Several forms of congenital haemolytic anaemia (erythrocyte enzyme disorders such as glucose-6-phosphate dehydrogenase (G6PD) deficiency, cell membrane structure abnormalities such as hereditary spherocytosis and acquired haemolytic anaemia such as autoimmune haemolytic anaemia) manifest clinically as:

Haemolytic crises during febrile illness are mostly due to HPV B19 infection. The accompanying fever is usually mild and reflects the infection. The antigen that causes the haemolysis is phagocytosed by macrophages, inducing a febrile response. Fever occurs in about two third of cases and may be associated with:

- Warm-autoimmune haemolytic anaemia, with the antibody being directed against the rhesus (Rh) erythrocyte antigen. This antigen-antibody reaction has a maximal activity at 37 °C.
- Cold autoimmune haemolytic anaemia occurring in an idiopathic form, in association with febrile infectious mononucleosis, Hodgkin's disease or underlying collagen vascular disease. The autoantibody agglutinates RBCs at a temperature below 37 °C. In addition to manifestations of the underlying disease, patients have anaemia, with splenomegaly. A positive direct Coombs' antiglobulin test and a high cold agglutinin titre confirm the autoimmune diagnosis.

6.1.2 Iron-Deficiency Anaemia (IDA)

Iron deficiency (ID) is the most common cause of anaemia in children, due to diminished iron intake, decreased absorption or increased iron loss or requirement.

Clinical findings include irritability, tiredness, poor weight gain due to anorexia, glossitis and pica. In advanced cases there may be dysphagia or koilonychia.

Diagnosis is established by the following findings:

- Microcytic and hypochromic anaemia
- Reduced serum ferritin (<10 ng/mL, normal concentration 30–300 ng/mL) and reduced serum iron concentration (<30, normal range 70–140 μg/dL) in association with increased iron-binding capacity (>350 μg)
- Demonstration of a rise in reticulocytes (normally < 1%) and Hb concentration following a therapeutic trial with iron

Although fever is not a common finding in IDA, children may present with fever in the following conditions:

- Common childhood febrile illnesses. In tropical countries, ID is often caused by malaria, hookworm, schistosomiasis or HIV infection. ID may impair the cell-mediated immunity and the bactericidal activity of neutrophils, thus predisposing to infection. Iron supplement may reduce these infections. Conversely, some studies have shown that ID may be an important defence mechanism in preventing bacterial growth (nutritional immunity). For example, the administration of iron to ID children was found to increase their susceptibility to malaria [5]. However, systematic reviews of randomized controlled trials concluded that iron supplement does not significantly increase the risk of overall infection [6].
- Infection by HPV B19. Although this infection mainly affects patients with chronic haemolytic anaemia, patients suffering from decreased production, increased destruction or loss of blood red cells are also at risk of developing aplastic crisis. Patients present with 2–3 days of fever due to viraemia, followed by a sudden onset of anaemia.
- As a rare side effect of iron treatment, along with increased sweating.

6.1.3 Megaloblastic Anaemia

Megaloblastic anaemia is uncommon in children but may occur as a result of:

- Deficient or defective utilization of folic acid (intestinal malabsorption, tropical sprue, long-term anticonvulsant therapy, anti-metabolite such as methotrexate and antimicrobials such as trimethoprim-sulphamethoxazole).
- Increased demand of folic acid, e.g. in chronic haemolytic anaemia.
- Vitamin B12 deficiency, which is less common than folic acid deficiency. Congenital deficiency of the intrinsic factor (a product of parietal cells of the

gastric mucosa that transports the vitamin across the intestinal mucosa) and autoimmune diseases that lead to gastric mucosal atrophy are the main causes of vitamin B12 deficiency.

Clinical signs of folic acid deficiency are those of anaemia. In contrast to vitamin B12 deficiency, neurological manifestations do not occur. Patients with vitamin B12 deficiency may present with glossitis, intermittent diarrhoea and constipation, weight loss and neurological involvement (peripheral neuropathy, ataxia, loss of vibratory and position senses).

Laboratory findings of megaloblastic anaemia include macrocytosis (mean corpuscular volume > 90 beyond the first few days of life), reticulocytopenia and hypersegmentation of the granular leukocytes. The smear shows anisocytosis and poikilocytosis, basophilic stippling of the RBCs and Howell-Jolly bodies (a remnant of the nucleus). Diagnosis is established by low folic acid (serum level < 5 ng/mL) or low vitamin B12 (serum level < 150 pg/mL).

Fever may occur with megaloblastic anaemia. It was present in approximately 40% in one study [7] and 46% in another study [8] of patients with either folic acid or vitamin B12 deficiency. The elevation of temperature was usually minimal but sometimes exceeded 40 °C and was usually associated with a more severe anaemia. No cause for the fever is usually found, and temperature subsides once the patients are treated with folic acid or vitamin B12.

6.1.4 Neutropenia (See Also Fever in Neoplastic Diseases)

Neutropenia, defined as a polymorphonuclear leukocyte (PMN) concentration of less than 1000/mm^3, results from either impaired cell production of the bone marrow or increased peripheral utilization. If the concentration is less than 500/mm^3, the neutropenia is considered severe. About two thirds of cases do not show a focus of infection. The main causes of neutropenia are shown in Table 6.2. The principal risk of neutropenia is infection, e.g. bacteraemia. Table 6.3 lists high- and low-risk factors leading to infection.

Specific symptoms of neutropenia are lacking. Children may present with:

- Painful ulceration of the mouth and perirectal area or recurrent pneumonia.
- Fever (often high with rigors) without a focus of infection (Chap. 2) in about two thirds of cases. Bacteraemia is detected in about a third of cases. Fever can be suppressed by therapeutic medications, such as steroids and nonsteroidal anti-inflammatory agents.
- Rarely hypothermia, which carries a poor prognosis.

Cyclic neutropenia is a sporadic or familial disorder, characteristically recurring every 3 weeks, each episode lasting 3–6 days. The condition is caused by mutations in the gene encoding neutrophil elastase (ELA2). Recurrent bouts of fever accompanying cyclic neutropenia are associated with the appearance of an endotoxin-like

Table 6.2 Main causes of neutropenia

Causes	Diseases
Impaired cell production	
Congenital	Fanconi syndrome, associated with pancreatic insufficiency (Shwachman-Diamond syndrome)
Acquired	
Viral infections	Human herpes-6, rubella
Bacterial	Typhoid and paratyphoid, brucellosis
Antibiotics	Sulphonamides, chloramphenicol
Other drugs	Antithyroid, anticonvulsants, phenothiazines
Autoimmune diseases	SLE
Anaemia	Advanced megaloblastic anaemia
Cyclic neutropenia	(See text)
Storage diseases	Glycogen storage disease
Bone marrow failure	Malignancy, cytotoxic therapy (see next section)

Table 6.3 High- and low-risk factors for infections in patients with neutropenia

High-risk causes of neutropenia	Low-risk causes of neutropenia
• Neutropenia <500 mm^3	• Viral-induced
• Neutropenia >10 days	• Solid tumours
• Defects in humoral or cellular immunity, e.g. low CD4	• No underlying disease
• History of splenectomy	• With normal mucosal immunity
• Bone marrow transplantation	
• Indwelling catheter	
• High fever >39 °C, chills	
• Hypotension or shock	

material in the blood, presumably resulting from the escape of endotoxins across the bowel wall. Prophylactic antibiotics and granulocyte colony-stimulating factor (G-CSF) are effective treatments.

Although endogenous pyrogens responsible for fever induction were thought to originate in the polymorphonuclear cells, patients with marked neutropenia can develop high fevers, suggesting that these endogenous pyrogens are also produced by sites other than neutrophils such as monocytes and macrophages (Chap. 3).

6.1.5 Febrile Reactions to Blood Transfusion

Febrile and afebrile reactions to blood transfusion may occur (Table 6.4):

- Haemolytic reactions of the recipient's or the donor's RBC (usually the latter) may occur during or after the administration of blood or blood products due to incompatibility. An infusion of as little as 20 mL of incompatible red cells can

Table 6.4 Blood transfusion reactions and their management

Reactions	Management
Febrile	
Haemolytic reactions	Discontinue the transfusion and commence plasma expander or normal saline. Mannitol and frusemide may be considered
Nonhaemolytic	Antipyretic (paracetamol), transfusion may continue
Bacterial	Discontinue the transfusion. Antibiotic after BC is taken
Non-cardiogenic	Discontinue the transfusion
Posttransfusion	Prevention through appropriate laboratory tests
Non-febrile	
Urticaria	Antihistamine. Transfusion may continue
Anaphylaxis	Discontinue the blood transfusion

BC blood culture

trigger the haemolysis. These reactions occur in 1:7000 transfusions, causing a mortality of around 10% [9]. The most severe reaction results in intravascular destruction of the donor RBCs in the receipt's plasma. Clinical manifestations include immediate onset of fever, chills, headache, dyspnoea, chest pain and possibly signs of shock. After the acute phase, signs of renal failure may occur in some patients. The most common cause of haemolytic reactions is human error (e.g. mislabelling, mixing up the samples and incorrect identification of blood group) or antibodies against blood group antigens other than ABO or Rh.

- Febrile reactions without haemolysis are most common reactions. One in every 200–500 transfused blood units causes these reactions. These are characterized by chills, fever with a rise of temperature of at least 1 °C within 4 h of blood transfusion (usually within a few minutes) and defervescence within 48 h. Occasionally, headache, shock or cyanosis is observed. These reactions are primarily due to antileukocyte antibodies in the recipient, which react to antigens of transfused WBCs. The resulting antigen-antibody complement complexes may activate recipient macrophages to release IL-1. Cytokines such as IL-6 and IL-8 may also play a role. The use of WBC-reduced blood components is an effective way to prevent these febrile reactions. Premedication with an oral antihistamine and an oral antipyretic agent may also modify these reactions.
- Bacterial febrile reactions could be due to bacterial antigens or endotoxin in the carrying solution or the tubing. The latter complications have been almost eliminated by using disposable transfusion sets. In most blood transfusion services, donor blood is cooled to 4 °C within 6 h of blood collection to minimize bacterial multiplication. Platelet concentrates are most often implicated as a source of bacterial contamination. Fever (in 80%), chills, tachycardia, vomiting, shock, disseminated intravascular coagulation and acute renal failure may rapidly occur. Bacteria (such as pseudomonas) are usually introduced into blood products during collection, processing and transfusion. *Yersinia enterocolitica* is one of the few human pathogens that can grow at 4 °C and may contaminate blood products, but the risk is low. Fever and shock may occur immediately after the infusion has been started. About one third of all patients with this complication die.

- Non-cardiogenic pulmonary oedema occurs in 1 in 5000 transfusions. Donor anti-leukocyte antibodies form complexes with the recipient's granulocytes, which become trapped in the pulmonary vasculature. Clinical symptoms include dyspnoea, chills and fever. A chest X-ray confirms the diagnosis of this reaction.
- Posttransfusion-transmitted infections, such as hepatitis B and C viruses, HIV types 1 and 2, human T-cell lymphotropic virus types 1 and 2, cytomegalovirus, malaria and toxoplasmosis, remain a serious threat to the recipient of a transfusion. In contrast to bacterial contamination, these viral and protozoal infections manifest clinically days to months after the transfusion, and the donor is always the source of infection. Laboratory tests screen most of these diseases, and therefore the chances of contracting one of these diseases are low (about 3 in 10.000 blood transfusions).
- Allergic reactions may commonly occur as a result of hypersensitivity of the patient to various proteins in donor plasma. The reaction is very common with the administration of fresh frozen plasma and may also occur with intravenous IgG infusions. The manifestations include urticaria/pruritus, oedema, dizziness and headache. Anaphylaxis, though a rare reaction, may occur particularly in patients with hereditary IgA deficiency. Common complaints are dyspnoea, chest and abdominal pain and shock. Fever is characteristically absent.

Box 1 summarizes the important aspects of fever discussed in this section of haematology.

Box 1 Summary Points of Febrile Children with Haematological Disorders

- Fever is common in haemolytic diseases, and SCA is the most common single cause of fever among haemolytic anaemias.
- Fever may be the first sign of a serious bacterial infection, such as septicaemia, so it is essential for the parents to know what to do when their child is feverish.
- Although bacterial infections are not confirmed in the majority of cases with SCA, prompt administration of antibiotics is indicated if the aetiology of fever or the presence of vasoocclusive crisis is uncertain.
- An acutely febrile child with a sudden decrease of Hb should be suspected and screened for infection by human parvovirus B19 (HPV B19).
- Fever caused by bacterial infection is usually greater than 39 °C, does not respond to rehydration and analgesics and is associated with an ill appearance and with leukocytosis >20,000 with high CRP. Children younger than 2 years are at particular risk for bacterial infection.
- If the temperature is > 39 °C, the child should immediately seek medical attention. If it is <39 °C for over 24 h, your GP should be consulted.
- If the temperature is < 39 °C and the child is well with signs of an upper respiratory tract infection, a simple antipyretic, e.g. paracetamol, is offered, and the temperature is checked in an hour time. An increase in temperature above the first measurement indicates the need for medical attention.
- If the child is unwell (irrespective of the temperature level) and pale and has a rapid breathing or more than mild pain, medical attention should be sought immediately.

6.2 Neoplastic Diseases

6.2.1 Fevers in Neoplastic Diseases (Febrile Neutropenia)

Fever with or without associated infection is common in oncology patients who are often neutropenic. It is arbitrarily defined as a single temperature measurement exceeding 38.5 °C or a 38.0 °C recorded on two occasions 1 h apart.

In general, the incidence of fever is higher in children than in adults, occurring most commonly with leukaemia and Hodgkin's disease. Fever may either be due to the disease (neoplastic fever) or to infection. The differential diagnosis can be difficult, and therefore the diagnosis of neoplastic fever is only likely after exclusion of infection. Table 6.5 shows the difference between the two causes. Screening tests for infection, such as WBC and CRP, are helpful, particularly if they are highly abnormal.

Most fevers in oncology patients are non-infectious in origin or an infection cannot be confirmed. Neoplastic fever of non-infectious origin may be caused by:

- Cells of certain tumours, e.g. leukaemia, renal carcinoma and Hodgkin's disease, releasing IL-1 spontaneously, which acts upon the hypothalamus to produce fever. The necrosis of tumours may also be pyrogenic.
- Certain neoplasms, which are capable of increasing metabolic rate.
- Complications occurring during the course of the disease, e.g. haemolytic anaemia or haemorrhage into the brain or adrenal glands.
- Psychogenic fever, leading to a mild fever, which is abolished by sedatives.
- Treatment with chemotherapy, e.g. bleomycin, daunorubicin and interferon.
- Irradiation of the tumour mass (radiation fever).
- Blood transfusion (see above).
- An absent or delayed antibody production, leading to persistence of certain viruses in bone marrow. This occurs particularly during chemotherapy. Parvovirus B19 is the classical example of these viruses.

Classically the neoplastic fever is intermittent, as suggested by the German physician Wunderlich in 1856. Sustained, hectic or remittent fevers may also occur. Fever usually does not respond to common antipyretics (such as paracetamol or aspirin), but it does respond to indomethacin or naproxen. Naproxen causes a prompt and complete lysis of neoplastic fever with sustained normal temperature

Table 6.5 Factors that are in favour of either neoplastic or infection fever

	Infection fever	Neoplastic fever
Fever	>39.5 °C	38–39.5 °C
Rigor	Yes	No
Relative bradycardia	Yes	No
Ill looking	Often	Usually nontoxic
Neutropenia	Main cause	No
Response to antipyretics	Yes	No response, but responds to naproxen
WBC, CRP, ESR	Elevated	Elevated to less extent

while receiving this therapy (naproxen test). Naproxen is therefore useful in the differential diagnosis between neoplastic and non-infectious fevers. During the first 24 h of naproxen therapy, patients with lymphoma may develop hallucination and hypotension. Steroid therapy is usually associated with striking but transient antipyretic effect in both neoplastic and infectious fever.

Fevers in patients with cancer are frequently caused by infections, which are the leading cause of death in these children. High fever (>39.5 °C), particularly if it is associated with chills, is suggestive of infection. Factors that increase the susceptibility of oncology patients to infections are:

- Marked and prolonged neutropenia
- Underlying cancer, particularly leukaemia and advanced stage lymphoma
- The use of high-dose chemotherapy (cytosine arabinoside) and stem cell transplantation
- Malnutrition, which affects lymphocyte function, neutrophils, monocyte cells and complement system
- Indwelling catheter or tubes
- Associated defects of humoral- and cell-mediated immunity, causing increased susceptibility particularly to encapsulated bacteria (*S. pneumoniae*, *H. influenzae*, *N. meningitidis*), listeria, salmonella and viruses

Table 6.6 shows the main causes of fever and infection in neutropenic patients.

Patients with febrile neutropenia should be rapidly evaluated and treated with antibiotics without awaiting culture results. Any delay in antibiotic treatment may

Table 6.6 Predominant pathogens causing infections in children with cancer

Gram-positive
• *Staphylococcus aureus*, *S. epidermidis*
• Alpha-haemolytic streptococci
• *Enterococci*
• *Listeria*
Gram-negative
• *Enterobacteriae*, e.g. *E. coli*, *Klebsiella*
• *Pseudomonas aeruginosa*
Viruses
• Herpes simplex
• Herpes zoster
• EB virus
Fungi
• *Candida* species
• *Aspergillus*
Protozoan
• *Pneumocystis carinii*
• *Toxoplasma gondii*

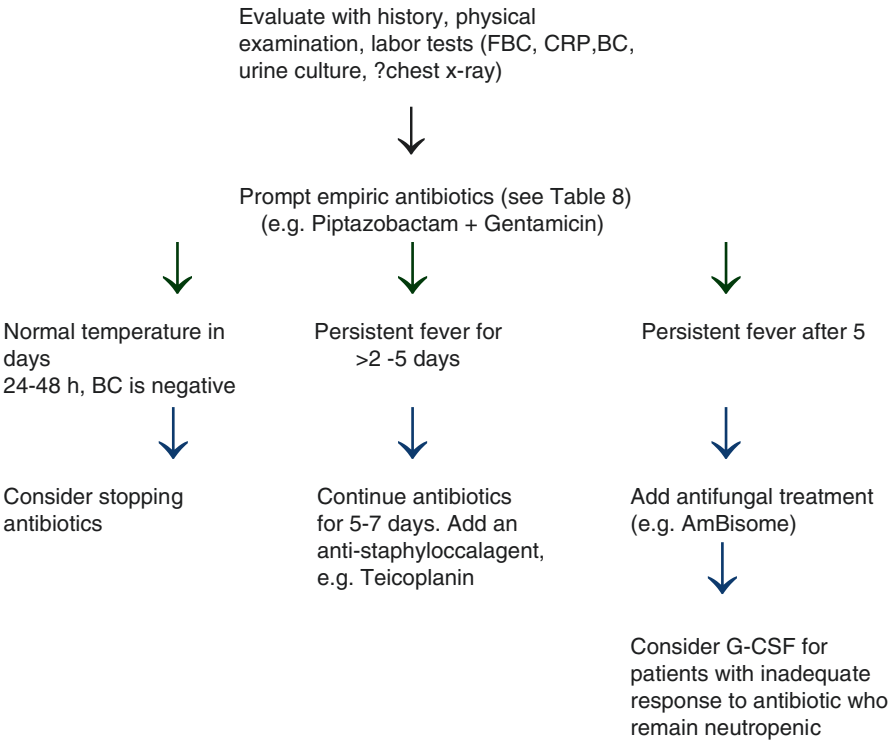

Fig. 6.1 Summary of the management of a febrile child with cancer without a focus of infection

Table 6.7 Commonly used antibiotics for patients with cancer and febrile neutropenia

Drug	Dose (mg/kg)	Frequency	Route
Piperacillin/tazobactam	90	4	IV
Ceftazidime	100–150		IV
Gentamicin	6–7.5	Once daily	IV
Teicoplanin	10	Twice daily for 3 doses, then once daily	IV
AmBisome	1	Once daily	IV

lead to uncontrolled progression of infection and death. Figure 6.1 shows an algorithm for antibiotic treatment. Table 6.7 shows frequently and empirically used antibiotics while waiting for culture results. In children with neutropenia and persistent fever refractory to antibiotics, invasive fungal infection should be considered. Liposomal amphotericin (AmBisome) is an effective treatment.

Granulocyte colony-stimulating factor (G-CSF) has been used to promote neutrophil recovery after cytotoxic chemotherapy or for patients with cancer undergoing bone marrow transplantation. The administration of this growth factor is

frequently associated with the development of fever, which occurs during or shortly after the end of infusion. The fever induction by GM-CSF may be partly mediated through prostaglandin pathways since it is blocked by premedication with ibuprofen. A recent systematic review [10] concluded that the role of treatment with this growth factor remains uncertain. It shortens hospitalization and fever duration, but there was no evidence for a shortened duration of neutropenia.

Febrile non-neutropenic patients with cancer remain susceptible to infection because of associated lymphocyte dysfunction. These patients should be evaluated with CRP, BC, urine and chest X-ray. If they do not have an indwelling catheter, antibiotics are rarely indicated.

Leukaemia

Leukaemia is the most common form of malignancy in children, occurring in about 4 per 100,000 children. Peak incidence occurs in the age group 2–6 years (mean age 4 years). Of the approximately 2000 cases diagnosed in the USA each year, three quarters of the cases are acute lymphoblastic leukaemia. The cause of leukaemia is largely unknown. Ionizing radiation and chemotherapy are the only established causes of leukaemia. Symptoms and signs of leukaemia are shown in Table 6.8. These features are mainly caused by bone marrow infiltration and extramedullary spread.

Findings associated with poor prognosis include high initial leukocyte count, severe thrombocytopenia, lymphoblasts of L2 or L3 subtypes, massive organomegaly and lymphadenopathy, patients younger than 2 years or older than 10 years, CNS involvement at diagnosis and failure to achieve complete remission after 4–6 weeks of induction therapy.

Fever occurs in around 60% in children, being frequently neoplastic in origin. In contrast, the fever of adult leukaemia is largely due to infection. Pyrogenic cytokines involved in fever generation include:

- IL-1 and IL-2 production is elevated in many patients, which may play an important role in the immunological response to the leukaemic cells.
- Tumour necrosis factor (TNF), which is usually high at presentation and to undetectable levels after remission.

Table 6.8 Clinical data in children with leukaemia

Symptoms/signs	%	Laboratory findings	%
Hepatosplenomegaly	68	Leukocytes	
		<10,000	53
Splenomegaly	63	10,000–49,000	30
Fever	61		
Lymphadenopathy	50		
Bleeding (purpura)	48		
Bone pain	23		
CNS involvement	5		

- High IL-6 levels, which significantly correlate with fever and acute-phase proteins such as CRP. IL-6 may stimulate the release of prostaglandin E2 into the blood, which reaches and increases the hypothalamic set point. Il-6, in support of IL-3, may also induce the differentiation and proliferation of leukaemic blast cells.

Fever due to infection is more frequently present during the neutropenic and terminal stages in lymphoblastic leukaemia. In acute myelogenous leukaemia, fever caused by infection in patients with neutropenia occurs in the majority of instances during the induction of remission and during relapse. In both types of leukaemia, infections are responsible for death in at least 50% of children.

Treatment of acute lymphoblastic leukaemia consists of induction therapy with vincristine and prednisolone which induces remission in 85% of cases, while the addition of L-asparginase and/or anthracyclines (especially doxorubicin) increases the rate to 95%. CNS prophylaxis of radiotherapy is no longer recommended; instead five doses of intrathecal methotrexate are given. Maintenance therapy is best achieved with methotrexate once or twice a week and 6-mercaptopurine daily. Intermittent pulses of vincristine and prednisolone added to prolong remission.

Children with neutropenia and fever are best treated with third-generation cephalosporins and aminoglycoside. The addition of gammaglobulin may shorten the duration of fever.

Hodgkin's Disease (HD)

Hodgkin's disease is a malignant neoplasm of lymphoreticular cells of unknown aetiology. Reed-Sternberg cells are the malignant cells of the disease. The cell lines secrete TNF, macrophage, colony-stimulating factor and prostaglandin E2 (PGE2). The currently accepted staging classification of HD is summarized in the Table 6.9.

Most children with HD present with cervical lymphadenopathy, involvement of the mediastinal and/or hilar masses, which may be discovered on routine chest X-ray. Systemic manifestation of HD includes fever, weight loss, anorexia, pruritus and night sweats. Tumour cell lines spontaneously synthesize and release IL-1, TNF, macrophage, colony-stimulating factor and PGE2. Some constitutional symptoms, termed B-symptoms (fever, weight loss and night sweats), are mediated by IL-1.

Fever is a frequent and important manifestation of HD because:

- It occurs in about 30% of cases at presentation and in about 60% during the course of illness. The pattern of fever was found to be remittent in 67%, intermittent in 20% and relapsing in the remaining 13% [11].Only a small number of patients during the course of fever have the relapsing Pel-Ebstein fever (high

Table 6.9 Stages of Hodgkin's disease

Stage	Involvement
I	Single lymph node
II	Two or more lymph nodes
III	Lymph node region
IV	Disseminated involvement of one or more

fever for about 10 days, regularly alternating with an afebrile period of similar duration). This pattern was described in 1887 and was thought at that time to be diagnostic of HD.

- The commonest cause of fever is the disease itself (neoplastic fever). Fever may also due to increased susceptibility of patients to viral, bacterial and fungal infections as a result of impairment of T-lymphocyte-mediated immunity or chemotherapy.
- There is a positive correlation between the fever and the clinical stage of HD. Fever occurs more frequently in the advanced stage owing to increased incidence of infection. As survival is related to the clinical stage of the disease, fever is more frequently encountered at terminal stages (similar to leukaemia).
- The presence of fever at the time of diagnosis was found to be a bad prognostic sign, and febrile patients in stages II b and III lived significantly shorter than afebrile patients [11].

Mild to moderate leukocytosis, lymphopenia, eosinophilia, thrombocytosis, mild to moderate anaemia and increased inflammatory markers (ESR, CRP) are common findings. Investigations include FBC, ESR, CRP, liver and renal function tests, chest X-ray, thoracic CT scan, lymphangiogram (or abdominal CT), biopsy of lymph nodes and liver and bone marrow aspiration (demonstrating Reed-Sternberg cells).

Treatment includes full mantle irradiation (all lymph nodes above the diaphragm) for stages I and II. Such treatment cures 85–90% of patients. A combined regimen of radiotherapy with chemotherapy (mechlorethamine, vincristine, procarbazine and prednisolone (the MOPP programme)) is used for stages III and IV. This regimen cures about 75–50% of patients in stages III and IV, respectively. Others recommend surgical treatment of all patients with a negative bone marrow biopsy in order to limit the toxicity of radiation, such as sterility and the risk of a second malignancy. Patients with HD who receive radiation therapy are also at risk of thyroid disease (hypothyroidism, Graves' disease, thyroid cancer).

Neuroblastoma

Neuroblastoma originates in the neural crest cells of the sympathetic nervous system, mostly from the adrenal medulla. It is the most common extracranial solid tumour of childhood, accounting for 7% of all cases. Over two thirds of cases occur during the first 5 years of life (median age 2 years).

Children may present with the following features:

- An abdominal mass arising from adrenal medulla may extend beyond the midline of the abdomen. An abdominal plain X-ray or ultrasound scan may detect stippled calcification in the adrenal gland. Intravenous urography (rarely used nowadays) may show inferior displacement of the kidney without distortion of the pyelocalyceal system.

- Metastasis into the skull (producing signs of increased intracranial pressure and lytic lesions), tubular bones (producing pain and tenderness), the liver (causing rapidly growing abdominal mass), the orbit (causing proptosis) or the skin as the subcutaneous nodules may occur during the neonatal period.
- Horner's syndrome (meiosis, ptosis, enophthalmia, anhydrosis) may be seen.

Fever may be a feature of these localized tumours. Children with disseminated neuroblastoma, usually involving bone marrow, often present with fever up to 40 °C, irritability and weight loss. Because of the absence of localized features, children may be evaluated for pyrexia of unknown origin.

Diagnosis is suggested by the radiological appearance of the tumour and confirmed by biopsy, by increased levels of catecholamines and their metabolites in the urine (vanillylmandelic acid and homovanillic acid) or by bone marrow aspiration in cases with disseminated neuroblastoma. Increased uptake of Tc diphosphate is often positive before the bony lesions can be detected radiologically.

Young children less than 1 year of age have the best prognosis and can generally be cured regardless of their disease stage. Other children with advanced disease and metastasis have a poor prognosis (less than 20%). The DNA content of tumour cells and the presence of chromosome 1 p abnormalities are also of prognostic value. Mass screening of urine for increased catecholamine is feasible and can further improve the prognosis.

Treatment consists of tumour excision at stages I and II. Localized but unresectable tumours can be treated with a 4-month course of cyclophosphamide and doxorubicin. Treatment with disseminated neuroblastoma may also benefit from this combination, with or without cisplatin and etoposide.

Nephroblastoma (Wilms' Tumour)

This is the second most common malignant retroperitoneal tumour in children, occurring at a rate of 7.5 cases per million children in the USA. The tumour commonly presents as an abdominal mass in a young child (median age 3 years), often detected by a parent (in over 80% of cases). Other presentations include fever (reported incidence 23–50% of cases), haematuria and hypertension (caused by rennin secretion). Cough and dyspnoea may occur due to pulmonary metastasis.

Fever is not a usual part of the symptomatology. However, children may occasionally present with fever, abdominal pain and vomiting. A rapidly enlarging flank mass with hypertension, anaemia and fever may result from massive haemorrhage into the tumour.

Diagnostic features include IV urography, showing characteristic distortion and displacement of the pyelocalyceal system, and abdominal ultrasound scan. A chest X-ray is required to exclude pulmonary metastasis.

The therapy consists of excision of the tumour, radiation therapy and chemotherapy.

6.2.2 Tumours of the CNS

Most children with tumours arising from the CNS present with headache, vomiting, ataxia, visual defects, hemiparesis, double vision, lethargy or irritability. Fever is not a common finding in these patients. Fever, however, may occur:

- In hypothalamic tumours (mostly astrocytoma), which affect the thermoregulatory centres. Hypothermia may also occur. There may be emaciation with marked loss of subcutaneous tissue despite a normal or increased appetite, excessive sweating, diabetes insipidus, precocious puberty and hypogonadism.
- In astrocytomas, which are relatively benign tumours of the CNS and known to produce IL-1, mediating the induction of fever. Within the CNS, IL-1 may be involved in immunological processes and haemorrhage. Despite the production of IL-1, patients with astrocytomas do not often have fever.
- In the highly malignant medulloblastoma. This tumour requires chemotherapy and/or radiation therapy to the brain and spine. As a result, bone marrow suppression (causing anaemia, leucopenia and thrombocytopenia) is common, predisposing to infection and fever production.
- With immunotherapy. This therapy uses several cytokines such as lymphokine-activated killer cells, IL-2 and interferon-alpha (INF-alpha) and INF-beta, to treat intracranial tumours, particularly astrocytomas. These cytokines commonly produce fever as an adverse reaction. A combination of lymphokine-activated killer cells and Il-2 can induce tumour regression by lysing malignant glioma cells while sparing normal brain tissue. The use of this approach is limited owing to the toxicity of IL-2 and the higher success rate of alternative forms of therapy.

Hyperthermia has been used as a treatment. Multiple microwave sources were implanted to raise the patient's temperature above 43 °C. This technique has not gained wide use.

6.3 Rheumatic Diseases and Vasculitis

Fever has important diagnostic, therapeutic and prognostic values and remains a challenge to the paediatricians and rheumatologists despite the advance made in the field of medical diagnosis and technology. Fever can be the initial symptom of a rheumatic disease or its flare, of an infectious complication or therapeutic failure.

6.3.1 Rheumatic Fever (RF)

RF is an inflammatory disease occurring subsequent to infection with group A streptococci. Protein M and lipoteichoic acid (antigenic fragments of Gram-positive bacteria) are the chief virulence factors of this group. Antibodies (e.g. cross-reacting antibodies) may cross-react with cardiac myocytes (causing carditis), joint cartilage

Table 6.10 Accepted Jones criteria of RF

Criterion	Presentation
Major	
Carditis	Tachycardia, gallop rhythm, cardiomegaly, intractable cardiac failure
Polyarthritis	Migratory polyarthritis, often persists for weeks if untreated, but responds in 12–24 h to aspirin
Chorea	Abrupt aimless movement, emotional instability
Erythema marginatum	Transient erythematous rash over the trunk, with later occurring blanching in the centre
Subcutaneous nodules	Non-tender, pea-sized nodules on the extensor surface of the joints
Minor	
Fever, arthralgia, grade 1 heart block (ECG	
In addition to: supporting evidence of recent streptococcal infection	

(causing arthritis) and thalamic and subthalamic nuclei of the CNS (causing chorea). The pathogenic feature is the Aschoff body, which is a granuloma with localized areas of fibrinoid swelling of collagen and perivascular infiltration. An altered response to streptococcal antigens has been implicated in the pathogenesis of RF. These antigens may stimulate the secretion of IL-2 from lymphocytes, which result in an increased natural killer (NK) cell cytotoxicity and to the pathological changes in RF.

The diagnosis is established by criteria of two major manifestations or one major plus two minor criteria in addition to an evidence of increasing titres of antibody to streptococcal antigens (Table 6.10).

Carditis occurs in approximately 90% of children with RF who are younger than 3 years of age and in about 40% of older children. The most common manifestation is an apical murmur of mitral regurgitation. Severe carditis may manifest as cardiomegaly or congestive cardiac failure. If carditis does not occur in the initial attack of RF, the heart is usually not involved in subsequent attacks. A child with carditis may have tachycardia disproportional to the degree of fever (relative tachycardia).

Fever of <39 °C occurs in 70% and > 39 °C in 25%. Fever is one of the minor criteria and is not of great value in assisting in the diagnosis. In addition:

- Fever is present in the majority of cases, but its absence does not exclude RF.
- The fever of RF has no characteristic pattern. Diurnal variations are common, but large daily swings, as seen commonly with rheumatoid arthritis, are not observed. Relative bradycardia is common with conduction defects.
- A high degree of fever is mainly found when the clinical manifestations occur acutely. With a more insidious onset, low-grade fever is detectable only in the afternoon with a tendency to persist for several weeks.
- During the acute attack, fever subsides in a few days even without medication.
- High fever characteristically responds abruptly to aspirin treatment, unlike the fever in rheumatoid arthritis.
- Children with chorea are usually afebrile.

During the acute phase of RF, both the ESR and CRP are high. A rise of ASO-titre above 320 is evident within 1–2 weeks after the streptococcal infection, reaching a maximum level in 3–5 weeks after the infection. A rise of ASO-titre has a more diagnostic value than a positive throat culture. Two-dimensional echocardiography is an important diagnostic tool for evaluation of cardiac lesions.

Bed rest is advisable for febrile children with acute symptoms of RF and should be strict for cases with carditis. Penicillin orally 250 mg qds is used for treatment for 10 days and bd to prevent recurrences of the RF. Salicylate alone is used to treat cases uncomplicated by carditis. Symptoms, such as polyarthritis and fever, respond dramatically to salicylate therapy, and the diagnosis of acute RF is in doubt if patients treated with salicylate are not improved substantially within 48 h. Rebounds of inflammatory activity may occur when aspirin therapy is tapered off or discontinued. Steroids (prednisolone 2 mg/kg/day) are more effective in controlling symptoms of carditis.

The most effective prophylaxis consists of 1.2 million units of monthly benzathine penicillin injection or oral penicillin 250 mg bd. For patients with carditis, this prophylaxis should continue for life.

6.3.2 Juvenile Idiopathic Arthritis (JIA)

JIA indicates a childhood disease (before the age of 16 years) characterized primarily by arthritis, which lasts at least 6 weeks and in which no other cause has been found. The cause of JIA remains obscure. Different arthritogenic stimuli (exogenous infection or endogenous antigens) may activate the immune response seen in this type of arthritis. Antigen-presenting cells (macrophage or dendritic cells) in the synovial membrane ingest process and present these antigens to the lymphocytes, which initiate a cellular immune response and stimulate the differentiation of B-lymphocytes into plasma cells that secrete antibodies. In addition, cytokines (IL-1, IL-6, TNF-alpha and GM-CSF) are present in large quantity in the synovial fluid, which participate in the inflammatory process of the joint, such as increasing production of collagenase and PGE2. Only a small quantity of T-cell products, such as IL-2 and INF-gamma, are present.

IL-1 is a powerful stimulus of bone and cartilage resorption. It induces the acute-phase response and fever and also potentiates chronic inflammation of arthritis by induction of lymphocyte growth factors, such as IL-2 and its receptors. IL-1 receptor antagonist, which is produced by the same cells that produce IL-1 (monocytes and macrophages), is greatly increased in the synovial fluid in patients with JRA. This antagonist competes with IL-1 alpha and IL-1 beta for binding to IL-1 receptors. The relative amount of IL-1 and IL-1 receptor antagonist in JRA may influence whether the inflammation remains active or suppressed.

There are three major presentations of JIA:

- About a quarter of all patients with JIA present with systemic JIA (Still's disease) characterized by high fever and other systemic manifestations. Arthritis may occur during the course of the disease. Males and females are equally

affected with a mean age of 4 years. The rash characteristically is fleeting, salmon-coloured macular or maculopapular, occurring particularly when the temperature is elevated. Other features include lymphadenopathy, splenomegaly, leukocytosis, anaemia, myocarditis and pericarditis.

- The polyarticular onset or adult type occurs in about half of the patients, with an abrupt or insidious arthritis of several joints (more than four joints). Occasionally the patients present with systemic manifestation such as low-grade fever, lymphadenopathy and recurrent rash. This type of onset occurs in females more than males, with a mean age of 12 years. Essentially this presentation is the classical version of JIA.
- In the remaining cases, presentation involves monoarthritis or pauciarticular arthritis. There are further subdivisions of these groups for classification purposes. Knee, ankle or hip joints are usually involved. Systemic manifestations are usually absent or mild. Iridocyclitis is an important sign.

Fever is a prominent feature in Still's disease:

- It has been found in 84% of cases in one report and has been noted in 24–90% of nearly 1000 cases reported in the literature since 1958 [12].
- The commonest pattern of fever is intermittent, often hectic, with a daily rise in the evening, then falling to normal in the morning (Table 6.11). As the fever continues, the pattern may become double quotidian (Fig. 6.2). Other encountered febrile patterns include continuous and periodic fever.
- Chills frequently precede the febrile episodes.
- Fever is usually high ranging from 39.5 °C to 41.2 °C, which is usually associated with the occurrence of rash, generalized lymphadenopathy and splenomegaly, whereas these manifestations are usually absent with no fever. Pericarditis may occur more frequently in the presence of high fever, accompanied by rash and leukocytosis.
- Fever may precede articular manifestations by weeks, months and even years (mean 3.5 months) in about one third of the patients with JIA. Children who present with only fever are considered as having persistent fever of unknown origin (PUO) and subjected to intensive investigations, including many trials of antibiotics and occasionally laparotomy. The appearance of the characteristic rash is an important sign in suggesting the diagnosis.
- The fever of the Still's type of JIA tends to be higher than that of RF, the swings are more pronounced and it does not respond to antibiotics and does not respond promptly to salicylate therapy.

Table 6.11 Variety of fever pattern observed in patients with JIA

• Intermittent, hectic, higher in the evening
• Double quotidian, often follows the above pattern
• Continuous, with little or no variation
• Periodic fever, occurring every few days
• Pyrexia of unknown origin, lasting many weeks

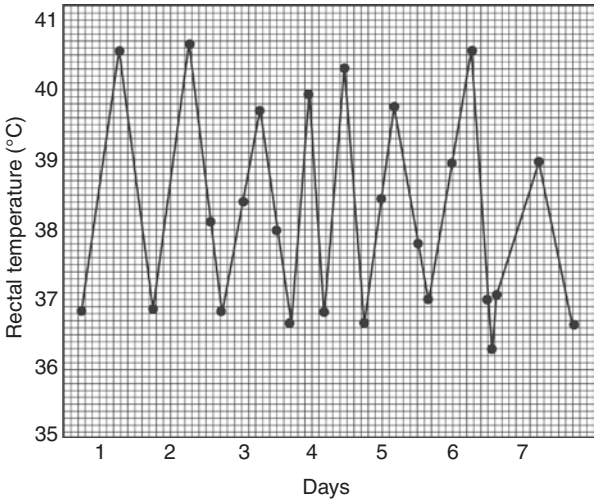

Fig. 6.2 JIA fever pattern

Common laboratory findings include leukocytosis, increased ASO titres (noted in as many as 40%), antinuclear factors (present in 30%) and positive rheumatoid factor (in 10–30%). The concentration of IL-1 beta correlates with clinical and laboratory disease activity.

The basic treatment regimen consists of non-steroidal anti-inflammatory drugs (NSAID), mainly ibuprofen 10 mg/kg or diclofenac 1 mg/kg three times daily. Intra-articular steroid injection is a first line of treatment in oligoarthritis. Immunosuppressive agents (methotrexate, cyclosporine) are often first-line therapy in polyarthritis. Immunomodulators (TNF antagonists) and a supportive programme such as physiotherapy are also used. Antibodies directed against the early phase of the immune response, such as anti-IL-2 receptor antibodies, anti-CD4 antibodies and antithymocyte globulin, have been tried with limited success.

6.3.3 SLE and Other Connective Tissue Diseases

SLE is an acute inflammatory connective tissue disorder of unknown aetiology. Autoantibodies are important for the diagnosis and are responsible for many of its clinical manifestations. Beyond the neonatal age, females account for 90% of cases although during infancy and old age, the male and female prevalence are more similar. The presence of antinuclear antibodies, including anti-DNA, is usually present suggesting that SLE is an autoimmune disease.

Clinical features are shown in Table 6.12.

Neonatal SLE is characterized by cutaneous lesions with or without congenital heart block. Fever is not a sign of neonatal SLE. Manifestations of neonatal SLE are caused by transplacental transfer of maternal IgG antibody to the foetus (particularly anti-Ro antibodies). Mothers of affected children may be asymptomatic at the time of delivery. Approximately 40% of the mothers have active SLE or Sjogren's syndrome.

Table 6.12 Main clinical findings in SLE

Newborn infant (neonatal lupus)	Lupus rash, congenital heart block
Older child's skin	Malar rash, discoid lupus
Mouth	Ulcers
Joints	Non-erosive polyarthralgia/arthritis
CNS	
Renal	Lupus nephritis (nephritic/nephrotic syndrome
Cardiac	Pleuropericarditis
Other	Fatigue, malaise, fever, Hughes (antiphospholipid) syndrome
Laboratory finding	High ESR, normal CRP, lymphopenia, thrombocytopenia, haemolytic anaemia ANA, dsDNA, antiphospholipid antibodies

In older children, clinical features related to fever include:

- SLE may present abruptly with fever, simulating an acute infection, or may develop over months with only episodes of fever, malaise, arthralgia and weight loss.
- Fever, which ranges from moderate to high degree, occurring in about 80–85% of cases and accompanying the facial erythematous rash in about 40% of cases.
- Fever is more common in childhood than adult SLE [13]. A close correlation usually exists between the degree of fever and serum concentrations of INF, rather than IL-4.
- Active SLE is often associated with a raised ESR but normal CRP. This serves as a clue that infection is not a cause of the fever.

Fever, mild to moderate arthritis, pleuropericarditis and lymphadenopathy usually respond to NSAIDs or a low dose of prednisolone. Aspirin in a dose of 80 mg/kg is now rarely used. Interestingly, it frequently causes hepatotoxicity in lupus patients. High fever associated with severe arthritis, active glomerulonephritis, severe thrombocytopenia, severe haemolytic anaemia and neurological abnormalities may require prednisolone (0.5–1 mg/kg/day) for 4–6 weeks before being tapered off. The patients are maintained at the lowest possible dose that will control clinical and laboratory abnormalities. An intravenous bolus of 500 mg of methylprednisolone may be required for initial control of active SLE.

Dermatomyositis is a systemic connective tissue disease, characterized by inflammatory and degenerative changes of the muscles and skin. There is evidence of immune-mediated microangiopathy underlying the pathogenesis of childhood dermatomyositis. The most common finding is a symmetric, dusky erythema of the face and extensor surfaces of the extremities. Periorbital oedema with a heliotrope hue is characteristic. The skin rash may be slightly elevated, smooth or scaly, with associated atrophy and telangiectasia in the V-shaped area of the face and upper chest. In contrast to the adult form, dermatomyositis in children is not associated with malignancies.

Symmetrical proximal muscle weakness may appear insidiously as difficulty in raising the arms above the shoulders or rising from sitting position. A more acute onset occurs in approximately one third of patients.

The fever associated with DM is:

- Generally in the range of 38–39 °C in 50–75% of patients, with 5–10% having high spikes (usually associated with the acute fulminant form of this disease).
- The second most common presenting sign (after muscle weakness) of the disease; its onset often follows the development of the weakness.
- More likely in individuals who have specific autoantibodies for myositis such as the anti-synthetase antibodies [14].

The ESR, CRP and muscle enzymes are usually elevated. Electromyography shows spontaneous fibrillation, positive sharp potentials and polyphasic short potentials during voluntary contraction. Muscle biopsy may show necrosis, phagocytosis and lymphocytic infiltrations.

6.3.4 Other Connective Tissue Diseases

Fever can also be a part of a number of other connective tissue diseases such as Sjogren's syndrome and scleroderma. However, these are not common in childhood.

Progressive systemic sclerosis is characterized by fibrosis, degenerative changes and vascular abnormalities. T-cell hyperactivity may correlate with disease activity. Vascular injury could be mediated by cytokines, including IL-2, IL-4 and IL-6.

Clinically, the most common presentation is tightening and swelling of the extremities, particularly the fingers, Raynaud's phenomenon and polyarthralgia. Subcutaneous calcifications often develop later. Progressive systemic sclerosis is rare in children, and fever is not often present on presentation or during the course of the disease.

6.3.5 Macrophage Activation Syndrome (MAS)

MAS has been reported in association with many rheumatic diseases, connective tissue diseases or malignancy but most commonly systemic-onset JIA (SOJIA). High-grade fever (spiking and intermittent), pancytopenia, encephalopathy, coagulopathy and elevated transaminases are the common presenting manifestations. MAS is a serious complication of childhood systemic inflammatory disorders that is caused by activation and proliferation of T-lymphocytes and macrophages. Measurement of the serum ferritin level may assist in the diagnosis and may be an

Table 6.13 Diagnostic criteria of Kawasaki disease

Fever persisting for at least 5 days plus at least four of the following five:
1. Bilateral, painless conjunctival inflammation without exudates
2. Changes of the oropharynx mucosa, cracking lips, strawberry tongue
3. Acute unilateral non-purulent cervical lymphadenopathy >1.5 cm
4. Polymorphous rash, primarily truncal
5. Changes of peripheral extremities: oedema and/or erythema of hands and feet

indicator of disease activity. MAS is related to the haemophagocytic syndromes and may be fatal. MAS is differentiated from SOJIA by its persistent fever (the fever in SOJIA is quotidian = febrile episode with a spike occurring daily) and the presence of encephalopathy and pancytopenia.

6.3.6 Kawasaki Disease

KD is an acute inflammatory disease that principally affects infants and young children: 85% being less than 5 years of age with a peak incidence at 1–2 years. Initially described by Kawasaki in Japan, where KD is endemic, the condition has been recognized worldwide.

The disease is a form of vasculitis of unknown origin. Speculation as to aetiology ranges from infectious causes to hyperimmune response. The production of most acute-phase reactants, such as IL-1, IL-6, TNF-alpha and CRP, is increased. The circulating B cells are increased, while the T cells are decreased.

The diagnosis is established on criteria shown in Table 6.13. Features include:

- Bilateral conjunctival inflammation without exudates. Anterior uveitis is frequently present, usually beginning shortly after the onset of fever and lasting as long as 2 weeks.
- Mucosal changes, including erythema, cracking and peeling of the lips, strawberry tongue and erythema of the oropharyngeal mucosa.
- Cervical lymphadenopathy with a minimum of one lymph node of at least 1.5 cm in diameter, involvement being usually unilateral without suppuration.
- The rash appearing within 5 days of onset of fever and consisting of morbilliform maculopapular, scarlatiniform erythroderma or an urticarial rash, mainly on the trunk.
- Changes of the hands and feet including erythema and/or firm induration. Characteristic finger and toe desquamation begins in the periungual regions and typically develops 10–20 days after the onset of fever.

Other less specific features include arthritis/arthralgia, aseptic meningitis, hepatic dysfunction, hydrops of the gallbladder, vomiting, diarrhoea abdominal pain and pneumonia.

The most serious features are those affecting the cardiovascular system:

- Myocarditis occurs in about 25% with the findings which include tachycardia, gallop rhythm and non-specific ST-T wave changes on the ECG. Myocarditis generally resolves completely.
- Mild self-limiting pericardial effusion may develop towards the second week.
- Coronary artery aneurysm (CAA) is the major feature affecting the otherwise excellent prognosis. Dilatation may be noted as early as 6 days after the appearance of fever, with the peak of detection by echocardiography at 2 weeks. New lesions are rarely identified beyond 4 weeks after the onset of fever. Coronary artery aneurysms occur in 15–20% of cases. Aneurysms may also occur in other arteries, such as renal, axillary and iliac arteries. The prognosis for resolution of aneurysms is good unless the aneurysm is giant.

Echocardiography is usually performed 14, 21 and 60 days after the onset of illness. Fatality may occur in about 2% and is usually the consequence of myocardial infarction secondary to thrombosis in the coronary artery aneurysms.

Several risk factors associated with coronary involvement include:

- Higher temperature during days 10–13 of the disease, prolonged more than 14 days [15].
- Age under 1 year.
- Anaemia, high platelet count, WBC greater than 30x109/L, prolonged elevated ESR or CRP.
- Aneurysms of other arteries.
- High Il-6 and IL-8 levels may predict coronary artery formation.

Fever is always present in KD and reflects elevated levels of proinflammatory cytokines, particularly IL-1 and TNF, which are mediating the vascular inflammation. KD should be considered in any child with prolonged and unexplained fever. Fever is generally hectic and high at 39–41 °C, spiking and often remittent daily for 5 days to as long 4 weeks. It is minimally or not responsive to antipyretics and remains above 38.5 °C during most of the illness. Untreated fever usually lasts 5–17 days, with a mean duration of 8 days [16].Fever usually resolves within 1–2 days after initiation of aspirin and gammaglobulin treatment.

Laboratory findings are not diagnostic, but characteristically include leukocytosis with increased neutrophils, mild to moderate normocytic normochromic anaemia, almost universally increased ESR and CRP and thrombocytosis, which begins in the second week and peaks at about 3 weeks (mean count 800,000/mm^3). Less characteristic findings include raised aspartate and alanine aminotransferase, increased ASO titre, IgG, IgA and IgM, and pyuria and proteinuria.

Aspirin is recommended in a dose of 30–50 mg/kg/day, divided into four doses. After the resolution of the acute symptoms (usually after 14 days), aspirin dose is reduced to 3–5 mg/kg/day in a single dose for its antithrombiotic effect. Aspirin is continued for 3–4 months if there is no CAA, until CAA resolves (coronary aneurysm <8 mm) or indefinitely if the coronary aneurysm persists (CAA >8 mm). If the patient cannot take aspirin, dipyridamole (persantin) is recommended.

Intravenous immune gammaglobulin (IVIG) plus aspirin reduces the incidence of coronary artery abnormalities. A large single dose of gammaglobulin (2 g/kg body weight) infused over 10 h is more effective than the previously recommended regimen of four smaller daily doses. In addition, children treated with a single-infusion regimen had a lower mean temperature while hospitalized, as well as shorter mean duration of fever. The mechanisms by which gammaglobulin prevents the coronary vasculitis are unclear, but the effect of IVIG in vitro is to decrease the percentage of B cells and increase T cells. If there is no defervescence within 48 h, a repeat IVIG and pulse methylprednisolone 600 mg/m^2 twice daily for 3 days should be considered.

6.4 Unclassified

6.4.1 Postoperative Fever

Postoperative fever is defined as a temperature greater than 38 °C on two consecutive postoperative days or 39 °C on any postoperative day. Fever during the postoperative period is common, occurring in 25–50% of cases. The magnitude of fever is correlated with the extent of the surgery; i.e. minor surgery is rarely associated with fever.

The importance of postoperative fever exists in the possibility of infection, which can lead to death if not properly treated. Serious infection may exist in the absence of fever, e.g. during the neonatal period and in immunosuppressed children.

Early postoperative fever (within 48 h postoperatively) is often caused by the trauma of surgery and involves pyrogenic cytokines, such as IL-1β, IL-6 and TNF-α. IL-6 is the main mediator of acute-phase response and fever.

Infection is the cause of fever in about 10–25% of febrile postoperative patients, usually occurring after 48 h. Fever associated with an ill appearance, the finding of a source of infection (e.g. wound infection) or abnormal laboratory tests such as leukocytosis, elevated ESR or CRP also suggest an infectious source.

Factors that increase the likelihood of infection include:

- Long postoperative stay in hospital
- Major and/or long operation
- Fever commencing on the third postoperative day or later and fever over 39 °C that persists or has a hectic pattern
- The presence of intravascular catheter, the prolonged use of nasogastric or endotracheal tube and indwelling urinary catheter or shunt

Table 6.14 Main causes of postoperative fever

Infectious causes	Non-infectious causes
Wound infection	Dehydration
Peritonitis	Haematoma
Intravenous line infection	Pulmonary atelectasis
Viral infection	Transfusion reaction
Pneumonia	Drug reaction
Urinary tract infection	Warm ambient temperature
Infectious diarrhoea	
Bacteraemia	
Osteomyelitis	

Table 6.14 shows the main infectious and non-infectious causes of postoperative fever.

Physical examination should focus on sites most likely to be the cause of fever, including the operative site, abdomen (for distension, tenderness, absence of bowel sounds), upper respiratory tract for infection and lung auscultation.

The extent of investigation required to elucidate the cause of fever depends on the results of detailed history, such as pre-existing diseases, and findings on examination that may be related to infection. Investigations that are frequently performed in the absence of a clear cause of fever include full blood count, liver function tests, blood and urine cultures, chest X-ray and occasionally viral studies. A CT scan and/or ultrasonography is sometimes required for detecting intra-abdominal abscess.

6.4.2 Fever Following Vaccination

The current UK childhood immunization programme has been revised so that the children should receive:

- Three doses of combined DTaP/IPV/HIB vaccine and two doses of pneumococcal vaccine and meningococcal C vaccine by 4 months
- A booster dose of HIB, meningitis C and pneumococcal vaccine and first dose of MMR by 14 months
- A fourth dose of DTaP/IPV and second dose of MMR by school entry
- A fifth dose of Td/IPV before leaving school

The immune response forms the basis of an adequate vaccination; hence, fever is common. Vaccine, like other antigens, activates antigen-presenting cells (macrophages) to initiate antigen processing and production of interleukins. The subsequent activation of B and T cells initiates the production of memory cells. The persistence of the vaccine as an antigen in lymphoid tissue causes the B cells to become antibody-secreting cells that will continue to produce antibody to protect against infection.

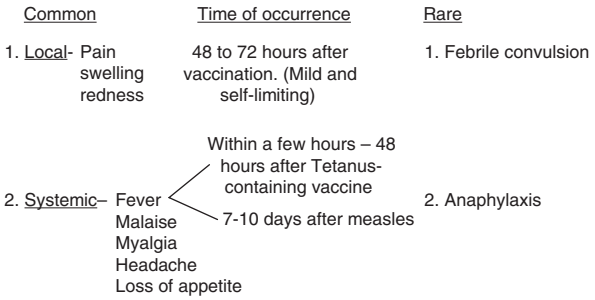

Fig. 6.3 Common and rare complications from scheduled vaccination

Table 6.15 DTP and DT adverse effects following 15,752 and DTP immunization

	DTP %	DT %
Systemic reactions		
Fever>38 °C	46.5	9.3
Fever>39 °C	6.1	0.7
Fretfulness	53.4	22.6
Drowsiness	31.5	14.9
Anorexia	20.9	7.0
Vomiting	6.2	2.6
Local reactions		
Redness	37.4	7.6
Swelling	40.7	7.6
Pain	50.9	9.9

The rate and severity of systemic adverse reactions are:

- Significantly greater with DTP compared with DT vaccinated children (Fig. 6.3, Table 6.15). This suggests that the pertussis component of DTP is the main cause of these reactions. Approximately half of DTP recipients develop fever, usually within 48 h of the vaccination. The temperature elevation is usually mild, ranging between 38 °C and 39 °C and occurs more frequently after the third DTP vaccination. A temperature higher than 39 °C is rare (6% in DTP recipients), which may be caused by unusual susceptibility to the vaccine.
- Significantly lower with acellular pertussis vaccine than with the whole-cell pertussis vaccine [17].

Fever is a common adverse systemic reaction following vaccination. The timing of onset of fever will vary according to the characteristics of the vaccine received, the age of the recipient and the biological response to that vaccine. For example, fever may start within 48 h of tetanus-containing vaccine (DTaP/IPV/HIB vaccines) but occurs 6–11 days after measles-containing vaccine, MMR. Children aged 6 months to 4 years have the highest incidence of fever. Fever occurs:

- With equally frequency after both DTaP and DT vaccines [18].
- Commonly after pneumococcal and meningitis vaccines (10–20%, usually low-grade fever).

- About a week (range 6–11 days) following the first dose of MMR vaccine and lasts 2–3 days. This is due to an effective replication of the vaccine virus in the recipient. Fever is less common after a second dose.

Febrile seizures (FSs) are the most commonly reported neurological event following measles immunization. They occur during the 6–11th day in about 1 in 1000 children vaccinated with MMR. This rate is similar to that reported in the same period after the single measles vaccine. They do not increase the risk of subsequent epilepsy. FSs used to occur following DTP (or pertussis) vaccination, with an incidence of 1: 1750 when the third dose of DTP was given after 6 months of age.

Other more serious but fortunately exceedingly rare adverse reactions include infantile spasms, hypotonic, hypotensive episodes or permanent neurological damage. Considerable controversy exists as to whether the pertussis vaccine is actually the cause of these neurological disasters. Neurological complications, such as encephalitis, Reye's syndrome and Guillain-Barre syndrome, may occur in one per million vaccinated as compared to 1 per 1000 following natural measles. Subacute sclerosing panencephalitis has an incidence of approximately one per two million vaccinated.

Antipyretics before and after the vaccination can reduce the fever and pain associated with vaccination. Parents should receive information on the possibility of fever and advice for reducing it. The advice should include the information that fever following vaccine is not a contraindication to further doses (Box 2 shows summary points).

Box 2 Summary Points of Adverse Reactions Following Vaccinations

- Febrile reaction (fever ≥38 °C) is common in children following vaccination.
- Timing of fever is related to the type of vaccine used and the biological response to that vaccine.
- Fever following vaccination is not a contraindication to further doses.
- Leaflet about common adverse events and their management given to parents at the time of vaccination will help in the management.
- Newer combined vaccines particularly the acellular component of pertussis vaccine are less reactogenic and cause less adverse reactions.

The serious life-threatening events are rare, and the fear of these should not deter clinicians in continuing to advise vaccinations to all children.

6.4.3 Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease of unknown aetiology. The disease most commonly affects the lungs, intrathoracic lymph nodes, the eyes and the skin. Characteristic histological findings are multiple non-caseating granulomas

Table 6.16 Diagnostic criteria of sarcoidosis

• Histological evidence of granulomata and absence of tubercle bacilli	Frequent findings
	Elevated ACE
	Hypercalcaemia
• Microbiology	Hypercalciuria
Negative cultures of sputum and gastric washing	Leukopenia
	Hyperuricaemia
	Hypergammaglobulinaemia
• Radiology	
Bilateral hilar adenopathy or pulmonary infiltration	
• Skin test	
Negative tuberculin test	
Positive Kveim test (in 50%)	

ACE angiotensin-converting enzyme

without necrosis. The lymphocytes within the granulomas are T and B cells with many monocytes and macrophages in various stages of activation.

Children may present with fever, weight loss, arthralgia, erythema nodosum, peripheral lymphadenopathy or loss of vision (due to granulomatous uveitis). Cases are frequently discovered by routine chest X-ray, which classically shows bilateral hilar adenopathy with or without diffuse pulmonary infiltration. Sarcoid granulomas are present in either pulmonary parenchyma or thoracic lymph nodes in 90% of the cases.

Diagnostic criteria are shown in Table 6.16.

Fever has been neglected in studies on sarcoidosis, and some consider fever to be inconsistent with the diagnosis. Studies [19, 20] on fever in sarcoidosis concluded that:

- The incidence of fever ranges between 2 and 21% of cases, usually low-grade fever.
- It may be the only presenting manifestation, which lasts up to several months as PUO. This is particularly common with hepatic granulomas.

A large study [21] of 75 patients with sarcoidosis found that 41% exhibited fever of significant magnitude and duration, often accompanied by night sweats and chills. Fever reached a peak level of 38.3–39.4 °C in 77% of the febrile patients and exceeded 39.4 °C in the remaining. The most common type of fever was intermittent, with a daily rise of temperature and subsequent fall to a normal level.

The pathogenesis of fever in sarcoidosis is obscure. Stimulated monocytes from patients with sarcoidosis may produce more IL-1 than normal monocytes do. As there is expansion of the lymphocytes, particularly T-helper cells, these cells spontaneously release IL-2 and INF-γ that may activate alveolar macrophages to induce fever.

Therapy includes the use of prednisolone 1–2 mg/kg which is the mainstay of therapy. Methotrexate also seems effective.

6.4.4 Familial Mediterranean Fever, FMF (See Also Chap. 1)

FMF is a hereditary auto-inflammatory disease characterized by recurrent brief episodes of fever and polyserositis. Persons of Mediterranean ancestry (Armenian and Sephardic Jews) are primarily affected. The disease also occurs among individuals of Arab descent. Inheritance is autosomal recessive. The disease is caused by a mutant MEFV on the short arm of chromosome 16. The defective protein is termed pyrin (from the Greek word for fire and fever), which is present in neutrophils and normally inhibits the pro-inflammatory IL-1β [22]. FMF is confirmed by genetic testing. The onset of clinical manifestations occurs in 20% prior to the age of 5 years, and 80–90% of cases are seen by the age of 20 years.

Diagnostic criteria are:

- Recurring episodes of fever
- Pain in the abdomen (peritonitis), the chest (pleuritis) or the joints (arthritis)

A prodromal period of 4–12 h is usually present and is characterized by loss of appetite and abdominal pain due to peritonitis. About 6–10 h later, fever occurs and rapid recovery ensues within 24–72 h. Many patients undergo at least one abdominal operation for suspected appendicitis before FMF is diagnosed. Recurrent oral aphthae are often present. Pericarditis occurs in less than 1%. Amyloidosis is the principal long-term complication of FMF.

Fever is a constant finding and it may be present before other manifestations. It is characterized by:

- A level ranging from 38.5 °C to as high as 40 °C
- A duration ranging from a few hours up to 3 days (mean 2 days)
- Recurrences at irregular intervals, sometimes over a course of many months and even years

Cytokines involved in the pathogenesis of FMF include the proinflammatory IL-1β, IL-6, IL-8, TNF-α and INF-γ. Laboratory tests show elevated CRP (or ESR), a mild decrease in serum albumin and increased levels of fibrinogen, haptoglobins and lipoproteins. Proteinuria is the first sign of amyloidosis, and renal or rectal biopsy confirms the diagnosis. Continuous prophylactic colchicine (0.6–1.8 mg daily) is effective in decreasing the frequency of the febrile episodes and preventing the formation of amyloidosis [23].

6.4.5 Hypohidrotic Ectodermal Dysplasia (HED)

This genetic condition results from faulty development of the embryonic ectoderm and its derivatives. The two recognized forms are:

- The anhidrotic form (sex-linked) characterized by inability to sweat (anhidrosis), absent or defective teeth (anodontia or hypodontia) and scanty hair (hypotricho-

sis). Less constant features include depressed nasal bridge, large, deformed ears, wrinkling of the orbital skin, dry skin, lack of body odour, chronic rhinitis, recurrent otitis and hoarseness of the voice.
- The hidrotic form (autosomal dominant) showing similar teeth and hair defects but differing by demonstrating normal sweating, dystrophic nails, recurrent paronychia, hperkeratosis of the palms and soles and nerve deafness. In patients with the hypohidrotic form, sweating is severely diminished or absent owing to a paucity or absence of eccrine glands.

The diagnosis can be confirmed by X-ray of the jaw looking for the absence of unerupted teeth, skin biopsy (showing absence of eccrine sweat glands) and microscopic study of the finger tips for sweat pores.

The main concerns of the anhidrotic and hypohidrotic forms are the:

- Unexplained "fever" (more correctly hyperthermia), which may be considered as pyrexia of unknown origin as the first clue of the diagnosis before the appearance of other signs. The absence of sweating decreases the normal heat loss by evaporation, resulting in recurrent bouts of hyperthermia as high as 42 °C, seizures, brain damage and sometimes death.
- Extreme discomfort in hot weather and the body temperature increases following physical exertion or whenever the environmental temperature rises. Therefore, the condition is much more serious in a hot climate.

The condition is particularly problematic in infants and young children. Older children and adults experience heat intolerance, but they learn to control their body temperature by drinking cold liquids, wetting their skin and clothes and seeking out cool environments. Heterozygote females experience minor heat intolerance.

Children must be kept in a cool environment with a minimum of clothing. Fans and air conditioning are often required. Activities causing sweating (e.g. sport) should be avoided. An external lubricant may be used regularly if the skin is excessively dry.

6.4.6 Sweet's Syndrome (Acute Febrile Neutrophilic Dermatosis)

Sweet's syndrome, first described in 1964 by Sweet [24], is an acute febrile dermatosis which is rare in children [25]. Most patients are female (around 75%). The widely held view is that the syndrome represents a hypersensitivity reaction. The syndrome is characterized by:

- Acute febrile illness (noted in 50% of cases) (body temperature 38.5–39.5 °C)
- Leukocytosis with neutrophilia
- Raised painful plaques on the upper extremities, face and neck
- Characteristic histological proof of these lesions showing dense polymorphonuclear infiltrates of the dermis, with sparing of the epidermis

The syndrome is commonly associated with neoplastic diseases, such as myelogenous leukaemia and immunodeficiency (e.g. HIV infection). Steroid therapy is effective in treating this usually self-limiting disease (if there is no an underlying disease).

6.4.7 Familial Dysautonomia (Riley-Day Syndrome)

This is an autosomal recessive genetic disorder that affects the autonomic, peripheral sensory and motor nerve functions. Ashkenazi Jews are primarily affected. Diagnosis is based on:

- Localization of the gene on chromosome 9 (perinatal diagnosis is possible)
- Presence of cardinal features, including decreased pain perception, absence of tears, failure to thrive, increased sweating, swallowing incoordination (which leads to recurrent aspiration pneumonia), skin blotching, diminished deep tendon and corneal reflexes, mental retardation and hypertension
- Absent fungiform papillae on the tongue
- Absent flare after intradermal injection of histamine
- Abnormal vanillylmandelic acid to homovanillic acid ratio in the urine
- Abnormal histological findings of nerve biopsy showing reduced numbers of small myelinated and unmyelinated axons

In a study of 49 neonates, poor sucking was the most frequent clinical neonatal problem, followed by hypotonia and hypothermia [26]. Decreased temperature perception is a cardinal symptom. Defective temperature regulation results in recurrent bouts of hypothermia alternating with periods of hyperthermia. Before the diagnosis is established, children may present as a case of PUO. Aspiration leads to pneumonia and recurrent fevers. Heat stroke with a temperature of 41.6 °C has been reported [27]. There is no effective treatment and the prognosis is poor.

6.4.8 Infantile Cortical Hyperostosis (Caffey's Disease)

The symptoms of this rare disease (described by Caffey in 1945) usually appear at the age 6–8 weeks of life and are characterized by soft tissue swelling (particularly facial swelling), cortical thickening, fever and irritability. These symptoms are often mistaken as infection. Although the cause is largely unknown, autosomal dominance inheritance has been suggested for some cases of perinatal-onset, which are severe and may be lethal. The condition is otherwise benign, and after several exacerbations and relapses, the affected child undergoes spontaneous regression within the first few years of life.

Fever is usually present in the early stage of the disease. Some affected children may have persistent fever and present as PUO. Temperature is usually low grade but

may occasionally reach 40 °C. Prostaglandins may play a role in fever induction. The symptoms, including the fever, often respond to corticosteroids and indomethacin. Indomethacin is known to inhibit bone formation.

Laboratory findings include mild increase of CRP, ESR, alkaline phosphatase and leukocytosis. Diagnosis is made by plain X-rays. Biopsy confirms the bone changes.

6.4.9 Fever Associated with Teething

The question as to whether teeth eruption causes further symptoms is controversial:

- In the past, serious diseases were attributed to teething. Hippocrates thought that teething caused itching gums, fever, convulsions and diarrhoea. In 1842, teething was the registered cause of death in 4.8% of all infants who died in London under the age of 1 year and 7.3% of those between the age of 1 and 3 years [28].
- Nowadays, while some still believe that teething produces nothing but teeth [29], others believe, as the majority of mothers do, that it is associated with increased body temperature [30].

There is no strong evidence to support claims of systemic signs, including fever, at the time of teeth eruption. The time of tooth eruption may be associated with increased salivation and irritability in children.

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Febrile Seizures

7

Core Messages

- Attacks precipitated by fever can be epileptic or non-epileptic.
- Children with febrile seizures (FS) are not considered to have epilepsy since their seizure only occurs when the child is febrile (acute symptomatic seizure).
- FSs do not constitute a homogeneous entity.
- The cumulative incidence of FSs in most countries is 2–5%.
- FSs usually occur between 6 months and 3 years. They peak at 18 months, and it is rare for their onset to be after 6 years of age.
- FSs are divided into simple and complex. The latter have focal features and/or are prolonged and/or are repeated in the same illness.
- Viral illnesses, particularly human herpes virus–6, precipitate most FSs.
- One third of children who have one FS will have at least one recurrence.
- Recurrent FSs are more likely if the child was young at the time of the first seizure, the fever provoking the first seizure was relatively low and the child suffers from a lot of illness episodes and has a family history of FS.
- The risk of epilepsy following febrile seizures is 7% at 25 years.
- Following one or more FS, risk factors for developing epilepsy are family history of epilepsy, neurodevelopmental problems and complex FS.
- The risk that a child with a FS will have bacterial meningitis is 0–4%.
- Routine brain imaging and EEG are not indicated following a FS.
- Regular prophylactic medication to prevent recurrent FSs is not recommended, but rectal diazepam or buccal midazolam may be useful to stop further prolonged febrile seizures.

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_7

7.1 Introduction and Definitions

The provocation of seizures is one of the best known consequences of fever. Fever can be associated with the provocation of seizures at all ages, in those with or without non-febrile seizures and in those with or without other neurological impairments. Previously, the term FS was used loosely to cover all these situations. However, with time it has come to have a much more restricted use.

Clinical terms include:

- The term "seizure" implies a paroxysmal alteration of neurological function caused by excessive, hypersynchronous discharge of neurons in the brain. Seizures can arise as a consequence of cerebral or non-cerebral mechanisms. The latter include cardiac, anoxic and metabolic causes.
- Convulsions are paroxysmal events involving prominent muscular activity. Previously the term "febrile convulsions" was often used synonymously with FS. This is however discouraged as not all FSs are convulsive.
- Epilepsy implies recurrent, unprovoked afebrile seizures. A seizure provoked by a reversible cause, e.g. fever pr hypoglycaemia, is not epilepsy.
- An epileptic seizure is a clinical event caused by abnormal electrical activity of neurones in the brain. The principal features of epileptic activity are excessive and/or hypersynchronous. Epileptic seizures are protean in their manifestations, ranging from subjective feelings or perceptions to states of altered consciousness and convulsions.
- Febrile seizures: two definitions are in widespread use. The US National Institutes of Health [1] defined a FS as:

> "An event in infancy or childhood, usually occurring between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined cause'. Seizures with fever in children who have suffered a previous nonfebrile seizure are excluded".

The International League Against Epilepsy (ILAE) [2] defined a febrile seizure as:

> "A seizure occurring in childhood after age 1 month, associated with a febrile illness not caused by an infection of the CNS, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures".

Bottom Line

Febrile seizures, even if recurrent, do not constitute a form of epilepsy, despite the seizures having an epileptic mechanism. The main reason for this is that the seizures only occur when the child is febrile. In the same way, a seizure provoked by hypoglycaemic or electrolyte disturbances is not considered epilepsy.

7.2 Epidemiology of Febrile Seizure (FS)

Febrile seizures are most common between 6 months and 5 years with a peak incidence of 18 months of age.

The cumulative incidence or prevalence of FS is:

- 2–5% in Western Europe and the USA
- 8.3% in Japan
- 14% in Guam (Mathai et al. 1968; Stanhope et al. 1972)
- 0.5–1.5% in China

Relevant data concerning the incidence of FS suggest:

- If malaria is excluded, the rates of FS are similar developing, including tropical and developed temperate countries.
- There is no evidence of significant differences between races living in the same country.
- Boys are consistently reported to have a higher incidence of febrile seizures than girls, although this is statistically not significant.
- Febrile seizures peak in the early evening.

Bottom Line

Febrile seizures are the commonest types of seizures affecting children: Between 2 and 5 children in every 100 will be affected.

7.3 Mechanisms Underlying Febrile Seizures

Genetic Factors

Although polygenic, autosomal dominant and autosomal recessive models have been proposed, polygenic inheritance is the underlying mechanism of most cases of FS. Positive family history of FS can be found in 25–40% of cases. Significant higher rates of FS are seen monozygotic twins compared to dizygotic twins.

Epileptic syndromes that may present as FSs with known gene defects are:

- Generalized epilepsy with febrile seizures plus (GEFS+) is characterized by individuals in the same family who have both febrile and non-febrile seizures, in which febrile seizures persist beyond the age of 6 and are associated with generalized or occasionally focal non-febrile seizures. GEFS+ is an autosomal dominant condition in which mutations in four genes have been identified to date. Sodium channels play a crucial role in neuronal membrane excitability. GABA is the principle inhibitory neurotransmitter in the CNS, and GABA-ergic drugs generally inhibit seizures.

- Doose syndrome (myoclonic-atonic epilepsy) is a rare familial type of primary generalized epilepsy affecting children usually 1–5 years of age without neurological deficits before onset and that is often resistant to AED.
- Dravet syndrome is an epileptic encephalopathy characterized by the occurrence of FSs, which are often prolonged and focal and associated with relatively low-grade fever. The onset is usually in the second half of the first year of life followed by polymorphous epilepsy starting in the second or third year of life. Although initial development is normal, with the onset of the polymorphous epilepsy stagnation in development and often a true loss of skills occurs leaving the child with severe learning difficulties. Genetic sodium channel mutation causes the seizures and encephalopathy.

Factors Relating to the Immature Brain

During the period when infants are vulnerable to FS, important maturational changes, such as synaptogenesis are occurring in the brain. Excitatory synaptic neurotransmission mediated by glutamate receptors is central to this. At the same time, important changes are occurring in other neurotransmitter systems, such as the GABA system and in neuromodulatory peptide systems and in voltage-gated ion channels. It is postulated that these changes confer upon the infants brain an enhanced excitability and vulnerability to epileptic and febrile seizures (Jensen & Sanchez 2002).

Fever-Related Mechanisms

Fever involves the expression and then release of pro-inflammatory cytokines mainly from monocytic cells which act as endogenous pyrogens. Microglia and astroglia in the CNS can also produce pro-inflammatory cytokines. Prostaglandins, particularly PGE_2 which is locally produced in the anterior hypothalamus, act as common final mediators for the effect of endogenous pyrogens in controlling the core body temperature set point. A large number of ion channels, including some involved in neuronal excitability, are now known to be highly sensitive to temperature. Pro-inflammatory cytokines as well as inducing the fever which characterizes FS may also directly affect neuronal excitability and hence seizure threshold. Other mechanisms include certain neuronal populations, e.g. those in the hippocampus carry various cytokine receptors.

The Bottom Line

The brain of the infant has a lower threshold for epileptic seizures. There may be many reasons for this. We are about to experience an explosion in our understanding of the molecular basis for febrile seizures.

7.4 The Fever and Its Causes

As there are important differences between rectal and axillary measurements, some authorities require a temperature of 38.4 or 38.5 °C, while others accept 38.0 °C. The rapid rise of fever was previously thought to be precipitating factor for FS, but this is no longer thought to be true. However, evidence for the height of fever is strong. Most febrile seizures occur early in the course of the febrile illness and are sometimes the initial presenting feature. There is strong evidence that children whose initial FS has occurred with a relatively low fever are at significantly increased risk of recurrences.

FS are precipitated by:

- Viruses, particularly viral upper respiratory tract infections, are the commonest precipitants.
  - In Europe and the USA, human herpesvirus (HHV)-6, the cause of exanthem subitum (roseola infantum), is particularly implicated, being responsible for up to a third of initial FS. HHV-7 is to a lesser degree also linked to the precipitation of FS.
  - In Asia and in other countries as well as during epidemics, influenza A virus is a particularly important cause of FS. Other implicated viruses include adenovirus, respiratory syncytial virus and enteroviruses.
- Bacterial illnesses are less frequently implicated in the precipitation of FS, and the rate of bacteraemia in children with febrile seizures is less than 2%. FSs are caused by malaria and dysentery due to *Shigella*, but it seems that this is probably related to the height of the fever and electrolyte disturbances rather than the effect of a specific neurotoxin.
- Vaccinations. Fever is a common reaction to vaccination, and FS may occur after it, particularly with live-virus vaccines such as measles-mumps-rubella (MMR) vaccine. Although MMR is generally well tolerated, the vaccination almost triples the risk of FS in the second week after vaccination. MMR-containing varicella has a higher risk of FS than MMR-separated varicella. There is twofold increased risk of FSs 1–3 days after influenza A (H1N1) vaccination. Diphtheria, tetanus and acellular pertussis and 7-valent pneumococcal conjugate vaccines have small risk of FS. In all vaccines, children less than 2 years of age have an increased risk of FS than those older than 4 years.

There is no evidence that prophylactic antipyretic use reduces the risk of FS [3]. There is a possibility that vaccines may have a significant decrease in postvaccination antibody levels in patients who received paracetamol with or without ibuprofen at the time of vaccination with DTaP alone or with pneumococcal- or H influenza type B-containing vaccines.

Bottom Line

HHV-6 is a particularly common precipitant of febrile seizures. Although there is a risk of increased FS following vaccination, vaccinating children outweighs the risk of not being vaccinated. Prophylactic antipyretics to prevent FSs are ineffective and may be harmful in reducing the postvaccination antibody levels.

7.5 Clinical Features

Presentation of the Febrile Seizures

- FSs are usually convulsive and most are generalized tonic clonic seizures (GTCS) which are either primarily or secondarily generalized. There is an initial tonic phase, characterized by body stiffening, followed by the clonic phase of repetitive, rhythmical jerking of the limbs. A significant minority is tonic or clonic seizure rather than tonic clonic in type.
- Myoclonic seizures: In some children runs of myoclonic jerks have led to GTCS (as is sometimes seen in juvenile myoclonic epilepsy), strongly suggesting that the myoclonic jerks are epileptic in origin.
- Atonic features. Such children may appear floppy and unresponsive, and this may not suggest an epileptic origin to eyewitnesses. The autonomic seizures characterizing Panayiotopoulos syndrome often occur in association with fever or are accompanied by fever as an ictal manifestation [4].This is a relatively common epilepsy syndrome which usually occurs in children of about 4–5 years of age.

Febrile seizures are usually classified as simple or complex:

- Seventy percent of FS are simple (generalized, brief and do not recur within 24 h).
- Thirty percent are complex.

Febrile seizures are complex if they have one or more of the following features:

- They have focal features (including the occurrence of a postictal Todd's paresis).
- They are repeated in the same illness; some definitions stipulate a recurrence within 24 h of the initial seizure.
- They are prolonged. Mostly this is defined as lasting 15 min or longer, although some use a cut of point of 10 min and others of 20 min.

A report [5] indicated that:

- Thirty five percent of initial primarily febrile seizures were complex and that in 16.1% this was because of the presence of focal features.
- 13.8% of seizures were multiple.

- 13.1% of seizures were prolonged (defined as 10 min or more).
- 6.5% of seizures were associated with two complex features (e.g. prolonged and multiple) and 0.7% with three complex features (multiple, prolonged and focal).

Complex febrile seizures are more common in younger children. Children with an initial prolonged febrile seizure who have further febrile seizures tend to have prolonged recurrent febrile seizures as well. Although febrile seizures are defined as prolonged if they last 15 min or more, most are considerably shorter than this. Following febrile seizures the recovery time is usually quite short. Full consciousness is regained within 20 min, compared with over an hour for seizures of other aetiologies.

Bottom Line

Remember – not all febrile seizures are tonic clonic, but if they are, classify them as simple or complex.

7.6 Recurrent Febrile Seizures

Population and birth-cohort studies suggest that about one third of children who have had one febrile seizure will have at least one recurrence, 15% will have at least two recurrences and 10% will have three or more recurrences. Recurrences usually occur within the first year of the initial FS with around 90% occurring within 2 years.

Four main factors have been found to influence the rate or recurrent FS:

- Age at first febrile seizure. A young age at first FS is associated with a greatly increased risk of at least one recurrence. The risk of a recurrence in a child whose initial FS occurred at less than 12 months of age is about 40% and falls to about 20% if the initial FS occurred after 18 months of age (Berg 2002).
- Height of temperature at first febrile seizure. The risk of a recurrence in those children whose first febrile seizure occurred with a fever <40 °C is several times higher than in those with a fever >40 °C [6–8]. This finding has subsequently been confirmed by others, and it seems that the lower the temperature at the initial febrile seizure, the greater the risk of recurrence.
- Illness frequency. Several studies have found a strong association between the numbers of illnesses a child experiences following an initial FS and the risk of recurrent FSs (34, 56, 64, 68). This is also likely to explain reports that recurrent FSs are more common in those attending day-care facilities.
- Family history of febrile seizures. Other factors which are either not associated with an increased risk of recurrence or else of only a modest increased risk or in whom the data are conflicting are sex, family history of epilepsy, type of initial FS (i.e. whether simple or complex), and pre-existing neurodevelopmental abnormalities.

Calculated individualized risks for recurrences [9]:

- A child with none of young age at onset (<18 months), relatively low temperature (<40 °C) and positive family history of FSs had a recurrence risk of 15%.
- A child with one, two and three of the factors had a recurrence risk of 27, 39 and 65%, respectively.

Bottom Line

One third of children who have one febrile seizure will have at least one more. There are well-established risk factors for recurrent febrile seizures.

7.7 Differential Diagnosis

There is an important differential diagnosis to consider:

- Epileptic seizure
- Rigours
- Febrile syncope
- Blue breath holding spells and reflex anoxic seizures
- Toxic delirium
- Temper tantrums
- Paroxysmal non-epileptic events resembling seizures in association with otitis media

In addition epileptic seizures in infancy and young children may be triggered by minor illness without the child being febrile. It has been suggested that this is a distinct condition.

Bottom Line

The most important aspect in the differential diagnosis of a child with seizure is the presence of associated fever (that is FS) or its absence (that is an epileptic seizure). Hence it is essential to measure body temperature at the onset at these events as soon as possible.

7.8 Prognosis

7.8.1 Risk of Epilepsy

Children who have had one or more febrile seizures are at greater risk of developing epilepsy than those who have not. The main factors which influence whether epilepsy will follow FSs are:

- Family history of epilepsy, the type of FS (whether complex or not) and pre-existing neurodevelopmental problems. Following a FS, a child with a family history of epilepsy has a threefold increase in the risk of subsequently developing epilepsy, and the risk is more than doubled following complex FSs.

- The effect of pre-existing neurodevelopmental problems. Children who were neurologically abnormal at birth but later had a FS are at risk of epilepsy estimated to be 55% at the age 25 years compared to 7% in those who were neurologically normal at birth [10, 11].
- Previous complex febrile seizures

The risk of epilepsy following FSs increases as the number of risk factors increases. If only one of family history of epilepsy, neurodevelopmental abnormalities or complex febrile seizures is present, the risk is increased twofold. If two are present, the risk is increased 5–8-fold and if all three are present, 14-fold [12]. The increased risk of developing epilepsy following FSs persists throughout childhood and into adult life. Hence in previously neurologically normal children who had had a febrile seizure, Annegers et al. (1987) found the risk of epilepsy is 2% at 5 years, 4.5% at 10 years, 5.5% at 15 years and 7% at 25 years [13].

An alternative way at exploring the association of FS and epilepsy is to look at subjects with epilepsy and antecedent febrile seizures. Studies have shown that:

- Overall 13–18% of children with new-onset epilepsy have had preceding FSs [14].
- The onset of epilepsy tends to be earlier in those with preceding FSs.
- Both focal and generalized epilepsies are often preceded by FSs.
- Simple FSs are more likely to be followed by idiopathic generalized epilepsies, while complex febrile seizures are more likely to be followed by focal epilepsies [15].

One of the most important unresolved questions in clinical epileptology is whether FSs cause mesial temporal sclerosis and subsequent temporal lobe epilepsy. There are arguments in favour and against such a causal link.

Such a sequence has been shown in animal experiments, and retrospective series of adult patients operated upon for temporal lobe epilepsy have found that 30% of those with mesial temporal sclerosis have had FSs, particularly complex FSs in early childhood. A number of studies have described acute hippocampal abnormalities on MRI scans following prolonged FSs. In one large prospective study, 4 of 44 infants who had had febrile status epilepticus had acute hippocampal abnormalities on MRI, followed by the hippocampal sclerosis [16]. On the other hand, there is a possibility that pre-existing developmental abnormalities in the hippocampus may predispose to prolonged FSs with the potential for then causing further neurodevelopmental damage. In conclusion, mesial temporal sclerosis and hippocampal atrophy are uncommon even after prolonged FS, confirming the good clinical outcome of FS.

Bottom Line

Febrile seizures usually have a good outcome. However, the risk of epilepsy is definitely increased, especially if the febrile seizures were complex.

7.9 Febrile Status Epilepticus (FSE)

Approximately 5% of febrile seizures meet the usual definition of status epilepticus (i.e. a single seizure lasting at least 30 min or a series of seizures lasting at least 30 min without full recovery of consciousness between seizures), and about a

quarter of all episodes of convulsive status epilepticus in children are febrile. HHV-6 and HHV-7 are commonly associated with FSE.

The outcome after febrile status is controversial: There has been no conclusion as to whether febrile status is associated with subsequent neurological problems. In a group of 180 children, around a third of the episodes was focal. There was a strikingly high number (21%) who had pre-existing neurological abnormalities, but none had developed new neurological problems during the relatively short follow-up period [17].

Bottom Line

If a child has had one episode of febrile status (or prolonged febrile seizures), he or she is at significantly increased risk of another prolonged febrile seizure.

7.10 Management

7.10.1 Initial Management

Acute management for a child who is still convulsing on admission includes rapid termination of the seizure, best achieved with intravenous route with either diazepam or lorazepam (the latter has significant advantages) as used in the paramedical, hospital setting or GP surgeries. Intranasal midazolam is as safe and effective as intravenous diazepam; the latter has more rapid action than intranasal midazolam.

The examination includes a thorough search for the source of the fever as an essential part of the examination. Meningitis should be excluded on clinical ground, looking for evidence of raised intracranial pressure and for clues, such as the skin lesions of tuberous sclerosis, which might indicate a susceptibility to epilepsy. Finally, it is important to measure and record the state of consciousness. This is best done using the Glasgow Coma Score.

Laboratory investigation is not always required. Children usually do not require investigation except a urinalysis. However, investigations, such as a full blood count, measurement of the CRP and bacteriological and viral studies are not required in the majority of cases. Other investigations include:

Lumbar puncture (LP): The probability that a child with a febrile seizure will have bacterial meningitis is low. Children usually regain full consciousness quickly after FS. A depressed Glasgow Coma Score 1 h after an apparent FS should be viewed with suspicion. However, signs of meningism may be absent in young children with meningitis, and meningitis can coexist with evidence of a septic focus elsewhere. It is advisable that infants without meningeal signs (irritability, lethargy or bulging fontanelle) who have recovered from their seizure are admitted and reviewed at 4 h. If no deterioration has occurred and the child appears well, LP is considered unnecessary and meningitis is very unlikely. There may be a necessity to consider LP in children a complex febrile seizure. If there are focal neurological signs or papilloedema, empirical treatment with antibiotics and antiviral agents to cover bacterial meningitis and herpes encephalitis should be started and LP deferred until clinical and radiological evidence suggests it is safe to do so.

Routine brain imaging, either by CT or MRI, is not indicated in children with either simple or complex febrile seizures. However, emergency CT scanning would be appropriate following febrile status or in a child who fails to show the expected rapid recovery following a febrile seizure. Neuroimaging would also be indicated if there were persistent neurological signs after a febrile seizure and in some children whose family, perinatal or developmental history suggested the possibility of a structural brain abnormality. MRI will be more sensitive but is likely to require sedation or an anaesthetic.

EEG in children who have had a febrile seizure is often abnormal. Slow-wave activity and even paroxysmal epileptiform abnormalities may be found shortly after the seizure and may persist for some days. However, detecting such abnormalities is not helpful in guiding either management or prognosis, and therefore EEG is not indicated in FS.

Bottom Line

There are no hard and fast rules about which children should have a lumbar puncture after a febrile seizure: Even in those under a year, it may not be necessary if the child has no meningeal signs, recovers quickly to full consciousness and can be observed for a few hours. However, the threshold should be lower following a complex febrile seizure.

7.10.2 Prevention of Recurrences

Antipyretic Measures

As the essential precursor of a febrile seizure is a fever, physicians and paediatric nurses have concluded that antipyretic measures should prevent febrile seizures. Antipyretics continue to be among the most commonly prescribed medications, especially for children at risk of such seizures. Parents are usually advised that the administration of antipyretics to at-risk children may reduce the risk of further convulsions.

Children with high risk of recurrences of FS (complex features of FS, family history of FS, age less than 1 year, low-grade fever at the onset of FS) develop recurrences in at least 80%, while those without these risk factors rarely develop recurrences. Antipyretics are used for both groups of children, suggesting that it is these risk factors, and not antipyretics, which are the crucial determinants of the risk of recurrence. While antipyretics may have a role in improving comfort and general well-being, we should surely not be advocating medication for purposes that have been shown not to work.

Controlled studies of antipyretic medications, given during the original acute illness following a febrile seizure or during subsequent febrile episodes, have failed to demonstrate a preventive effect in children at risk of FS [18]. A systematic review of RCTs concluded that the antipyretics paracetamol and ibuprofen as well as physical methods (e.g. tepid sponging) had no preventive effect on the recurrence of FS [19]. In conclusion, trials have failed to demonstrate any convincing evidence that paracetamol is effective in reducing fever or preventing FS.

Bottom Lines

- There is no evidence that antipyretics reduce the risk of subsequent febrile convulsions even when using around-the-clock prophylactic administration.
- Prescription of paracetamol following FS may provide symptomatic relief including comfort, but should not be recommended to prevent further FS.

Antiepileptic Drugs (AED)

Meta-analysis has shown sodium valproate and phenobarbitone to be effective agents in the prevention of recurrences of febrile seizures, although four children would need to be treated with valproate and eight with phenobarbitone to prevent one febrile seizure [20]. Phenytoin and carbamazepine appear to be ineffective. Until the 1990s continuous prophylactic treatment with antiepileptic drugs was the norm in most countries for children who had had one or more febrile seizure. Now there is unanimity that such treatment is not appropriate, except in exceptional circumstances. The reason for this change is:

- The recognition of the benign nature of febrile seizures
- A lack of evidence that such treatment alters the outcome in the relatively small number of children with febrile seizures who subsequently develop epilepsy
- The increased concern regarding the potential adverse effects of the available prophylactic agents

There are numerous reports of the intermittent use of various drugs during febrile episodes to prevent recurrences. The use of phenobarbitone in this way is considered ineffective, and the data on which to judge the efficacy of sodium valproate and chloral hydrate is very limited. Most interest has centred on the use of benzodiazepines, particularly diazepam given either orally or rectally. The results have been conflicting, although a meta-analysis found that 11.2% of children treated with diazepam to cover febrile episodes had one or more recurrences compared with 17.2% treated with placebo [21]. Given the benign nature of febrile seizures, the difficulty in recognizing the fever before the seizure and the possible risks of such treatment, most authorities do not recommend this treatment.

Many clinicians prescribe benzodiazepines for the immediate treatment of ongoing seizures, whether febrile or afebrile—"rescue medication". There is no consensus as to when this should be offered, but most clinicians only use it in selected cases. These include children who have had one prolonged febrile seizure including febrile status and who are at considerably increased risk of further prolonged FS, including further episodes of febrile status. Medications, which have been used, are:

- Rectal administration of diazepam (0.5 mg/kg/dose) has been widely used. Rectal lorazepam is an alternative. Some advise administration as soon as possible after the seizure has begun others only for seizures lasting longer than a certain period of time, often 5 min.

- More recently midazolam, which can be given bucally, nasally, rectally and intravenously (the last by paramedics or in hospital), has become popular. The buccal and nasal routes have clear advantages to the rectal route in terms of acceptability. Buccal midazolam, 0.5 mg/kg, has been shown to terminate seizures more quickly (median of 8 min) than rectal diazepam, 0.5 mg/kg, (median 15 min) and to have a more sustained action. Therapeutic success (seizure cessation within 10 min, no respiratory depression and no recurrence within an hour) was achieved with midazolam in 56% of cases compared to 27% of cases with diazepam. Families who are given "rescue medication" to stop seizures must have clear instruction regarding how and when to administer the medication, how to monitor their child afterwards and when to seek further help.

Advice to Parents

The trauma of witnessing your child having any form of epileptic seizure is very considerable. Parents and other witnesses require much reassurance. Fortunately, the fact that the vast majority of children with febrile seizures have an excellent prognosis makes this easier than is the case for many other childhood conditions. Topics which should be covered include:

- The nature of febrile seizures – explained in language appropriate for the understanding of the family
- The risk of the child having suffered damage as a result of the initial seizure (no risk, unless it was febrile status)
- The risk of one or more recurrences
- The risk of subsequent non-febrile seizures, including epilepsy
- The effect on cognition and behaviour
- Prevention of further febrile seizures, including use of rescue medication
- First aid measures
- What to tell others, including nurseries and schools

Although a positive approach is justified, it is a mistake to trivialize the event or to underplay the risk of subsequent epilepsy.

The Bottom Line

The most important point of managing children with febrile seizures long term is to reassure the parents and ensure they know what to do should there be a recurrence of FS.

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Hypothermia

8

Core Messages

- In paediatrics, most cases of hypothermia occur neonatally, particularly in the immediate period after birth.
- At birth, the delivery room should be warm. The baby is dried and placed in direct skin-to-skin contact with the mother to prevent hypothermia and facilitate breast-feeding.
- Hypothermia in a child who was previously normothermic is suggestive of an underlying infection.
- Antibiotics should be given to all children with unexplained hypothermia prior to laboratory proof of infection except those with mild early-onset hypothermia.
- In older children, drowning is one of the leading causes of death. Determining accurately the body temperature (rectal or tympanic site) has important clinical implications.
- Hypothermia has potential therapeutic use as neuroprotective agent in newborn infants with hypoxic ischaemic encephalopathy.

Hypothermia

Hypothermia is defined as a core body temperature (pulmonary, oesophageal, rectal, tympanic) of less than 35 °C, resulting from increased heat loss or decreased heat production. This temperature is more than two standard deviations below the mean core temperature. In paediatric practice, most cases of hypothermia occur during the neonatal period.

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_8

8.1 Neonatal Hypothermia

The World Health Organization (WHO) defines neonatal hypothermia [1] as a body temperature below 36.5 °C (97.7 °F) and classifies it as:

- Mild (cold stress): 36.0–36.5 °C (96.8–97.7 °F)
- Moderate: 32–36 °C (89.6–96.8 °F)
- Severe: below 32 °C (89.6 °F)

Neonatal hypothermia is common in infants born in hospitals (prevalence range: 32–85%) and at homes (prevalence range: 11–92%) [2]. Neonatal hypothermia is a major cause of mortality globally, even in tropical countries and warm climates, mostly occurring in winter months. The number of neonatal deaths (less than 28 days of age) was estimated to be 3.1–3.6 million in 2009, being 4.6 million deaths in 1990 [3]. There is no evidence that hypothermia has any beneficial effect immediately after birth or at any time later. Immediately after birth, an infant is at highest risk of dying with 25–45% of neonatal mortality occurring during the first 24 h of life. Low-birth-weight infants account for 60–80% of neonatal deaths. Infections (mainly sepsis and pneumonia) account for an estimated 36% of all neonatal deaths; prematurity-associated problems account for 29%, birth asphyxia 23% and congenital malformations for 19%. While all these causes of death are associated with hypothermia, it is unclear whether infections are the cause or the result of hypothermia.

8.1.1 Physiological Considerations

An optimal thermal environment during the first few days of life is associated with an increased survival rate of neonates, particularly among preterm infants. Such an environment is known as "neutral thermal environment" (NTE), defined as a thermal condition in which the metabolic rate of a resting subject (as evidenced by oxygen consumption) is minimal. NTE is also defined as "the ambient temperature at which the rectal temperature of the infant at rest is between 36.7 and 37.3 °C". This thermal environment exerts minimal demands on the infant's limited thermoregulatory and metabolic capabilities, so that available energy can be utilized for immune response and growth. Examples of neutral thermal environmental temperatures are shown in Table 8.1.

During gestation, the body temperature of the foetus at about 38 °C (equal to the temperature inside the mother's uterus) is on average 0.5 °C above the maternal core temperature. The wet neonate starts losing heat in the first few minutes after birth through:

- Conduction: heat transfer to cooler surfaces in contact with the infant's skin, e.g. table or weighing scale.
- Evaporation: transcutaneous evaporation of amniotic fluid from the infant's skin. This depends primarily on air velocity, environmental temperature and relative humidity.

Table 8.1 Example of neutral thermal environment temperature ranges in infants weighing <2500 g (low birth weight) and >2500

Age	Weight (g)	Temperature range (°C)
0–6 h	1500–2500	32.8–33.8
	>2500	32.0–33.8
6–12 h	1500–2500	32.2–33.8
	>2500	31.4–33.8
24–36 h	1500–2500	31.6–33.6
	>2500	30.733.5
36–48 h	1500–2500	31.4–33.5
	>2500	30.5–33.3
72–96 h	1500–2500	31.1–33.2
	>2500	29.8–32.8
>96 h	1500–2500	31.0–33.2
	>2500	29.5–32.0

- Radiation: heat transfer from the infant's warm skin to cooler surrounding objects, e.g. wall or a window.
- Convection: heat loss from the infant's skin to moving air, which depends on air velocity and environmental temperature.

Factors responsible for the increased heat loss are:

- Large surface area in relation to body mass. The body mass of an infant is about 5% of that of an adult, while his or her surface area is about 15% of that of an adult. The infant's heat loss is three to four times that of an adult.
- Damp skin of the newly born neonate.
- Low subcutaneous fat. Fat insulates against heat loss because of its low thermal conductivity. Vernix caseosa (the white cheesy material coating the skin of neonates) also offers some protection against heat loss.
- Low ambient temperature. In most delivery rooms, the temperature is 22–25 °C, resulting in a continuing fall in body temperature at a rate of 0.1–0.3 °C/min unless measures are taken to prevent it.

Means to counteract hypothermia and produce heat are:

- Non-shivering thermogenesis is an increase in the metabolic rate without shivering, which begins as early as 15 min after birth. The site of non-shivering thermogenesis is brown adipose tissue, which is found predominately in the interscapular area, axillae, perirenal area and around the large vessels in the chest. These areas feel warmer to the touch. Gradually, the brown adipose tissue is replaced by white adipose tissue as shivering becomes the predominant mode of heat production. In contrast to white adipose tissue, the brown tissue is rich in blood and nerve supply, with high mitochondrial content and high metabolic activity, consuming 20 times more oxygen than white adipose tissue. During cold stress, there is increased lipolysis, induced by noradrenaline. Most of the released free fatty acids (FFA) are re-esterified or oxidized, and both of these reactions produce heat. Although shivering, as seen in adults, does not occur in

the newborn infant, muscular activity and restlessness in response to cold have been reported.

- Postprandial thermogenesis is an increase in metabolic rate (range 12–26%) after feeding to meet the metabolic demand of ingestion and absorption. Following feeding of neonates with room temperature formula, their body temperatures usually fall, particularly in preterm infants. This fall in body temperature triggers a metabolic response, which is greater when neonates are fed by cold milk bottles.
- The infant's response to cold, though not fully developed, is still active particularly full-term babies. Although debatable whether a newborn infant, particularly the premature, responds to a cold environment as a temporary poikilotherm (no metabolic increase) or as an inefficient homeotherm (weak metabolic response), newborn infants, including large preterms, are potentially homeotherms (defined as organism capable of maintaining its body temperature at a constant level, above that of the environment, by its metabolic activity). They are capable of vasoconstrictive response, which is followed by vasodilatation during rewarming. High ambient temperatures produce sweating. However, smaller premature infants behave as poikilotherms, requiring an intervention to maintain body temperature.

Factors interfering with the above thermoregulation include low birth weight, infection, hypoxia, hypercarbia, hypotension and the child's nutritional state.

8.1.2 Early-Onset Hypothermia

Hypothermia occurring during the first 3 days of life is common due to certain risk factors shown in Table 8.2. Body temperature is usually mildly to moderately low (temperature > 32 °C). Infants at particular risk include:

- Neonate who are left unattended at birth even for a few minutes or who have not received adequate warmth during resuscitation.
- Preterm infants, those with asphyxia, CNS haemorrhage or brain malformation or those receiving infusion of cold blood for exchange transfusion. Infection is infrequent cause of early hypothermia.

Table 8.2 Summary of risk factors leading to early hypothermia (1–3 days old)

At birth	Cold delivery room, early bathing Drugs used, e.g. hypnotic-sedatives used for the mother Delay in: • Drying the baby • Wrapping • Placing it in contact with mother skin to skin • Initiating breast-feeding
Weight	Low birth weight
Gestation	Preterm, small for dates
Condition	Asphyxia, infection, cerebral haemorrhage
Laboratory	Hypoglycaemia
Socioeconomic	Poverty

Table 8.3 Details of 138 children with neonatal hypothermia [4]

	No		Weight (kg)		Temperature		
Age (days)	Boys	Girls	<2.5	>2.5	Mean	Range	Mortality
1–3	17	10	15	12	32.4	30.0–34.8	1
4–7	18	11	17	12	31.7	22.0–34.6	8
8–14	21	19	26	14	32.0	22.7–34.7 11	
15–21	11	8	11	10	33.3	32.0–34.8	6
22–28	15	8	11	10	30.7	23.0–34.0	9
Total	82	46	80	58			35

The prognosis of early-onset hypothermia is generally good because it is primarily caused by exposure to environmental cooling, and infections are not usually the underlying cause. Therefore mortality is rare. In a report [4] of 138 children with neonatal hypothermia born at home in a warm climate country, there was one death among 27 children (3.7%) with early hypothermia and 34 deaths among the remaining 111 (30% or almost ten times greater) children who were older than 3 days (Table 8.3).

8.1.3 Late-Onset Hypothermia

Hypothermia in older neonates (4–28 days) is less common than the early-onset hypothermia in developed countries, mainly because of provision of thermoprotective care and adequate metabolic response to maintain body temperature that becomes effective from the second or third day of life. In many developing countries, late-onset hypothermia, often with classic cold injury, is common enough to be an important cause of neonatal death, particularly during winter months [5]. Infection and malnutrition, rather than exposure to cold, are the most causes of this late hypothermia in developing countries. Severe infection (the most common cause of late-onset hypothermia) can be overwhelming and lead to a breakdown of the normal physiological response to cold. Therefore, hypothermia in a child who had been previously normothermic is suggestive of an underlying infection. Common bacterial infections causing hypothermia are shown in Table 8.4. Hypothermia may lead to aspiration pneumonia because lethargy causes swallowing reflexes to be more impaired than suckling reflexes. The following investigations should be carried out:

- A chest X-ray to exclude pneumonia.
- LP may be required to confirm or exclude meningitis.
- Serum bilirubin as hypothermia interferes with the ability of albumin to bind bilirubin, thus increasing the risk of kernicterus.
- Blood and urine cultures.

Table 8.5 lists the main symptoms and signs in hypothermic children. Hypoglycaemia is common and may occur in about half of affected children.

Because of the high incidence of infection and its unreliable symptoms and signs of infection, appropriate antibiotics should be initiated at the outset to all these children

Table 8.4 Results of investigation in 138 with neonatal hypothermia [5]

Site of infection	No of	%
Urinary tract infection	30	22
Meningitis	19	14
Septicaemia	30	22
Pneumonia	64	46
Osteomyelitis	2	1
Pneumothorax	16	12
Total no with infection	83	60

Table 8.5 Symptoms and signs of neonatal hypothermia and cold injury

Neonatal hypothermia	
• Body temperature	<35 °C
• General	Refusal to feed, lethargy
• Pulmonary	Shallow and slow respiration, grunting
• Skin	Feels cold to touch
Neonatal cold injury	
• Body temperature	Usually less than 32 °C
• General	Refusal to feed, marked lethargy, feeble or no cry
• Pulmonary	As above, in addition pulmonary haemorrhage
• Skin	Red face, hands and feet, swelling of the soft tissue, pitting oedema, localized hardening (sclerema)
• Intestinal	Vomiting, diarrhoea
• Renal	Oliguria
• CNS	Seizures
• Blood	Haemorrhagic diathesis
• Laboratory findings	Hypoglycaemia, coagulopathy, thrombocytopenia, hyperkalaemia, high creatinine

with late-onset hypothermia without waiting for laboratory proof of infection. The overall mortality rate in infants in developing countries is high. Death may occur subsequent to massive pulmonary haemorrhage due to coagulopathy or cardiac arrhythmia.

8.1.4 Cold Injury

The syndrome is characterized by hypothermia in association with the symptoms listed in Table 8.5. Cold injury was first described in 1889 by Henoch as a case of "oedema in the newborn". In 1957, Mann and Elliot described the full clinical picture of classic cold injury in 14 cases [6]. Body temperature ranged between 27 and 32 °C, and hypoglycaemia was often present. The most important causative factor reported from developed countries has been cold stress (rather than infection) caused by low environmental temperature during cold winter months. Repeated and lengthy exposures to cold were usually required to produce the syndrome. Neonates were predominately affected. The prognosis of children with cold injury is generally worse than that

in children with similar body temperature but without cold injury. Mortality used to be high, ranging between 25 and 60%. Eight out of the 14 children described in this study died. Postmortem findings include pulmonary haemorrhage and pneumonia.

8.1.5 Management of Neonatal Hypothermia

Prevention
Hypothermia can be prevented by:

- Ensuring that the delivery room is warm: 25–28 °C (77–82 °F).
- Drying and wrapping the baby immediately after birth (before the cord is cut) using a warm blanket or synthetic insulating material, such as an aluminized polyester sheath. Simple drying and wrapping the baby reduce the postdelivery heat loss by more than 50%.
- Bathing and weighing should be postponed, no water bottles or hot stones.
- Placing the baby in direct skin-to-skin contact with the mother and covering the baby and mother together. This is particularly important in developing countries where supervision by nursing staff and temperature in the delivery room are often inadequate. The mother and baby should be kept together.
- Putting a warm cap on the baby's head, as much as 25% of heat loss occurs from uncovered head.
- Facilitating breast-feeding within the first hour of life, which prevents hypothermia because of the close body contact with the mother.
- Body temperature from premature and sick babies should be measured at frequent intervals at the axilla.

For babies who are at particular risk of hypothermia (sick or preterm infants), additional measures include:

- Placing the baby in an incubator at a thermo-neutral temperature. Plastic heat shields, double-walled incubators and adequate humidity (around 65%) reduce water loss in low-birth-weight infants. Servocontrolled incubators maintain the surface temperature of neonates at a predetermined level by varying the input of a radiant heat. For naked infants, this is achieved by adjusting incubator heating to maintain an abdominal skin temperature of approximately 36.5 °C.
- The main risk of the servocontrolled device is hyperthermia, which may occur if the probe becomes detached from the infant's skin. They can also mask hypothermia or fever.
- The use of radiant warmers is required if resuscitation or anaesthetic procedure is anticipated. A plastic blanket placed over the baby further reduces evaporative heat loss.
- Routine nursing procedures (temperature measurement, nappy change, changing the probe sites, heel pricking) should be minimized. Whenever possible these should be performed through the portholes of the incubator.

In many developing countries, incubators may not be available. Measures to prevent hypothermia may be achieved in simpler ways by:

- Using electric heaters to produce an environmental temperature of 29 °C and even higher for the smallest babies.
- Maintaining close physical contact with the mother.
- Warming the cot by radiant heat or hot-water bottles, day and night.
- Remembering that lethargy and poor feeding in a baby who feels cold on touch are the earliest manifestations of hypothermia. Mothers should be alerted to these signals and taught to seek medical help early.

Treatment is focused on the following three measures:

- Rewarming, either gradually over an extended period, starting with an ambient temperature of about 20 °C and increasing by 1 °C every 3 h for infants with chronic cold exposure or (the preferred method) rapidly over a few hours, at a rate of 1–2 °C/h. Rapid rewarming is associated with fewer complications and higher survival rates. Rewarming can be accomplished using skin-to-skin contact with the mother, in an incubator (using the maximum air temperature setting), under a radiant heat source in a warm cubicle or using a heated mattress set at 37–38 °C. The latter two heat sources help hypothermic neonates achieve normothermia more rapidly than those treated in incubator. Neonates should be monitored by measuring oxygen saturation, blood gases, blood glucose, clotting factors and body temperature.
- Feeding by nasogastric tube to avoid the risk of aspiration pneumonia. Milk, preferably breast milk, should be warmed to body temperature of about 36 °C. An i.v. fluid containing 10% glucose is indicated not only to correct but also to prevent hypoglycaemia, which is arising from an increase in metabolic demand during the rewarming.
- Treatment with antibiotics. An infection should be suspected in any child with unexplained hypothermia. Those with mild early-onset hypothermia do not usually require antibiotic treatment.

8.2 Hypothermia in Older Children

In contrast to newborn infants, who rely on non-shivering thermogenesis to produce heat, older children utilize both metabolic activity and shivering to generate sufficient heat to maintain body temperature. The body temperature can be viewed as a core surrounded by skeletal muscles. At rest, the muscles provide relatively little heat, but when the core temperature falls below 36 °C, shivering generates considerable heat energy. Skeletal muscles are surrounded by thermoreceptors; these serve as an important regulator of heat exchange. Figure 8.1 shows the basic mechanisms of heat production in response to cold.

Table 8.6 shows the main causes of hypothermia in this age group.

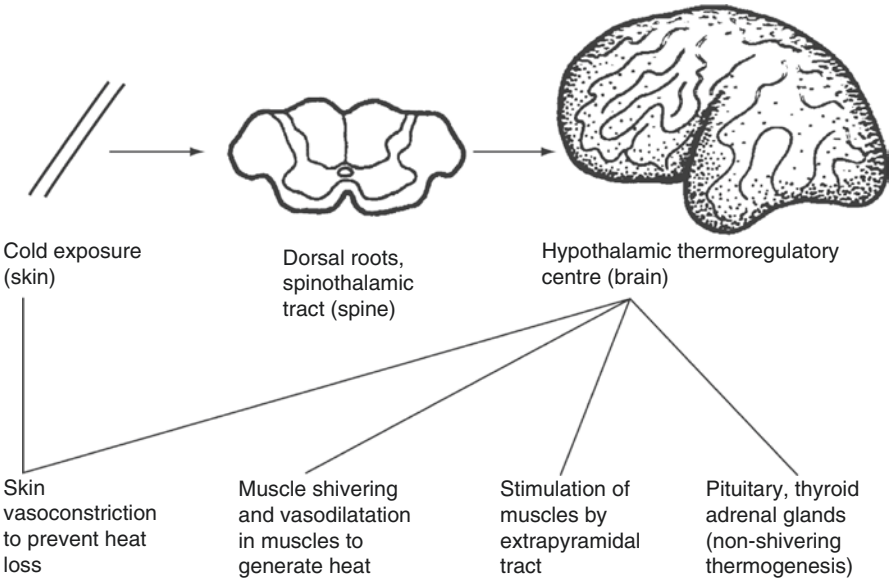

Fig. 8.1 Basic mechanisms of heat production in response to cold

Table 8.6 Main causes of hypothermia in older children

Accidental	Cold water immersion (e.g. home unfenced swimming pool)
Immunity	Compromised, e.g. chemotherapy
Environmental exposure	
Spontaneous	
• Spontaneous periodic hypothermia	
• Shapiro's syndrome	
Infection	Mainly pneumonia and sepsis
Metabolic	Hypoglycaemia
Drug induced	Sedative
CNS lesions	Brain haemorrhage
Malnutrition	Principally in the tropics

8.2.1 Accidental Hypothermia

Accidental hypothermia is defined as a decrease in core temperature usually in a cold environment, causing an acute clinical problem, which is not caused by failure of the hypothalamic thermoregulatory centre. The most common cause of accidental hypothermia in children is immersion.

Immersion or drowning: Drowning is defined as death by suffocation after immersion in a liquid. In near drowning, the individual survives, at least temporarily. The WHO estimates that 388,000 persons die from drowning worldwide annually [7]. In the USA, where there are 8000 deaths per year, drowning is the second

most common cause of accidental death (after road traffic accidents) and the third leading cause (after road traffic accidents and cancer) of all deaths in children aged 1–14 years (8.4% of all deaths). In Britain, with 700 deaths per year from immersion, drowning is the third leading cause of death (after road traffic accidents and cancer) in children [8].

The brain is sensitive to the duration and intensity of hypoxia. Irreversible damage develops to the hippocampus, basal ganglia and cerebral cortex within 4–10 min of hypoxia. Few additional minutes result in persistent coma [9].

Almost 100% of babies have an active diving reflex that persists until the age of 6 months and occurs with rapid immersion. In many older children and adolescents, this reflex may persist upon immersion preventing aspiration of water when the face is stimulated by cold water and causing maldistribution of oxygen to the heart and brain. This may explain that in children inhalation following immersion is less common than in adults; hence there is a higher survival rate in children than in adults. Immersion causes the following complications:

- Inhalation of fresh water, owing to its hypotonicity, causes haemodilution (from absorption of water into the intravascular space), haemolysis and hyponatraemia. In contrast, inhalation of salt water, which has an osmolality more than three times that of body fluid, causes withdrawal of water from capillaries and results in haemoconcentration and hypernatraemia but no haemolysis.
- Aspiration causes pulmonary oedema, pneumonia and pneumothorax.
- Hypothermia occurs more rapidly in a child than in an adult because of the child's relatively large surface area to body mass ratio and decreased insulation by fat. Hypothermia causes a decrease in oxygen consumption and metabolic rate. Metabolic processes decrease by about 6% for each 1 °C reduction in body temperature leading to lower oxygen demand. This contributes to the relatively high survival rate of victims.

Table 8.7 lists the main manifestations seen in hypothermic patients in relation to the fall in body temperature. At a core temperature of:

Table 8.7 Clinical signs of hypothermic victims in relation to body temperature

Core temperature	Physiology	Signs
35–32	BMR ↑	Lethargy, shivering, tachycardia
	Vasoconstriction	Cyanosis, slow respiration
	ADH ↑	Diuresis
32–30	BMR ↓	Absent shivering
	Cerebral blood flow ↓	Impaired consciousness, confusion, delirium
	Acidosis or alkalosis	Muscle tone increase, rigidity
30–27	BMR ↓ to 50%	Respiration: slow and shallow
	Vasodilatation (skin, brain)	Erythema, oedema, loss of consciousness
	Cardiac conduction defects	Arrhythmia
<27	Cessation of cardiac function	Apnoea, asystole, imminent death from VF

BMR basal metabolic rate, *VF* ventricular fibrillation, *ADH* antidiuretic hormone

- 35–30 °C, compensatory mechanisms work to restore homeostasis.
- <30 °C, thermoregulation begins to fail. Unconsciousness and cardiac arrhythmias usually occur. Therefore if a child is conscious, he or she is unlikely to have severe hypothermia. ECG abnormalities include bradycardia, prolonged P-R and QT intervals and widening QRS complex with characteristic J (Osborn) waves (Fig. 8.2). Atrial and ventricular fibrillations are common.
- <28 °C, many hypothermic victims appear dead with asystole and ventricular fibrillation. Other complications include cold diuresis, due to increased antidiuretic hormone (ADH) activity, acute tubular necrosis, hypotension (after an initial rise in blood pressure), sepsis, rhabdomyolysis, thrombocytopenia and cerebral oedema. Metabolic acidosis and pancreatitis may accompany the severe hypothermic state. Hypoglycaemia is a common finding; hyperglycaemia may also occur.

Hypothermia victims may respond to resuscitative measures despite the presence of asystole and other complications. Survival and normal cerebral function may occur even with hypoxia for up to 60 min or longer at a body temperature 20 °C.

Table 8.8 lists the main investigations for near-drowning victims with moderate to severe hypothermia. The prognosis is related to the duration and the degree of hypothermia. Treatment of hypothermia is discussed at the end of the chapter.

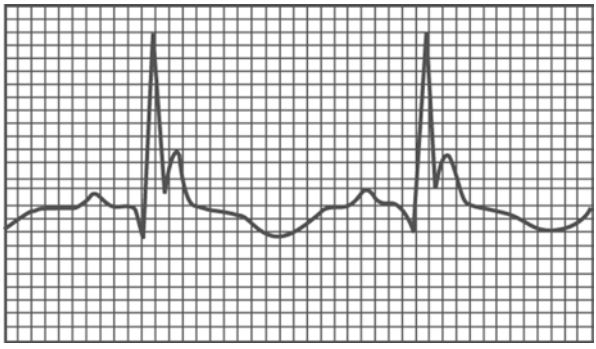

Fig. 8.2 ECG sign in hypothermia

Table 8.8 Suggested laboratory investigations for patients with moderate to severe hypothermia

Blood investigations	Other investigations
Full blood count	Chest X-ray
Calcium	Abdomen X-ray
Liver function test	Continuous monitoring of ECG
Prothrombin time, fibrinogen	Pulse oximetry[b]
Monitoring of:	
Glucose	
Creatinine and urea	
Amylase	
Electrolytes	
Arterial blood gases[a]	

[a]Arterial blood gases must be corrected for patient's temperature
[b]Measurement of oxygen saturation may be inaccurate due to poor perfusion

8.2.2 Spontaneous Hypothermia

Spontaneous hypothermia is very rare in children. It is characterized by episodes of hypothermia in individuals who are otherwise well. Shivering may occur at a body temperature of 33.0 °C (shivering usually commences in normal people at a body temperature of 36.0 °C). Prodromal sweating is found in most cases. No cause has been identified, and CT scan does not usually detect any CNS abnormalities.

Spontaneous hypothermia can occur periodically. Several cases of spontaneous hypothermia have been associated with agenesis of the corpus callosum (Shapiro's syndrome), which generally has a benign, nonprogressive clinical course. There are no associated hypothalamic or CNS lesions.

The prognosis of spontaneous hypothermia is good. Management includes adequate insulation to prevent heat loss, particularly during cold exposure.

8.2.3 Infection

Exposure to cold adversely affects host defence by suppressing the immune response against the infection. In vitro studies have demonstrated decreased WBC motility, diminished phagocytosis and decreased antibody formation at reduced temperature. Animals rendered hypothermic by exposure to cold had decreased survival after challenge with *Salmonella typhimurium* and *Staphylococcus aureus*. Although hypothermia depresses the growth of most pathogenic bacteria, suggesting an apparent beneficial effect during infection, such an effect is usually insignificant compared to the detrimental effect of hypothermia on host defence mechanisms. The rate of mortality due to infection is significantly higher in patients with hypothermia than in febrile or euthermic patients: 71 vs. 37%, respectively, in one study [10]. Infection is a frequent cause of hypothermia in older children and adults, accounting for around 40% of cases in one study [11]. Acute and severe infection, such as pneumonia, septicaemia or meningitis, can cause thermoregulatory failure. Therefore, if a child presents with unexplained hypothermia, investigation should always include a blood culture and a chest X-ray to exclude septicaemia or pneumonia. Immunosuppression and malnutrition are risk factors for hypothermia during infection.

8.2.4 Drug-Induced Hypothermia

Drugs, principally sedative-hypnotics, may induce hypothermia by counteracting the mechanisms responsible for maintaining the body temperature. Possible actions of these drugs include:

- Impairment of the metabolic response needed for non-shivering thermogenesis of the newborn infant.

- Depression of the hypothalamic thermoregulatory centre.
- Interference with the mechanisms for shivering and vasoconstriction. Ethanol predisposes to hypothermia by being a vasodilator, CNS depressant, a cause of hypoglycaemia (see metabolic causes below) and by increasing the risk of accidents.

Drugs capable of causing hypothermia include:

- Diazepam administered to mothers in labour may cause apnoeic spells, hypotonia, low Apgar scores and impaired metabolic response to cold in the newborn infants. A total maternal dose in excess of 30 mg in the 15 h before delivery is capable of producing these adverse effects.
- Chemotherapy for Hodgkin's disease may occasionally cause hypothermia, particularly in patients who were febrile prior to chemotherapy.
- Aspirin or paracetamol administered concomitantly with chemotherapy may increase the risk of hypothermia. The antipyretic ibuprofen may cause hypothermia in therapeutic doses.
- Other drugs which produce hypothermia include chlorpromazine, hexamethonium and barbiturate.

8.2.5 CNS Lesions

Occasionally, lesions in the vicinity of the hypothalamus, such as tumour, haemorrhage or sarcoidosis, may interfere with thermoregulatory mechanisms and produce hypothermia. The occurrence of hypothermia in cases of tumour and haemorrhage is usually terminal.

8.2.6 Metabolic Causes

Patients with hypothyroidism are at increased risk of hypothermia due to decreased metabolic rate. Hypothermia may be the sole manifestation of myxoedema coma. Rarely, hypoglycaemia may present as hypothermia as the only manifestation. Correction of the hypoglycaemia often increases body temperature. Other metabolic causes include hypopituitarism and hypoadrenalism.

8.2.7 Hypothermia in Malnourished Children: Tropical Hypothermia

Hypothermia may occur as early as a few weeks of age secondary to malnutrition. Typically the child fails to regain the weight lost during the first few days of life (physiological weight loss). Brown adipose tissue is found to be depleted, which explains why these children show a poor response to cold. Hypothermia is more frequent in marasmus than in kwashiorkor, possibly because of the insulating

properties of oedema, which may protect against hypothermia. The condition is mainly seen in developing countries.

Hypothermia has also been reported in older malnourished children in the tropics. Hypoglycaemia and serum electrolyte abnormalities were common, and pancreatic necrosis was found in 9 out of 19 children examined at autopsy [12]. Reduced subcutaneous fat, which normally serves as an insulating layer against heat loss, is the main predisposing factor to hypothermia.

8.2.8 Management of Hypothermia

Management varies with the nature and severity of hypothermia. Because specific therapy depends upon accurate measurement of core temperature, low-recording thermometers should be available in any emergency setting dealing with hypothermic victims. Body temperature should be measured as soon as possible after the initial rescue. Management consists primarily of urgent rewarming of the body core. Rewarming may be withheld if supportive measures are unavailable (e.g. during transport) to maintain the hypothermic protection. Methods used for rewarming for patients with mild, moderate and severe hypothermia are summarized in the Table 8.9.

- For patients with mild hypothermia (body temperature 33–35 °C), simple measures to raise body temperature are sufficient, including transport of the victim to a warm place, removal of wet clothes, covering with a blanket or sleeping bag, drinking warm fluids and passive as well as active exercise. For the apnoeic immersion victim, once taken from the water, immediate resuscitative measures include clearing water and debris from the airway and application of cardiopulmonary resuscitation (CPR). Chest compression alone by bystanders may be better than rescue breathing combined with chest compression. Reestablishing victim's breathing before cardiac arrest assures no long-term neurological damage. Postural drainage of inhaled water is only useful for seawater immersion. With freshwater immersion, the water has moved rapidly from the lung into the vascular system.
- For patients with moderate hypothermia (body temperature 30–33 °C), active external warming procedures are required (in addition to the measures used for mild hypothermia), such as immersion of the trunk in a warm bath at an initial temperature of 30 °C and increasing to around 40 °C over the next few minutes. If available, inhaled, moisturized air or oxygen warmed at 35–40 °C may also be used. Any near-drowning victim with moderate degree hypothermia should be observed in a hospital for a minimum of 1 day because late-onset pulmonary oedema may occur as late as 12 h after the accident.

Table 8.9 Methods used for rewarming patients with mild to severe hypothermia

Passive	Warm room, dry blanket, drinking warm fluids, vigorous passive and active muscle movement
Active external	Warmed blanket, pads, radiant warmer, immersion in hot bath, hot, humidified oxygen at 35–40 °C
Core	Warm IV fluids, heated and humidified oxygen, warmed gastric and colonic lavage

- For children with severe hypothermia (body temperature < 30 °C), rewarming the core temperature is indicated. One of the best methods for internal rewarming is to make the patient breathe hot, moist air or oxygen. Alternatively, or simultaneously with the above method, submersion in a warm bath aimed at increasing the body temperature slowly (e.g. 0.5–1.0°/h) may be used. Additional measures that are essential for survival include:
  - Oxygen therapy, 100%, (with or without ventilation). The oxygen flow should be warmed to 35–40 °C.
  - Mechanical ventilation as indicated by a rising pCO_2 or a falling pO_2.
  - Fluid and electrolytes therapy aimed at correcting the electrolyte abnormalities, the metabolic acidosis (resulting from carbon dioxide retention and lactic acid accumulation) and associated hypotension. Many victims have hypovolaemia, and volume expansion (0.9% sodium chloride, warmed to about 40 °C) is essential. Correction of metabolic acidosis with sodium bicarbonate may not be necessary because alkalosis often ensues during rewarming.
  - Intravenous mannitol infusion (1 g/kg/dose as 20% solution over 30–60 min) for cerebral and pulmonary oedema. Overhydration should be avoided. Diuretics and dexamethasone may be helpful.
  - Antibiotics are indicated if there is evidence of infection. Infection is unlikely if the hypothermia is due to immersion in clean water.
  - Treatment of cardiac arrhythmias according to the nature of the ECG abnormalities. Most, including atrial flutter and fibrillation, disappear spontaneously as the temperature rises. Serious cardiac arrhythmia, such as ventricular fibrillation, requires electrical defibrillation and additional CPR. Although CPR may precipitate ventricular fibrillation (VF), CPR is indicated if the patients have asystole and/or an ECG showing absent QRS-activity. The pulse of a patient with severe hypothermia may not be felt, simulating cardiac arrest and thereby falsely indicating cardiac arrest and the need for external compression. ECG monitoring is therefore vital.

Severe hypothermia may precipitate ventricular fibrillation, which is the most common cause of death. Minimal handling is important to avoid such a risk. Vigorous rewarming also carries the risk of ventricular fibrillation as well as rewarming shock secondary to circulatory insufficiency, which existed during hypothermia, and the additional metabolic burden of rewarming. Large and unresponsive pupils are associated with HIE. Returning pupillary response suggests good prognosis. The presence of normal sleep-wake pattern in the EEG is also associated with good prognosis.

8.3 Clinical Use of Hypothermia (Targeted Temperature Management)

Targeted temperature management (TTM), previously known as induced therapeutic hypothermia, is an active treatment that attempts to improve the outcome of tissue injury following lack of blood flow, e.g. after cardiac arrest. Brain oxygenation and glucose concentration decrease during hypoxia-ischaemia events causing ATP

depletion, lactic acid and acidosis accumulation. Hypothermia reduces cerebral oxygen consumption and inhibits the synthesis and release of neurotransmitters including glutamate, GABA and dopamine. Induced hypothermia can be traced back to the ancient times. The Egyptians, Greek and Romans first used induced cooling for battle-inflicted trauma and for other cerebral injuries [13].

Hypoxic-Ischaemic Encephalopathy (HIE)

Perinatal asphyxia or hypoxic ischaemic encephalopathy (HIE) is responsible for significant disability and death worldwide. Of the four million annual worldwide neonatal deaths, 23% are caused by HIE [14]. In the UK, HIE causes death and severe neurodisability in 1–2 per 1000 term infants [15].

Until recently, management of babies with HIE has consisted largely of supportive care to restore and maintain cerebral perfusion. The care included provision of oxygen, appropriate feeding methods and treatment of seizures. The current management for infants with HIE is supportive, with oxygenation, stabilization of physiologic parameters and treatment of seizures. Specific neuroprotective treatment was not available.

Animal studies and clinical trials have demonstrated that a reduction in temperature of about 3 °C (whole body or selective head cooling) applied soon after the onset of HIE was neuroprotective and reduced death and disability rates. A recent Cochrane meta-analysis identified 11 randomized controlled trials involving 1505 infants that compared mild induced hypothermia with normothermia. Hypothermia caused substantial reduction in death or moderate or severe neurodevelopmental disability to 18 months of age. Cooling was associated with both reduced mortality and reduced risk of neurodevelopmental disability in survivors [16]. Hypothermia should be initiated within the first 6 h after birth and, for a sufficient period of time, normally around 72 h. There were no clinically important complications associated with cooling. There is no evidence of increased risk of infection.

Induced hypothermia is either applied to the baby's head or as whole body cooling. Both methods are aiming at a body temperature reduction to 33–34 °C.

The exact mechanism of such neuroprotection is still unclear. Table 8.10 lists the likely effects of therapeutic hypothermia following cerebral insult. Hypothermia is associated with a decrease in oxygen demand and an increase in arterial oxygen content, allowing the brain to tolerate circulatory arrest for about 10 min without sustaining damage. The increase in arterial oxygen content is due to a shift of the haemoglobin dissociation curve to the left.

Cardiac Surgery

Surgery remains the main indication for therapeutic hypothermia. In cardiac surgery, induction of moderate hypothermia (about 28 °C) enables operations (e.g.

Table 8.10 Main effects of mild hypothermia of about 33 °C in HIE

Reduction	Increase
Excitatory neurotransmitters	IL-10 (anti-inflammatory cytokine)
Blood-brain barrier damage	Blood pressure
Cerebral metabolism (O_2 and glucose)	Heart rate
Loss of high energy phosphates	
Secondary cerebral energy failure	
Apoptosis	
Cardiac output	
Platelet function	

atrial septal defect) to be carried out on the heart with circulation safely arrested for up to 19 min. At a temperature of 18 °C, circulation can be safely arrested for 45 min to repair more complex heart lesions, such as a total anomalous pulmonary venous connection in neonates. In vascular surgery it is used for resection of aneurysms (aortic aneurysm). Neurosurgery also utilizes hypothermia to deal with some intracranial vascular catastrophes, such as a ruptured aneurysm. Cardiac surgery can be associated with postoperative morbidity and mortality, including seizures, choreoathetosis, neurodisability and acute renal failure.

Treatment of Cancer

Hypothermia has been used to treat patients with cancer. The first attempt to treat malignant tumours by hypothermia was undertaken in 1849 [17]. Systemic or local cooling was applied during 1936–1940 in Philadelphia for therapeutic purposes. The basic observation that stimulated the use of hypothermia to treat patients with cancer was that segments of the body (e.g. extremities) with a relatively low surface temperature of 34.4 °C rarely harbour metastasis.

Methods used for induction of cooling include packing the body in ice, use of a refrigerating machine, immersion in cold water or directing a steam of cold air over the body surface, all aimed at reducing the body temperature to 31–32 °C. Lowering the body temperature by drugs (artificial hibernation) also has been achieved by slow intravenous administration of a mixture containing chlorpromazine, promethazine and meperidine (1:1:2).

Treatment of Refractory Status Epilepticus

Status epilepticus is a life-threatening emergency with poor outcome and high morbidity and mortality. Hypothermia with a temperature of 29–33 °C is an effective adjunct treatment for this condition with the aim of terminating the seizure.

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Is Fever Beneficial?

9

Core Messages

- Fever has a long evolutionary history, which by itself supports the hypothesis that fever is an adaptive host response to infection.
- There is considerable evidence that fever promotes host defence against infection.
- Complications and mortality associated with high fever >40 °C are closely related to the severity of the underlying disease, not to the level of fever.
- Fever is effectively controlled by the hypothalamic centre and therefore does not climb up relentlessly. Temperatures >42 °C are often caused by hyperthermia, not by fever.
- If the febrile child is comfortable, there is little reason to support the practice of routine use of antipyretic medication.
- Parental education is critical in the management of the febrile child.
- Antipyretics do not prevent febrile seizures.
- There is a conflict between research evidence supporting a positive role of fever and the demands of current practice that fever be abolished.

9.1 Evolutionary Arguments for Fever Being Beneficial

9.1.1 Evolutionary History of Fever

One argument that has been used to support the notion that fever is adaptive is that it has a long evolutionary history [1]. Animals such as lizards, turtles, frogs, fish, crickets, scorpions and beetles develop fever when infected with bacteria, bacterial products or other "fever-producing" agents (e.g. prostaglandins or bacterial products such as endotoxin). How can a "cold-blooded" animal such as a lizard develop a fever? Since a fever is due to an elevation in the thermoregulatory "set-point", the "febrile" lizard seeks out a warmer microclimate, thus raising its core body

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_9

temperature. The same happens to febrile fish, frogs, beetles or other cold-blooded animals. Even febrile people rely to a large extent on behavioural means to raise body temperature during the rising phase of fever. A variety of behaviours to raise body temperature include curling into a foetal position to conserve heat, crawling under a blanket or drinking hot liquids.

9.1.2 Metabolic Cost of Fever

Why would the metabolic cost of fever be relevant to supporting the argument that fever is adaptive or beneficial? In endotherms such as birds and mammals, the maintenance of a body temperature of 2 or 3 °C above the afebrile level often results in a rise in energy consumption of 20% or more above baseline. This is the result of the Q_{10} effect of increased temperature on various biochemical reactions. If fever did not have some beneficial role, it is highly unlikely that it would have evolved in the first place, since it is so energetically expensive. And, having evolved, it is highly improbable that it would have persisted throughout the animal kingdom.

9.1.3 Might Fever Be a Vestige?

Of course, it is always possible that fever is the "appendix" of host responses to infection; that is a vestigial trait. How commonly does this occur? Are there examples of common responses to infection that are truly vestigial in nature (that is has no function)? As indicated through this book, the rise in body temperature during fever is the result of a highly coordinated series of physiological and behavioural responses (e.g. shivering, peripheral vasoconstriction, drinking warm liquids, wearing warm clothing). This rise in body temperature has a metabolic cost, which is associated, ultimately with wasting (unless the individual compensates by taking in additional calories, i.e. eats more). It appears the probability that fever is truly a "neutral" trait (or a vestige) is low.

9.2 Arguments for Fever Being Beneficial (Table 9.1)

9.2.1 Effects of Elevated Temperature on Microorganisms

- Animal studies have demonstrated that the bacterial growth rate in experimental pneumococcal meningitis was significantly reduced at elevated temperatures. Gram-negative bacteria, such as *Salmonella typhi*, were shown to be increasingly susceptible to the bactericidal effects of normal serum when cultivated at a temperature greater than 37 °C [2].The growth of viruses was impaired with increased temperatures. Most viruses ceased to replicate at a temperature between 40 and 42 °C. The replication rate of poliovirus at 37 °C was 250 times that at 40 °C [3].

Table 9.1 Arguments for believing fever to be beneficial

• Fever has a long evolutionary history that is found throughout the Animal Kingdom
• Fever is energetically expensive, and probably would not be maintained throughout evolution had it not been protective or adaptive
• There are numerous studies demonstrating a beneficial role of fever
• Fevers are self-limiting and rarely reaching levels that could be dangerous
• The evidence that antipyretic drugs protects against "febrile seizures" is poor
• Antipyretic drugs, by reducing fever, may counteract the protective effects of fever
• The principal beneficial effects of antipyretic drugs are their effects on providing comfort to the febrile child (via their "analgesic" or pain-reducing properties)

- Human studies: Ancient physicians such as Hippocrates and Rufus of Ephesus used fever to treat various ailments. Fever was the principal form of treatment for syphilis and gonorrhoea for centuries. Insufflation of humidified air at 43 °C (three 30-min sessions at 2–3 hourly intervals) into the nasal passages of patients suffering from coryza resulted in the suppression of symptoms in 78% of patients [4]. Fever may also be beneficial in patients with meningitis: the presence of fever greater than 40 °C did not indicate a poor prognosis, but all children presenting with hypothermia died [5]. A study of 102 children with salmonella gastroenteritis from Finland [6] demonstrated a significant negative correlation between the degree of fever and the duration of excretion of organisms. A fever of greater than 40 °C had the shortest and those without fever the longest duration of bacterial excretion. Fever has therefore a favourable prognostic influence on the length of bacterial excretion. It is, however, not clear whether the above studies are the result of the direct effect of temperature on the growth of the microorganisms or the effect of elevated temperature on host defence responses.

9.2.2 Effects of Elevated Temperature on Defence Mechanisms

- The mobility, phagocytosis and killing of bacteria by polymorphonuclear leukocytes are significantly greater at temperatures above 40 °C [7]. Elevated temperatures of 38 and 39 °C have a direct positive effect on lymphocyte transformation, the generation of cytolytic cells, B-cell activity, and immunoglobulin synthesis.
- Interleukin-1 is more active at febrile temperature than at an afebrile temperature [8, 9]. Interferon (INF), a potent antiviral agent, has enhanced antiviral activity above 40 °C [10, 11]. T-cell proliferative response to interleukin-2 and interleukin-1 was greatly increased at 39 °C compared to 37 °C.
- Fever may act synergistically with antibiotics. Penicillin was found to have a progressive increase of its bactericidal activity as the temperature was raised from 35 to 41.5 °C [12].
- There is evidence that elevated body temperatures in the range of 41–42 °C can affect the growth of certain tumours. Occasional remissions of Hodgkin's disease

occurred after an attack of measles. The metabolism of many types of cancer cell is selectively damaged at temperatures of 42–43 °C [13]. Lysosomal enzymes, IL-2 and INF have increased activity at such temperatures and contribute to tumour cell destruction.

9.2.3 Effects of Suppression of Fever on Underlying Disease

If fever is beneficial, it might be expected that suppression of fever can have a harmful effect. There is some evidence to support this.

- Probably the earliest demonstration of the protective effect of fever was shown in a study of lizards, *Dipsosaurus dorsalis*, infected with a natural pathogen, *Aeromonas hydrophila* [14]. In that study infected lizards were kept in incubators so as to maintain them at their febrile body temperature of 42 °C (high fever), 40 °C (moderate fever), at their non-febrile temperature of 38 °C or maintained at body temperatures below normal (36 °C or 34 °C). The results were striking. The febrile lizards had survival rates of 75% (those at 42 °C), 67% (those at 40 °C) and 25% (those at 38 °C). The lizards kept at the below normal body temperatures had even lower survival rates. In a follow-up study, the antipyretic drug sodium salicylate was administered to bacterially infected lizards. This led to an increase in their mortality only when the antipyretic drugs lowered body temperature. All feverish lizards survived, whereas the non-feverish lizards died [15].
- In human volunteers infected with rhinovirus, the use of antipyretics was associated with suppression of serum antibody response, increased symptoms and signs and a trend towards longer duration of viral shedding [16]. In a study of children with chickenpox, half of whom received paracetamol four times a day, and half received a placebo, the time to total scabbing was slightly shorter in the placebo group (5.6 days) than in the paracetamol group (6.7 days) [17]. Another study from Japan [18] found that the frequent administration of antipyretics to children with bacterial diseases led to a worsening of their illness. The use of antipyretics too diminishes fever correlated with a 5% increase in mortality in human populations infected with an influenza virus [19].
- Many studies have found that hypothermia may impair various defence mechanisms, including delayed and often depressed activity of leukocytes, decreased phagocytosis and antibody formation as well as increased susceptibility to viral infection. All animals infected with pneumococci, which were rendered hypothermic (body temperature between 30 and 34 °C) died, whereas only 5 of the 31 control animals infected with the same bacteria at normal to low febrile levels died [20]. More influenza virus was shed in the nasal washes of ferrets whose febrile response was suppressed by shaving or by treatment with sodium salicylate compared to untreated ones [21]. In a series of children presenting with severe infection, such as pneumonia or septicaemia, it was found that the lower the body temperature, the higher the mortality [22].

9.2.4 The Hygiene Theory

The prevalence of asthma and allergies as well as cancer has increased worldwide for many years, and the hygiene theory has been offered to explain the rise [23, 24]. The theory proposes that early exposure to fevers caused by infections (in particular infection of the upper airways, hepatitis A and *Helicobacter pylori*) might protect children against allergic diseases and cancer in later life. It postulates that atopy, or allergy, is Th2-driven, which is primarily associated with IL-4, IL-5, IL-10 and IL-13 production, whereas infection is Th-1-driven, which is dominated by production of INF-gamma and IL-12. In association with reduced exposure to infections, Th-2 immunity dominates through critical childhood periods, resulting in higher incidence of atopy.

In support of this theory are the following findings:

- The prevalence of atopy is lower among children of large families or those attending day-care nurseries than among children of small families or those not nurseries.
- Children with older siblings are less likely to develop allergies than children with younger siblings or none at all.
- Children who experienced several febrile episodes during the first year of life have lower incidence of allergy than those with only one or no febrile episode.
- Children exposed to high levels of endotoxin (a major product from Gram-negative bacteria) show reduced prevalence of atopy.
- The use of antibiotics administered during the first year of life is associated with asthma, hay fever and eczema later on in life. Antibiotics could destroy the beneficial bacteria (probiotics) in the digestive tract.
- Atopic diseases are rare in countries with parasitic infestation.
- A study from Switzerland [25] showed a significant association between febrile infectious childhood diseases and the risk of developing cancer in adulthood.

Thus, we conclude from these intriguing data that exposure to infectious diseases in early childhood, particularly those that may be associated with modest fevers, may protect the child against a wide array of future diseases.

These arguments in favour of fever being protective are facing arguments against fever being beneficial. The next section will review many of those.

9.3 Arguments for Fever Being Harmful

9.3.1 Parents' Attitude and Expectation

As fever frequently accompanies childhood illness, it is commonly perceived by parents and physicians as a harmful part of the illness requiring intervention. Part of the reason for this is that fever is often seen as the direct cause of the illness, rather than as a "host defence" response to the illness. Fever is easy to measure and furthermore even easier to "treat". Parents worry when their child is feverish and feel

that fever may spiral upwards with a possible fatal outcome. Parents often have unfounded anxiety about the possible risks of fever and little or no information about its beneficial role in diseases, and as a result they are convinced that antipyretic measures must be used to lower fever.

Fever phobia, an exaggerated fear of fever in their children, is common among parents of all socio-economic classes. In one study [26], parents began antipyretic medication when their child's temperature was equal or even less than 37.8 °C. One of the reasons that parents probably give their children antipyretic medication is not so much because it lowers body temperature (which, of course, it does) but because these drugs are also analgesics. So by giving their children the "antipyretic" medication, the child soon feels better. The parent is then relieved that the lowered fever is the cause of the improvement in her/his child. But, this is most likely simply due to the reduction in pain and discomfort caused by the medication.

9.3.2 Prevailing Concepts Among Physicians

Most paediatricians agree that treatment of a febrile child with antipyretics is mostly for the relief of the symptoms of fever. However, many tend to prescribe antipyretics for any child with fever on the basis that antipyretics could prevent its complications. In a study [27] exploring the beliefs and practices of paediatricians in Massachusetts, USA, the majority (65%) of respondent believed that fever itself could be dangerous to a child with seizures, death and brain damage being the most serious complications of fever if the temperature is 40 °C or greater. Paediatricians may be contributing to fever phobia by prescribing antipyretics for children who are only mildly febrile. As it is described in this chapter and in Chap. 10, this belief is unfounded.

9.3.3 Associated Discomfort

Children with fever often experience discomfort, headaches and myalgia as a result of cytokine-mediated production of prostaglandins. These symptoms occur during the phase of rising fever, causing reduced activity to the children and thus cause anxiety to their parents. As mentioned above, antipyretics, by also being analgesics, lead to an improvement in the children's level of activity and alertness. When children feel better, an assumption usually emerges that the severity of the disease has been reduced. The elimination of these symptoms (discomfort, pain and aches) is perhaps the main reason why antipyretics have maintained their popularity among parents and have continued in use for over a century.

9.3.4 Risk of Febrile Seizure

In a study [27] from the USA, 49% of paediatricians considered convulsions to be a principal danger of fever and 22% believed that brain damage could result from

typical febrile seizure (FS). Early literature [28] reported a mortality rate of 11% in children with FS.

As fever is generally considered to be an essential precursor of a febrile seizure, medical professionals have concluded that antipyretic measures should prevent febrile seizures. Antipyretics continue to be among the most commonly prescribed medications, especially for children at risk of such seizures. Parents are usually advised that the administration of antipyretics to at-risk child may reduce the risk of further convulsions. However, as reviewed by Rosman [29], antipyretic therapy has never been shown to prevent febrile seizures. There is now abundant evidence indicating that antipyretics have no effect on preventing further FS. Children with high risk of recurrences of FS (see Chap. 7 "Febrile Seizures") develop recurrences in 70–80%, while those without these risk factors rarely develop recurrences. Antipyretics are used for both groups of children, suggesting that it is the risk factors, and not the antipyretics, which are responsible for the seizure recurrences. Several randomized, placebo-controlled trials on children at risk of FS found no evidence that the antipyretic paracetamol or ibuprofen, with or without diazepam, was effective in preventing FS during subsequent febrile episodes [30–35]. Furthermore, numerous studies show that a temperature >40 °C is associated with decreased incidence of recurrence [36, 37]. Thus, a high temperature at the onset of FS is a useful predictor of non-recurrence.

9.3.5 Views Against the Argument that Fever Is Harmful

- Well-planned educational interventions about fever may change parental perceptions and reduce excessive use of health services. This information is best delivered during routine health checks, as parents' anxiety may interfere with their understanding of facts presented when their child is sick.
- About 20% of children seen in the accident and emergency department have a temperature over 40 °C, and they usually make a full recovery. Fever per se is self-limiting and rarely serious provided the cause is known and fluid loss is replaced. Fever is most commonly caused by a viral infection of the upper respiratory tract. 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. Although it has been difficult to define a critical threshold of tissue damage in man (defined as the temperature above which tissue damage occurs), a temperature above 42 °C is likely to cause the damage. However, temperatures that are high are generally caused by hyperthermia, not by fever.

A reduction of symptoms of infection by antipyretics/analgesic drugs is often difficult to contest. It may be considered unkind to withhold these drugs while we

have a simple and effective remedy to make children feel better. But, what if the use of this medication makes the infection worse? Furthermore, it is not unusual to see a febrile child with mild or no symptoms. In such circumstances there is little evidence to support the practice of routine antipyretic medication. Mild discomfort and myalgia may theoretically be beneficial by minimizing activity during the febrile illness so that available energy is channelled into useful biochemical reactions such as antibody formation.

9.3.6 When Might Fever Truly Be Harmful?

Situations whereby fever clearly worsens the prognosis of disease include:

- Acute stroke. A study [38] showed that high temperature was an independent predictor of poor outcome. Numerous other studies seem to support this observation. For example, Kammersgaard et al. [39] have shown that stroke patients admitted with febrile body temperatures have a worse prognosis than do patients admitted with low or normal body temperature. Some companies are starting to manufacturer helmets or other devices to allow the physician to selectively cool the brains of stroke patients.
- Severe sepsis. In a recent paper, Pollheimer et al. [40] put forth an intriguing hypothesis. Septic patients show a marked muscle depletion of glutamine, which is associated with poor survival. Pollheimer et al. [41] showed that monocytes cultured at "febrile" temperatures in the presence of low glutamine (to simulate severe sepsis) had decreased viability. Thus, these cells that are critically important in fighting infection were severely impeded at febrile temperatures but only in a low glutamine environment. They hypothesize that when glutamine is restored to the severely septic patient, the benefits of fever would be restored. However clinical studies are needed to confirm or refute this.
- Children with bronchiolitis. A study has shown that the presence of fever did not benefit children admitted with bronchiolitis [42].
- In situation associated with limited energy supply or increased metabolic rate (e.g. burn, cardiovascular and pulmonary diseases, prolonged febrile illness, young children, undernourishment and postoperative state). Fever can increase the metabolic rate and could exert a harmful effect on the disease
- Diseases associated with high fever (>40 °C) for the following reasons:
  - Children with this high degree of fever are likely to be symptomatic.
  - With the exception of a few diseases such as *Salmonella* gastroenteritis and febrile seizures mentioned above, there has been no scientific evidence that high fever is beneficial.
  - The prevailing view among physicians and parents is that high fever in particular is harmful, and omission of antipyretics seems unethical.

9.4 Summary

9.4.1 Lesson from History

- Many scholars of ancient civilizations, particularly the Greeks, believed in the beneficial effects of fever in disease. Hippocratic writings, for example, contain evidence that fever was thought to be beneficial to the infected host. Rufus of Ephesus in the second century AD strongly advocated the beneficial role of fever. He recommended the use of "fever therapy" (such as by malaria) to treat various diseases, including epilepsy. Fever therapy was the principal form of treatment, not only for syphilis and gonorrhoea but also for patients with rheumatoid arthritis and asthma. This belief, held for about 2000 years, should not be ignored. Virtually all cultures use some form of "fever therapy" in the form of "saunas", or "sweat lodges", or "steam baths" or other ways to raise body temperature artificially. This probably dates back to the Hippocratic era and is based on the "humoral" theory of disease, where one of the forms of therapy was to "cook" the bad "humour".
- Events in the history are known to repeat themselves, so are medical practice and concepts. It is possible that treatment with fever or hyperthermia could make a comeback and fever could play an important role (or as an adjunct to other therapeutic measures), to treat various diseases modern medicine may not be capable to do so.

9.4.2 Lesson from Recent Research

- Accumulated data from extensive research into the subject of fever and its role in disease suggest that fever has a protective role in promoting host defence against infection, rather than being a passive by-product.
- Fever exerts an overall adverse effect on the growth of bacteria and some tumours, as well as on replication of viruses. It also enhances immunological processes, including activity of IL-1, T-helper cells, cytolytic T-cells, B-cell and immunoglobulin synthesis. The clearest evidence on the relationship between fever and immunity is that the same pyrogenic cytokines that are produced during fever also enhance immunity through phagocytic and cytotoxic activities to limit infection.

Studies on the role of fever in disease in human, particularly in children conclude:

- Moderate fever has beneficial effects on a healthy child or adults.
- The effects of a high degree of fever (40–42 °C) on paediatric diseases have rarely been studied. Performing clinical studies on child has its own risk, and so it will be difficult to gather such data.

- Our knowledge is extrapolated from studies using animal models or in vitro studies using human tissues.
- There are medical conditions (see below), which do not benefit from associated fever even at lower degree of body temperatures, and these have to be treated vigorously with antipyretics.

9.4.3 Authors' Opinion

Fever is one of the oldest known signs of disease. Its description dates back as far as civilization itself, some 5000 years. Fever is a very common clinical problem, which usually alarms parents. Despite intensive research few issues in medicine have been more controversial than the biological role of the febrile response, that is, whether fever is beneficial or harmful. There is often a wide perception among doctors and parents that fever is dangerous. Parents have poor understanding of fever, and their temperature measurement techniques are inaccurate.

Paediatricians who work with children in hospitals have come to terms that antipyretics (paracetamol without or alternating with ibuprofen) are very often automatically prescribed on the treatment sheet for the single indication, that is, the presence of fever (usually above 38.0 °C, sometimes lower). Both, a child who is playful on the ward and another with a significant discomfort due to fever, receive antipyretics. This is the current practice, which is widely accepted. When we focus upon "treating" the fever, we are giving the impression to parents and health professionals that fever is harmful and that antipyresis is beneficial. Scientific evidence does not support this practice. It is the underlying disease not the fever which we should be concerned about. The presence of fever could well be of benefit to the infected host through activation of the immune system.

It is well established that:

- The reduction of fever by the use of antipyretics does not usually have a positive role on the underlying disease nor does it reduce the time of infection.
- The principal benefit of the antipyretic drug is to make children more comfortable; and that is because the antipyretic drug also has analgesic property.

Research indicates that we are at crossroads, divided between strong research evidence accumulated during the past few decades supporting a positive role of fever (with the exceptions noted earlier in this chapter) and the continued pressures of current practice to lower body temperature (i.e. "treat the fever" as though the fever were the disease). As clinicians, we need to educate our patients and health professionals that:

- There is accumulating evidence that supports the notion that fever evolved as a host defense mechanism.
- We should use antipyretic drugs sparingly in our clinical practice.

This may initially cause some dismay among parents because of their perception that their sick and needy children are not being treated. But, if we are to play a leadership role in our fields, we should help to educate the public about the results of research that have been coming forward over the past several decades. To continue the current practice of liberal use of antipyretics may mean that we are ignoring important messages from research.

Although this chapter of the book has stressed the beneficial effects of fever, the author does recognize that the issue as to whether fever is beneficial or not is still controversial, and there are scholars who maintain the view that the function of fever is still uncertain. Although it is difficult to isolate fever as a single parameter in a disease to investigate its function, more effort should be exerted to determine this function in every febrile disease. In particular, we need to know which diseases are likely to benefit from the presence of fever, so that minimal interference during their courses may be considered. On the other hand, we should investigate in which diseases the associated fever may be harmful so that steps are taken to treat it. Also it should be determined what degree of fever is harmful and thus ought to be reduced. Until these types of studies are conducted for a wide assortment of infections, the question of whether most fevers should be left alone or treated in the paediatric or adult patient will remain unanswered.

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Management of Fever (Antipyretics)

10

Core Messages

- Fever in children is a frequent reason for consultation to paediatricians and GPs, estimated to be 30% of the total visits.
- The principal indication for the use of antipyretics is not to reduce body temperature but to make the child comfortable.
- Antipyretics are ineffective in preventing febrile seizures.
- Currently, paracetamol is a first-line choice for fever and pain management.
- Combining two antipyretics has no scientific basis and does not achieve a greater antipyretic/analgesic effect than either agent alone.
- In therapeutic dose, antipyretics rarely cause adverse events.
- The use of tepid sponging for febrile children is unnecessary because of the availability of antipyretic drugs, which are simpler to use, more effective in reducing body temperature and produce less discomfort to children.
- One of the most important duties of paediatricians is to differentiate between an ill child (who may need prompt attention, including hospitalization) and a well child who can be sent home. This is learned by experience.
- Fever phobia is common among parents and doctors. This excessive fear of fever is unfounded. It is not the fever which is harmful but the underlying disease. The associated fever may be protective.

10.1 Historical Background of Antipyretics

Ancient Egyptian scholars and the Indians of North America knew the therapeutic benefit of willow tree bark, which contains salicylates. Hippocrates recommended chewing willow leaves as childbirth analgesia. In the mid-eighteenth century, Reverend Edmund Stone in England described the benefit of willow bark "in the cure fever" [1].

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_10

In the 1880s, the German synthetic dye industry accidentally discovered acetanilide and antipyrine (1883). These early antipyretics, along with phenacetin (discovered in 1887) and aminopyrine (discovered in 1896), were later withdrawn because of toxicity. Aspirin was synthesized in 1853 and introduced into clinical practice in 1899 by the German drug company Bayer, which gave it its name. By 1914, aspirin was the world's most widely used drug, not only as an antipyretic and analgesic but also against hay fever and diabetes mellitus. In 1988, aspirin was removed from the World Health Organization's list of essential drugs following reports linking aspirin and Reye's syndrome (encephalopathy associated with liver necrosis). Paracetamol (US: acetaminophen) was introduced in 1893.

10.2 Mechanisms of Action of Antipyretics

- Antipyretics act centrally by lowering the thermoregulatory set-point of the hypothalamic centre. This is achieved through inhibition of cyclooxygenase (COX), the enzyme responsible for the conversion of arachidonic acid to prostaglandins (PG) and leukotrienes. Although several prostaglandins can induce fever, PGE2 is the most important mediator. The lowering of the hypothalamic set-point leads to a series of physiological responses, including decreased heat production, increased blood flow to the skin and increased heat loss through the skin by radiation, convection and evaporation, resulting in a reduction in body temperature.
- Most antipyretics inhibit PG effects on pain receptors, capillary permeability and circulation and leukocyte migration, thereby reducing the classical signs of inflammation. Prostaglandins also produce bronchodilation and have an important effect on the gastrointestinal tract and renal medulla. Therefore, the expected side-effects of these drugs include bronchospasm, gastrointestinal haemorrhage and renal impairment.
- Antipyretics do not reduce fever to a normal level, reduce the duration of febrile episodes or interfere with the normal body temperature. They also do not directly interfere with pyrogen formation or with mechanisms of heat loss, such as sweating. Their effectiveness in reducing fever depends on the level of fever (the higher the fever, the more the reduction), the absorption rate and the dose of the antipyretic.

10.3 Choosing an Antipyretic

An ideal antipyretic is expected to have the characteristics shown in Table 10.1. The choice of antipyretics has been narrowed to paracetamol and ibuprofen following the recommendation against aspirin use. Before that, aspirin had the advantage over paracetamol because of its low cost and its anti-inflammatory effect. Ibuprofen is more expensive and has more side-effects than paracetamol (see later).

Table 10.1 Characteristics of an ideal antipyretic

An ideal antipyretic should:
• Give rapid result and be effective in reducing fever by at least 1 °C (1.8 °F)
• Be available in liquid and suppository form
• Have low rate of side-effects in therapeutic doses and low toxicity when taken in overdose
• Have low incidence of interaction with other medications and rarely contraindication in paediatric doses
• Be safe
• Be cost-effective

10.4 Indications for Antipyretics

Antipyretics are mainly used to lower fever and abolish pain. The primary goal of treating febrile children should be to improve the overall comfort rather than focusing on lowering body temperature and thereby reducing the parents' anxiety. Improving the comfort and evaluating for serious illness should be the therapeutical end points of fever management. There is no evidence that fever causes brain damage or that antipyretics prevent febrile seizures. There is also no evidence to suggest that reduction of body temperature reduces morbidity or mortality from a febrile illness. If there is morbidity or mortality, it comes from the underlying illness but not from the fever.

Current paediatric practice for a febrile child includes the use of antipyretics when the temperature is greater than 38.5 °C or 39 °C. With the reduction of fever, the activity and alertness of children may improve, while the improvement in mood or appetite is less pronounced. Improved activity should encourage children to take fluid, which is essential in the treatment of febrile children. Paracetamol and ibuprofen are frequently used as analgesics to reduce pain.

A common practice is to recommend the routine use paracetamol or ibuprofen before receiving immunization (aimed at reducing discomfort associated with the injection). This practice may decrease immune response to vaccination.

A practice frequently used to control fever is the alternating or combined use of paracetamol and ibuprofen. This practice has the potential of inaccurate dosing and overdosing and does not cause improved comfort. External cooling measures such as tepid sponging can reduce fever, but they do not improve comfort which is the goal of antipyretic use.

10.5 How Beneficial Are the Antipyretics?

Antipyretics are among the most commonly used medications in children. Fever is the leading cause for seeking a physician's attention (30% of consultations), and antipyretics are prescribed almost routinely to reduce it. The answer to the important question as to whether antipyretics should be used to lower body temperature

Table 10.2 Summary of arguments for and against the use of antipyretics

In favour of antipyretic use	Against antipyretic use
Prevailing concept that fever is harmful	Fever per se is self-limited and rarely serious
Fever if untreated may rise to a dangerous level, causing CNS damage	Fever, unlike hyperthermia, is regulated by an effective thermoregulatory centre. It does not climb up relentlessly
Relieving parental anxiety	Educating parents can reduce parental fear
Risk of fever seizures (FS)	No scientific evidence that they prevent FS Fever has a protective role against infection
	Antipyretic drugs have adverse effects and occasional fatalities

FS febrile seizures

depends on whether fever is deleterious or beneficial to children. Table 10.2 summarizes arguments for and against the use of antipyretics.

10.5.1 Arguments for the Use of Antipyretics

- Parents' attitude and expectation

Antipyretics are often prescribed because parents are worried when their child is feverish and feel that fever may spiral upwards with a possible fatal outcome. Parents often have unfounded anxiety about the possible risks of fever and no information about its beneficial role in diseases. Practically all parents remain convinced that antipyretic measures must be used to lower fever.

- Prevailing concepts among physicians

Most paediatricians agree that treatment of a febrile child with antipyretics is for the relief of the symptoms of fever. However, many tend to prescribe antipyretics for a child with any degree of fever. In a study [2] exploring the beliefs and practices of physicians, the majority (85%) of respondents believed that prescribing antipyretics could control fever and prevent complications, particularly febrile seizures. Paediatricians may be contributing to parental fever phobia by prescribing antipyretics for children with mild fever.

- The risk of febrile seizures (FS)

Fever can cause a brief benign convulsion in 3–4% of all children. In a study from the USA, 49% of paediatricians considered convulsions to be a principal danger of fever, and 22% believed that brain damage could result from FS [3]. As the essential precursor of a FS is fever, physicians have concluded that antipyretic measures should prevent FS. Parents with children at risk of FS are usually advised that the administration of antipyretics can prevent further FS.

There is now abundant evidence against the previously assumed risks of FS. It is also known that antipyretics are ineffective in the prevention of FS. Two large population-based studies [4, 5] found no deaths or persistent motor deficits directly attributed to FS. A temperature >40 °C with the first seizure was associated with a decreased incidence of recurrence of FS [6, 7]. An evidence-based search [8] concluded that antipyretic drugs are ineffective in preventing FS and should not be recommended for preventing further FS. Prophylactic antipyretics to prevent FS following vaccination are also ineffective [9].

- Associated discomfort

Febrile children often experience discomfort, headaches and myalgia resulting in reduced activity and causing anxiety to the parents. Antipyretics by being analgesics lead to an improvement in the children's level of activity and alertness. The elimination of these symptoms (discomfort, pain and aches) is the mean reason why antipyretics have maintained their popularity among parents.

This point, a reduction of symptoms of fever by antipyretics, is difficult to contest. It is unkind to withhold antipyretics while we have a simple and effective remedy to make children feel better. However, it is not unusual to see a febrile child with mild or no symptoms. In such circumstances if parents have received an explanation about the nature of their child's illness, there is little evidence to support the practice of routine antipyretic administration.

10.5.2 Arguments Against the Use of Antipyretics

- Fever is self-limiting and well controlled
- Fever per se is self-limiting and rarely serious provided that the cause is known and fluid loss is replaced. Fever is commonly caused by a viral infection of the upper respiratory tract. Antipyretics have no influence on the clinical course of the disease or on the number of subsequent febrile days. With fever, unlike hyperthermia, body temperature is well regulated by a hypothalamic set-point that balances heat production and 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, fever is not injurious to tissue. About 20% of children seen in the emergency room have temperatures over 40 °C, and they usually make a full recovery. If there is morbidity or mortality, it is due to the underlying disease. The associated fever may well be protective.
- The effects of fever on microorganisms and defence mechanisms
- Studies have demonstrated that the bacterial growth rate in experimental pneumococcal meningitis is significantly reduced at elevated temperatures [10]. Gram-negative bacteria, such as *Salmonella typhi*, were shown to be increasingly susceptible to the antibacterial effects of serum when cultivated at a temperature >37 °C [11]. There was a significant inverse correlation between the degree of fever and the duration of excretion of organisms. A fever of greater than 40 °C had the shortest and those without fever the longest duration of bacterial excretion [12].

- If fever is considered beneficial, antipyretics may have harmful effects. In one study the administration of the antipyretic sodium salicylate to lizards with bacterial infection increased their mortality. All febrile lizards survived, whereas all afebrile lizards died [13].A study from Japan [14] found that the frequent administration of antipyretics to children with bacterial diseases led to a worsening of their illness.
- Fever enhances immunological processes, including mobility of polymorphonuclear cells, activity of interleukin-1, T-helper cells and cytolytic T-cells, as well as B-cell activity and possibly immunoglobulin synthesis.
- Side-effects and fatalities
- Antipyretics are known to cause adverse reactions and some fatalities. In the UK, paracetamol has been one of the most popular choices for suicide attempts in adolescents and adults. In the USA, paracetamol-associated overdoses account for 56,000 emergency visits and 26,000 hospitalizations, with approximately 450 deaths each year. About 100 of these deaths are unintentional [15].

10.6 Antipyretics (Table 10.3: Summary for the Clinician)

Antipyretics are among the world's most used medications. As a group, these drugs differ chemically but have in common mechanisms of action, including antipyresis, analgesia, anti-inflammatory and platelet inhibition (paracetamol does not possess the latter two activities). A brief classification of antipyretics is shown in Table 10.4.

Table 10.3 Summary points of antipyretics

• The current practice considers the liberal use of antipyretics a necessity and demands measures to abolish it, often at low degree of fever. Fever phobia is widespread among parents and physicians. More education is needed to alleviate this excessive fear of parents about fever.
• Antipyretic drugs, by being analgesics, reduce not only the fever but also the pain. Children feel better, and we assume that when we reduce fever, we reduce the severity of the disease. The elimination of these symptoms (discomfort, pain and aches) is perhaps the mean reason why antipyretics have maintained their popularity among parents and have continued in use for over a century.
• There is no evidence that fever, in contrast to hyperthermia, is injurious to tissue. If there is morbidity or mortality, it is due to the underlying disease. The associated fever may well be protective.
• Until properly controlled studies have assessed the risk of combining the two antipyretics, paracetamol and ibuprofen, practitioners and parents may be advised to use paracetamol alone in the treatment of febrile children.
• Antipyretics have no influence on the clinical course of the disease and do not reduce the mean number of days of subsequent fever.
• Drastic measures to lower body temperature have no scientific basis, are distressful to patients and are counterproductive.
• Physical measures (fan, tepid sponging) for fever are unnecessary and unpleasant for the child; their use is discouraged. Instead offering extra fluids, keeping the room cool and dressing the child in light clothing are encouraged.

Table 10.4 Medications/measures known to lower body temperature

Para-aminophenols	Endogenous antipyretics
Paracetamol	Arginine vasopressin
	Alpha-melanocyte stimulating hormone
	Corticosteroids
Propionic acid derivatives	Endogenous corticosteroids
Ibuprofen	Hydrocortisone
Naproxen	Methyl prednisolone
Salicylates	Endogenous pyrogen antagonists
Aspirin	Interleukin-1 receptor antagonist
Other NSAIDs	Physical measures
Nimesulide	Tepid sponging
Diclofenac	Bed rest
Corticosteroids	

NSAIDs Non-steroidal anti-inflammatory drugs

10.6.1 Paracetamol (Acetaminophen)

Effects and Dose

Paracetamol is an active metabolite of acetanilide and phenacetin. Currently, paracetamol is the most commonly used antipyretic and analgesic drug in paediatric practice. Paracetamol has the following characteristics:

- It is the only available drug for fever and pain in children from birth and younger than 3 months of age. Ibuprofen cannot be used at this age. Clearance is reduced in neonates; a dose at 8–12 h intervals is recommended.
- It is the first choice for antipyresis and analgesia, but has no anti-inflammatory property. Unlike ibuprofen, paracetamol can be used in children with dehydration and with chickenpox.
- After 30 min, paracetamol 15 mg/kg decreases body temperature by 0.71 °C and by 0.36 °C when a dose of 10 mg/kg is used [16]. The mean maximum temperature reduction is 1.6 °C with a dose of 15 mg/kg and 1.17 °C with a dose of 10 mg/kg. Furthermore, 15 mg/kg paracetamol reduces the body temperature of about 1 °C greater than that found with the 10 mg/kg dose after 8 h. Therefore, the higher dose of paracetamol of 15 mg/kg is associated with early onset and longer duration of fever reduction than with 10 mg/kg dose.
- A dose of 5 mg/kg body weight paracetamol achieves an insignificant temperature reduction (Table 10.5). For analgesia a dose of 10–15 mg/kg is adequate, three to four times daily (no more than four times) with a maximum of 60 mg/kg/day.
- Following administration of a therapeutic dose, fever begins to fall in about 30 min, a nadir is reached in about 2 h and recurrence of fever is observed 3–4 h. A peak plasma level is reached in about 30 min
- Opioid-sparing effect. Perioperative pain in children often requires systemic opioids, and paracetamol can reduce this requirement.
- Prophylaxis to decrease postvaccination adverse local and systemic reactions (e.g. fever, pain). Such a prophylaxis may be associated with a decrease of antibody responses to the vaccine antigens

Table 10.5 Antipyretic effect of commonly used paracetamol doses 2–3 h after administration (initial body temperature 39.5 °C)

Dose	Expected temperature reduction (°C)
5 mg/kg	0.3–0.4
10–15 mg/kg	1.2–1.4
20 mg/kg	1.4–1.6

Table 10.6 Recommended doses of some paracetamol preparations, their advantages and disadvantages

Available:	Oral	Rectal	Intravenous
Dose:	Tab: Panadol 500 mg; liquid: Calpol (120 mg/5 mL; or 250 mg/5 mL 10–15 mg/kg at 4–6 h or 60–75 mg/kg/day for children; 4 g/day for adults	Paracetamol 60, 125 or 500 mg Same as oral	Paracetamol infusion 10 mg/mL 15 mg/kg
Neonate	20 mg/kg start, then 10–15 mg/kg every 8–12 h	20 mg/kg start, then 15 mg/kg BD	
Advantage:	Well tolerated, good absorption	Used if the oral route is unsuitable or impractical, e.g. vomiting, drowsiness, coma	Penetrates readily in CSF, rapid central analgesia, bypassing the delayed absorption of enteral route
Disadvantage:	May cause vomiting and abdominal pain. A high carbohydrate meal may reduce absorption and interfere with fever reduction	Absorption is slower and more variable than the oral form	Few indications, e.g. intra-operative or postoperative analgesia, not as an antipyretic. May cause transient hypotension

Table 10.6 shows some clinical data on the available preparations of paracetamol.

Side-effects: Paracetamol has remarkably few and mild side-effects when administered in ordinary doses. It does not cause gastrointestinal bleeding, analgesic nephropathy or coagulopathy. Table 10.7 shows the main reported side-effects, all of which are rare in clinical practice, except perhaps abdominal pain and vomiting (incidence around 1%). Paracetamol intake during pregnancy may be associated with increased risk of early childhood wheeze and asthma. Paracetamol may rarely interfere with glucose homeostasis in the liver causing hypoglycaemia.

Drugs reported to interact with paracetamol include warfarin, metoclopromide, beta-adrenergic blockers and chlorpromazine.

Overdose

Toxicity of paracetamol is infrequent in children, and fatalities below the age of 13 years are almost unknown. It has a wide therapeutic margin, and only a much higher dose (>15 gm in adult and 150 mg/kg in a child) is associated with significant hepatotoxic effects. It has been suggested that the sulphate (the predominant

Table 10.7 Adverse reactions of paracetamol

Gastrointestinal	Vomiting, abdominal pain
Dermatological	Urticaria, erythema multiforme, purpura
Respiratory	Bronchospasm
CNS	Dizziness, irritability, blurred vision, hypothermia
Other	May prolong viral shedding in some infections, e.g. varicella, causing no alleviation of symptoms and may prolong the illness

metabolite of paracetamol found in children below the age of 12 years), in contrast to the glucuronide (the predominate metabolite found in adults), protects children from liver toxicity. As paracetamol is minimally bound to plasma protein (10%, while salicylate is 70–90% bound), elimination from the body is rapid. Therefore, chronic toxicity from accumulation, seen commonly with salicylates, is unknown.

Paracetamol is the most common drug used for self-poisoning in the UK. Admissions caused by paracetamol poisoning in England and Wales have risen from 150 in 1968 to around 25,000 in 2001–2002, resulting in estimated 150–200 deaths and 15–20 liver transplants each year in England and Wales [17].

Major complications from paracetamol toxicity include:

- Liver necrosis. Paracetamol and its two major metabolites, sulphate and glucuronide, are not toxic. Instead, a minor intermediate (N-acetyl-p-benzoquinonimine) is highly reactive with hepatocytes, causing necrosis. The ingestion of a toxic dose or a blood level higher than 300 mg/dL at 4 h after intake is likely to produce liver necrosis.
- Other complications include acute pancreatitis, acute tubular necrosis, hypophosphataemia, renal failure, thrombocytopenia, hypothermia, encephalopathy, cardiomyopathy, hyperglycaemia, hypoglycaemia, metabolic acidosis and coagulation defects.

Management of paracetamol toxicity includes the following:

- Plasma paracetamol measurement should be performed 4 h after ingestion.
- Activated charcoal is administered to minimize the drug absorption.
- The specific antidote is N-acetylcysteine, which acts mainly by enhancing glutathione stores and providing a glutathione substitute. A standard dose consists of 300 mg/kg administered intravenously over a 20 h period. This treatment prevents most complications, including deaths. Hepatic toxicity rarely occurs when N-acetylcysteine is begun within 10 h of ingestion (Fig. 10.1).

Criteria associated with poor outcome include arterial pH <7.30 after the first day of overdose, prolonged prothrombin time, high serum creatinine and the presence of encephalopathy.

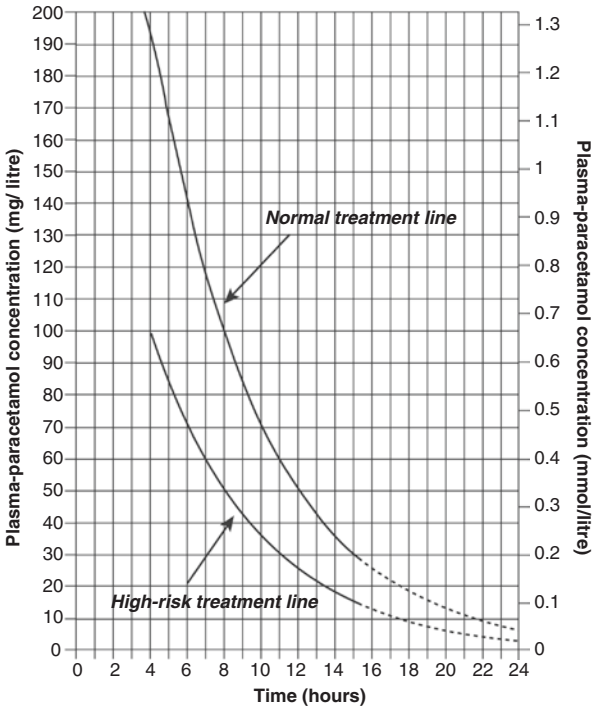

Fig. 10.1 Treatment of paracetamol poisoning according to its concentration and time of its intake

10.6.2 Ibuprofen

This drug (propionic acid derivative) became the only non-steroidal anti-inflammatory drug (NSAID), approved as an antipyretic in the USA since 1984 and in the UK since 1990. Ibuprofen is the mostly used NSAID for pain, and it is the treatment of choice for mild to moderate pain with an inflammatory component, such as arthritis or synovitis.

The drug is well absorbed from the gastrointestinal tract, reaching a peak serum concentration in about 1 h. An oral suspension (e.g. Nurofen) is available for children who are older than 3 months of age. Its anti-inflammatory and analgesic properties provide additional therapeutic advantages over paracetamol in the treatment of various febrile infectious diseases. Rectal ibuprofen is available, e.g. for perioperative pain control. In summary, ibuprofen is used as:

- Antipyretic: The maximal effective level of antipyresis can be achieved with a dose of 5 mg/kg for at least 3–4 h. A dose of 10 mg/kg is more potent and has longer-lasting fever suppression than paracetamol. The onset of antipyresis tends to be earlier, and the effect greater in infants than older children.
- Analgesic, antipyretic and anti-inflammatory effects in juvenile idiopathic arthritis (JIA). A dose of 20 mg/kg/day has a greater therapeutic effect and fewer side-effects compared to aspirin in a dose of 60–80 mg/kg/day.

- Anti-inflammatory agent, which has been shown to retard the progression of lung disease in cystic fibrosis.
- Prostaglandin inhibitor. Intravenous ibuprofen is effective in closing patent ductus arteriosus (PDA) in premature infants (comparable to indomethacin), with less side-effects including minimal effects on renal function.

Toxicity

Ibuprofen has favourable therapeutic benefits with few adverse effects compared to its widespread use. Children after an ingestion of 100 mg/kg are unlikely to present symptoms. Even doses of 300 mg/kg are often asymptomatic. Management of a case with toxicity includes activated charcoal and general supportive care. There is no specific antidote against ibuprofen toxicity.

Drug-related adverse reactions (Table 10.8) are mostly dose-related and occur more often than those associated with paracetamol. Adverse reactions from ibuprofen are less than those associated with aspirin:

- Ibuprofen is contraindicated in neonates (except for closure of PDA). It should not be used for children with wheezing, asthma and varicella.
- Fever, particularly with insufficient fluid intake, is a common cause of dehydration. Ibuprofen can cause renal insufficiency in association with dehydration. Therefore, ibuprofen should not be given to children who are dehydrated with diarrhoea and vomiting with fever.
- Prostaglandins protect the gastric mucosa. Bleeding from ibuprofen (as prostaglandin inhibitor) is rare but may occur particularly in patients taken other NSAIDs. In a meta-analysis involving 46,000 patients, the incidence of digestive adverse events was 5%, with 0.02% upper gastrointestinal bleeds [18].

Table 10.8 Dose-related adverse reactions to ibuprofen

Organ	Antipyretic/anti-inflammatory dose	Overdose
GI-system	Vomiting, nausea abdominal pain, diarrhoea	Vomiting, nausea abdominal pain, diarrhoea, blood in
CNS	Irritability, headache, agitation	Confusion, blurred vision, nystagmus, seizure, coma
Skin	Rash	Rash
Renal	Oedema, Na-retention, proteinuria, haemorrhage, increased creatinine	Renal failure
Liver	Increased enzymes	Increased enzyme
Respiratory	Possible increased risk of asthma after prenatal and infant exposure to ibuprofen	
Haematology	Agranulocytosis, haemolytic anaemia	
Other	Hyperthermia, systemic lupus, hearing loss? Teratogenic (gastroschisis)	

10.6.3 Aspirin

Until 1980 aspirin was the most widely used antipyretic and analgesic in paediatric practice. Aspirin had about 70% share of the USA market, with paracetamol taking the remaining 30% market. In the UK the trend was approximately the opposite. Trials comparing equal doses of aspirin and paracetamol demonstrated an identical antipyretic effectiveness, with aspirin being more effective for analgesia. Following reports linking Reye's syndrome and aspirin, the Committee on Infectious diseases of the American Academy of Pediatrics concluded in a report in 1982 that aspirin should not be given to any child with varicella or with possible influenza.

Aspirin is used as an:

- Antipyretic/analgesic. Although aspirin is no longer recommended for such an indication, it is still frequently used. As the half-life of salicylate blood level is 3–4 h, four to six times daily in a dose of 10–15 mg/kg is appropriate.
- Anti-inflammatory in rheumatic diseases, such as juvenile idiopathic arthritis (JIA) and rheumatic fever. An initial dose of 80 mg/kg in three to four divided doses is followed by a dose adjusted to maintain a serum salicylate level of 20–30 mg/dL. As Reye's syndrome has been reported in patients with JIA treated with aspirin, the drug has lost popularity in recent years to treat connective tissue diseases.
- Antithrombotic agent for its antiplatelet and fibrinolytic activity. This is recommended in children with Kawasaki disease, congenital heart diseases and in adults with coronary heart disease.

Adverse effects are shown in Table 10.9. Adverse effects occurring with a salicylate serum level of less than 20 mg/k100 mL are generally considered side-effects, while those occurring at a higher level are considered poisoning. Features of adverse effects and poisoning often overlap.

Groups who are at high risk of developing adverse effects include:

Table 10.9 Reported adverse reactions to aspirin

Organ	Manifestation
General	"Elevated body temperature", sweating, dehydration
Respiratory	Hyperventilation
Gastrointestinal	Vomiting, abdominal pain, gastric ulcer, haemorrhage
Liver	Increased liver enzymes, abdominal pain, hepatitis, RS
CNS	Headaches, dizziness, irritability, confusion, tinnitus
Skin	Rash, often urticarial, angioedema
Kidney	Interstitial nephritis, papillary necrosis
Platelets	Haemorrhage, diminished coagulation

RS Reye's syndrome

- Children with viral infections, particularly with upper respiratory tract infection or varicella (see below Reye's syndrome).
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency. Aspirin is considered to be a haemolytic agent in individuals with G6PD deficiency, and children with this disorder are advised against its use.
- Asthma. Aspirin-induced sensitivity includes wheezing, urticaria, rhinorrhoea and angioedema. Aspirin inhibits the synthesis of prostaglandin, which exerts a bronchodilatory effect.
- Patients with bleeding tendency or undergoing surgical procedure because of irreversible inhibition of platelet function.
- Pregnant women who are generally advised to avoid aspirin because of the increased risk of:
  - Perinatal haemorrhage for both mother and offspring if aspirin is ingested within 5 days of delivery.
  - Closure of ductus arteriosus in utero, which can contribute to persistent foetal circulation postnatally.
  - Interference with uterine contractility.
  - Possible stillbirth.
  - Possible (but unconfirmed) foetal malformation. Teratogenicity includes increased risk of certain cardiac defects, such as aortic stenosis.

Poisoning may result from:

- Accidental or therapeutic salicylate ingestion. The latter is more encountered in paediatric practice.
- Ingestion of oil of wintergreen (methyl salicylate). This can cause severe salicylate poisoning and death (one teaspoon may be lethal).

Table 10.10 summarizes the pathophysiological abnormalities leading to the main features of aspirin intoxication.

Table 10.10 Pathophysiological mechanisms and the resulting clinical findings in aspirin overdose

Pathophysiological findings	Leading to
Direct stimulation of respiratory centre in the CNS	Hyper- and tachypnoea, low pCO_2, increased pH, alkaluria
Inhibition of Krebs cycle enzymes	Acidosis (pH <7.32) due mainly to accumulation of pyruvate and lactic acid
Increased metabolism of lipids	Vomiting, acidosis, accumulation of ketone bodies and ketonuria
Stimulation of hepatic glucogenesis and failure of tissue to utilize glucose	Glucose↑, or↓ (the latter is often a feature of chronic intoxication)
Increased metabolism, osmotic diuresis, increased excretion of bicarbonate, starvation	Dehydration, loss of salute and water, accumulation of ketone bodies, hypokalaemia, hyponatraemia

Table 10.11 Signs of salicylate poisoning according to the amount of ingested salicylate and salicylate blood levels

Degree	Intake (mg/kg)	Serum level (mg/dL)	Expected findings
Mild	100–150	20–40	Hyperpnoea, vomiting, tinnitus, lethargy, mild dehydration
Moderate	150–300	40–60	As above, but more severe, plus disorientation, fever
Severe	300–500	60–100	Coma, seizure
Potentially fatal	>500	> 100	

Whereas in older children and adults respiratory alkalosis predominates the clinical picture, in young children the phase of respiratory alkalosis is brief, and by the time the child reaches the hospital, metabolic acidosis mixed with respiratory alkalosis is usually established. In infancy or in severe salicylate poisoning, marked disruption of the acid-base status may occur, manifesting as low blood pH. The presence of only respiratory alkalosis may signify either mild or early poisoning. Table 10.11 lists the clinical findings of aspirin poisoning according to the degree of severity.

Investigation should include:

- Blood for FBC, salicylate level, glucose, liver function tests, prothrombin time, gas analysis, bicarbonate, electrolytes and urea, ketone bodies and osmolality.
- Urine pH. The ferric chloride test is useful. When positive, the urine colour turns violet or purple indicating the presence of salicylate.
- ECG monitoring.

Management of aspirin poisoning: see Table 10.12.

Reye's Syndrome (RS)

This syndrome was first described as a clinical entity by Reye in Australia in 1963. It affects children of any age, but most patients are in the age group of 6–8 year.

RS is defined an acute noninflammatory encephalopathy associated with fatty metamorphosis of the liver. Diagnostic criteria are:

- Alteration in the level of consciousness.
- Threefold or greater rise in levels of alanine and aspartate transaminases (normal <40 U/L), ammonia (>100 micromol/L), hypoglycaemia (<2.4 mmol/L (40 mg/100 mL) and prolonged PT (>4 s).
- Normal CSF.
- No other explanation for the hepatic or cerebral abnormalities.
- Histological findings (not essential for the diagnosis), which include small droplets of fat infiltration without inflammatory changes under the light microscope and electron microscopy showing abnormal hepatocyte mitochondria with varying degree of enlargement, decrease in matrix density and loss of mitochondrial dense bodies.

Table 10.12 Management of aspirin poisoning and Reye's syndrome (RE)

• Admission to an intensive care facility, with monitoring of vital signs, water and electrolyte balance, blood gas analysis and pH of the urine. There is no specific antidote
• Activated charcoal
• Correction of fluid, electrolyte and blood gas imbalance. Large amount of fluid in the first hours of admission are often needed to correct dehydration
• Forced alkaline diuresis may be beneficial to increase salicylate elimination. Bicarbonate (1–2 mEq/kg) may be required to correct acidosis, but vigorous alkali therapy may be dangerous
• Coagulation defects are treated with vitamin K derivative
• In cases of RS, prompt blood exchange transfusion and early diagnosis can significantly reduce case fatality
• High body temperature is treated with tepid sponging
• In severe poisoning not responding to the above measures or if symptoms worsen, haemodialysis should be considered. Respiratory failure necessities artificial ventilation

The definite cause of RS remains unclear but appears to be the result of interactions between viruses (influenza A and B, adenoviruses, varicella) and medications. It is possible that aspirin enhances virulence of certain viruses by blocking the antiviral effect of interferon. Other factors such as toxins (aflatoxins) and genetic predisposition have also been suggested to cause RS.

Supporting the association between aspirin and RS is:

- A statistically significant correlation between the development of RS and administration of aspirin during a viral infection.
- A similarity between salicylate toxicity and RS. Both conditions may show vomiting, hyperventilation and confusion, acid-base abnormalities and most significantly similar hepatic histological findings with fatty infiltration and preservation of lobular structure.
- The occurrence of RS in children taking salicylate for connective tissue diseases.
- A progressive decline in the incidence of RS with the drastic reduction in the use of aspirin since 1988.

Clinical features are characterized by a mild prodromal viral illness (such as URI or varicella) followed abruptly by:

- Vomiting followed by alternation of consciousness (lethargy, delirium, coma) and often convulsions
- Varying degrees of hypertonicity, continuing convulsions and decerebrate rigidity, indicating a poor prognosis
- Liver enlargement
- An EEG with generalized slow-wave activity

Management of Reye's syndrome (See Table 10.12)

10.6.4 Other Antipyretics

- Naproxen, also anti-inflammatory and analgesic, has a long plasma half-life of about 14 h. Therefore, twice daily administration is appropriate. It is effective in patients with cancer.
- Indomethacin is not used as an antipyretic in children because of the availability of other antipyretics with less adverse reactions. Its complications include gastrointestinal (vomiting, bleeding, ulcers) and CNS symptoms (headache, dizziness, confusion). The drug is effective in the treatment of fever in cancer.
- Disprove is another pyrazolone derivative, but unlike paracetamol, it has a high rate of toxicity, particularly agranulocytosis, which led to its withdrawal from the USA market in 1977. It is still used in many parts of the world (dose: 15 mg/kg). The drug is no longer recommended for use in children.
- Salicylamide is rarely used nowadays as an antipyretic. It is less effective than paracetamol or aspirin in reducing fever.
- Antipyrine was widely used as an antipyretic throughout the world but has been withdrawn because of toxicity, particularly agranulocytosis.
- Nimesulide is an NSAID with antipyretic, anti-inflammatory and analgesic activities. A dose of 5 mg/kg/day three times daily has a prompt antipyretic effect. Adverse reactions include abdominal symptoms, gastrointestinal bleeds, hypothermia and elevated liver enzymes (to be avoided in liver disease).
- Chlorpromazine is an antipyretic through both a central hypothalamic and a peripheral vasodilatory effect. Surface cooling potentiates the effect of chlorpromazine and may result in hypothermia and postural hypotension.

10.6.5 Steroid Antipyresis

Steroids have an antipyretic effect, and patients receiving long-term steroids may have either no fever or a reduced fever in response to infection. Usually, fever suppression lasts about 3 days following withdrawal of steroids. The effect is due to:

- Suppression of the bacterial antigen lipopolysaccharide (LPS)
- Reduced production of interleukin-1 (IL-1) by macrophage
- Suppression of acute-phase responses with ongoing infections
- Suppression of lymphocyte activity and local inflammatory response
- Inhibition of prostaglandin release

10.7 Combining Antipyretics

In recent years it has become a common practice to combine the two antipyretics paracetamol and ibuprofen to treat febrile children in hospital and at home. This practice is discouraged (Table 10.13). Although there is some evidence that this practice of combining/alternating antipyretics may be more effective at reducing

Table 10.13 Combining antipyretics: key points

Paracetamol is frequently used in an alternating manner with ibuprofen for the treatment of febrile children. This practice is not recommended because:
• There is presently no scientific evidence in support of this practice
• There is no evidence that a greater antipyretic effect influences the underlying disease or duration of fever
• Combining/alternating antipyretic practice often leads to wrong dosage, particularly overdosing
• It may suggest to the parents that fever is a grave situation, and this may worsen parents' fever phobia
• Practitioners who choose this practice should council parents on proper dosing and intervals and emphasizing the child's comfort instead of reduction of fever

fever for a greater period of time than monotherapy, a recent Cochrane search found no evidence that it improves the child's comfort or changes the outcome of the underlying disease [19].

10.8 Physical Treatment

Physical methods used to lower body temperature include:

- Bed rest. Intense physical activity can increase body temperature in febrile and afebrile individuals. However, the movement of a febrile child during normal activity is usually not intense enough to do that. It is the general impression of many paediatricians that febrile children who are not resting in bed recover as quickly as children who rest in bed. Therefore enforcing bed rest in febrile children is not only ineffective but may be undesirable and psychologically harmful. In one controlled study of 1082 febrile children, bed rest was not found to have a significant effect on temperature reduction [20].
- Alcohol sponging using either 70% ethyl or 70% isopropyl alcohol in water is an effective method for reducing fever and may be superior to sponging with tepid water. Alcohol inhalation during sponging can induce hypoglycaemia and coma. This method is contraindicated.
- Tepid sponging. Tepid is the only recommended water temperature for sponging. The use of tepid sponging for febrile children is unnecessary because of the availability of antipyretic drugs, which are simpler to use, more effective in reducing body temperature and cause less discomfort to children. Furthermore, in treating fever vigorously by combining an antipyretic drug with physical methods, parents may be given the impression that fever is harmful and antipyresis is beneficial. The scientific evidence does not support this practice. When doctors and parents feel that sponging is necessary (e.g. high body temperature > 40 °C, which is not responding to antipyretic medications), it is important to use it after administering antipyretic medication to ensure lowering of the hypothalamic set-point.

- Using cool or cold sponging is contraindicated. This opposes the physiologically raised set-point of the thermoregulatory centre of the hypothalamus, which causes shivering leading to a rise of body temperature. Cold sponging causes vasoconstriction, which raises body temperature. Furthermore, the cold sponging is uncomfortable to the child.
- Total body surface cooling. Several methods have been used for total body surface cooling, including cooling blanket, ice packs, air conditioner and circulating ultrasonic humidifier. These methods are primarily indicated to treat patients with hyperthermia (Chap. 2 Hyperthermia).

10.9 Management of Fever in Hospital

10.9.1 Assessing a Febrile Child

A febrile child may present either with localized signs of infection (fever with a source), fever without localizing signs (found in 20% of all febrile children) or rarely with fever of unknown origin. This classification is clinically useful since each has different causes and management. For example, an upper respiratory tract infection is the most common cause of fever with localized signs, while urinary tract infection is the most common bacterial cause in febrile children without localizing signs (see detail Chap. 1).

Management should include taking history, performing physical examination and laboratory investigation:

History, focusing on:

- Onset, duration and the degree of fever recorded at home
- Presence of similar symptoms in other family members
- Pattern of feeding, degree of activity and playfulness at home
- Pre-existing disease
- Previous administration of antibiotics

Physical examination, which is performed in two parts:

- Observation of items to predict serious bacterial infection (Table 10.14). These items, combined with a history and physical examination, can identify most serious diseases in children.
- 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 a diagnostic test most likely to provide a diagnosis.
- Screening tests include full blood cell count (FBC), looking particularly at the WBC count, CRP and urine dipsticks.

Table 10.14 Observation Scale to differentiate between febrile ill and well children

Observation Item	Signs not suggestive of a serious (e.g. viral illness)	Signs suggestive of a serious illness (e.g. SBI)
• Cry	Strong	Weak and moaning
• Stimulation	Content	Continual cry, hardly respond
• Alertness	Alert, slightly drowsy	Falls asleep, difficult to arouse
• Colour	Pink	Pale, mottled, ashen
• Breathing	Normal	Tachypnoea, grunting
• Response	Smile	No smile, face dull or anxious
• Playfulness	Play	No
• Feeding	Well	Not interested
• Eye contact	Present	Absent

- In small children, chest auscultation is unreliable, and chest X-ray is usually necessary to diagnose pneumonia.
- Blood culture is essential in an ill child without a focus of infection.
- Pulse oximetry is mandatory test for any ill child.
- The ultimate goal of assessing a febrile child is to identify the child with serious bacterial infection so that appropriate antibiotics may commence to treat the infection (see later).

10.9.2 Measurement of Body Temperature (See Also Chap. 4)

Measurement of temperature is an essential part of the routine examination for all patients attending the A & E department and GP surgery. Disagreement still exists as to the best thermometer and anatomical site for temperature measurement.

An ideal thermometer should have the following characteristics:

1. Accuracy, i.e. a reliable thermometer for predicting fever, reflecting core body temperature, in various age groups
2. Easy and convenient usage by patient and practitioner
3. Short duration of temperature measurement
4. Comfort and avoidance of embarrassment
5. No cross infection
6. Not influenced by ambient temperature
7. High safety factor
8. Low cost and cost-effectiveness

Most hospitals and GP surgeries use the electronic thermometer, which has replaced mercury in glass thermometer. The major advantages of these electronic devices are their rapid response and the ease in reading the digital measurement. One question that still exists is the choice of anatomical site for the temperature measurement by the electronic thermometer: axillary (AT), rectal (RT), or sublingual (or oral) temperature (OT).

- There is universal agreement that AT is inaccurate and insensitive when compared to any core temperature (i.e. from the pulmonary artery, oesophagus or bladder) with the exception of afebrile neonates in neonatal units where the environmental temperature and humidity are maintained at optimum levels. A systematic review of 20 studies comprising 3201 children confirmed the inaccuracy of AT [21].
- RT measurement is more accurate than axillary measurement. However, the procedure is frightening for small children and may be psychologically harmful for older children. In addition, it is time-consuming, requiring often a private room, undressing and the attendance of a nurse. It may rarely cause rectal perforation. RT is reliable only if the body is in thermal balance and reacts slowly to changes in temperature. RT is contraindicated in certain children, such as neutropenic oncology or HIV-infected patients.
- The OT is not used in children less than 5 years of age, and this is the group with the highest incidence of fever.
- There are many potential benefits to infrared ear thermometry (IRET). The technique is fast and easy to use without risk of cross infection and is not influenced by environmental temperature. A reduction in the numbers involved in a nosocomial outbreak of vancomycin-resistant enterococcus and clostridium difficile infection has been achieved by replacing rectal and oral thermometers with tympanic membrane thermometers. The use of tympanic thermometers saves nursing time and is therefore cost-effective. In recent years, tympanic thermometers have become popular both with health professionals and at home.

In conclusion, an ideal thermometer involves a combination of the best instrument and most appropriate site. Tympanic thermometry appears to offer such a combination as it provides an accurate assessment of core body temperature in about 2 s. In addition, this technique is clean, safe and cost-effective.

10.9.3 When Should a Febrile Child Be Admitted to Hospital?

Febrile children should be considered for hospital admission if:

- They are neonates (less than 28 days).
- They appear toxic or ill-looking (irritability, inconsolable crying, lethargy).
- There is a history of PUO or prolonged fever.
- Serious bacterial infection (SBI) is suspected or present.
- They present with bloody diarrhoea, increased abdominal tenderness or drowsiness.
- There are associated skin petechiae.
- An infant has fever >40 °C, particularly >40 °C without a focus.
- The child has his/her first febrile seizure (FS).

- There is tachypnoea, grunting, rash, headaches or vomiting.
- Parents appear unreliable and follow-up is not assured.
- They have significant risk factors such as immunodeficiency or SCA.
- They have abnormal laboratory results such as WBC > 20,000, or high CRP.
- The patient is a young child with urinalysis suggestive of UTI.

Febrile children may be sent home provided that:

- They appear well and playful.
- A urine sample has been sent for culture, or urine dipsticks are negative for nitrate and WBC.
- A follow-up appointment is arranged within 24–48 h if fever persists.
- Parents are informed that children should return if condition worsens.

Children with fever usually do not require antibiotics. Children with suspected or confirmed SBI, or with abnormally high WBC or CRP and who appear well, can be managed with IV or IM ceftriaxone. A follow-up in 24 h should be arranged.

10.9.4 When to Use Antipyretics?

Antipyretics may be indicated as a matter of routine in the following conditions:

- Symptomatic fever with pain, discomfort, delirium and excessive lethargy. Antipyretics serve here to improve the child's well-being, allowing the child to take fluid and reduce parental anxiety.
- Children with bronchiolitis. A study has shown that the presence of fever did not benefit children admitted with bronchiolitis [22].
- In situations associated with limited energy supply or increased metabolic rate (e.g. burn, cardiovascular and pulmonary diseases, prolonged febrile illness, young children, undernourishment, postoperative state). Fever can increase the metabolic rate and could exert a harmful effect on the disease
- High fever (>40 °C) for the following reasons:
  - Children with this high degree of fever are likely to be symptomatic.
  - With the exception of a few diseases such as *Salmonella* gastroenteritis and febrile seizures mentioned above, there has been no scientific evidence that high fever is beneficial.
  - The overwhelming and prevailing view among physicians and parents is that high fever in particular is harmful and omission of antipyretics therefore seems unethical.
  - With the exception of a few diseases such as *Salmonella* gastroenteritis mentioned above, there has been no scientific evidence that high fever is beneficial in most situations.

When Not to Use Antipyretics?

- A child who does not have one of the above conditions, that is a child who is well with minimal symptoms despite the fever. This constitutes a substantial proportion group of febrile children.
- Physical measures such as a fan or tepid sponging are discouraged. These are unnecessary and unpleasant for the child. Rather keep the room cool and open the window.

10.9.5 Proposed Guidelines for the Use of Antibiotics

Antibiotics are indicated for febrile children in the following indications:

- All children with a focus of infection suggestive of a bacterial disease.
- All neonates and ill-looking children. (See the Observation Scale Table 10.14).
- Children with high fever >40 °C less than 36 months of age who have no focus of infection may receive ceftriaxone while waiting for culture results.
- Children without focus of infection whose screening tests (FBC, CRP, urine dipsticks) are abnormal.

10.10 Management of Fever at Home

10.10.1 Temperature Measurement

Parents use body temperature to determine their child's state of health. When their child is ill, they like to know their temperature and use touch and thermometers to determine fever. Although parents take temperatures regularly, many are unable to either accurately take a temperature or read a thermometer. Despite this, parents initiate activities to reduce fever based on incorrect readings and sometimes normal temperature. Parents judge how their child must feel by how they themselves feel when they have a similar temperature. This is inaccurate as children have higher body temperatures than adults; body temperature does not stabilize to adult levels until puberty.

It is unnecessary to monitor frequently the child's temperature, and parents must be advised against this. Daily temperature checking, preferably in the morning, is sufficient to determine continuation of fever. However, when children feel very hot or are miserable, it is advisable to take temperatures more frequently. An incorrectly high temperature measurement leads to unnecessary antipyretic use. Another unfortunate aspect of depending on temperature assessment is that parents might not seek medical assistance for a lethargic, toxic child with a low temperature reading.

Parents must be informed about circadian influences on body temperature and to not be overly concerned by a slight rise in temperature late afternoon and early evening, which can be as high as 1 °C. Health professionals must provide accurate, consistent advice about temperature taking and assist parents to accurately take their child's temperature with the thermometer they use at home.

10.10.2 Assessing a Febrile Child

Parents are alerted to the possibility their child may be febrile by:

- Changes in the child's normal behaviour. Over time parents learn to recognize their own child's fever specific behaviour and will touch the child to see if they are "hot", if so most take the child's temperature.
- The child being often flushed, refusing food and fluids and not sleeping well.

Guidelines for parents' assessment of their child have been developed by the National Collaborating Centre for Women's and Children's Health [23]and include the child's:

- Skin colour: does the child have normal colour of the skin, lips and tongue; or does the child look pale or is their skin mottled or ashen?
- Activity levels: are they normal and is the child responding normally to social cues, staying awake or able to be wakened easily; does the child have a strong normal cry; or is the child not responding normally to social cues, needing prolonged stimulation to awaken the child, listless and lethargic with reduced activity levels?
- Respiratory rate: are there signs of nasal flaring and tachypnoea, is their respiratory rate normal for the child, is their evidence of grunting or can they see moderate or severe drawing in of the chest?
- Hydration: do the child's skin, eyes and moist mucous membranes appear normal or do the mucous membranes look dry; in infants are they feeding normally or poorly, is there a reduction in urine output or skin turgor or is there bile stained vomiting?
- Fever: have they had a fever for more than 5 days, are they younger than 3 months and have a temperature 38.0 °C or greater or between 3 and 6 months and have a temperature 39.0 °C or greater?
- Joints: is there swelling of a limb or joint, is the child not weight-bearing on a limb or not using an extremity or is there a new lump?
- Other: does the child have a non-blanching rash, bulging fontanel, neck stiffness and fits or have any focal neurological signs?

10.10.3 Antipyretic Measures

The administration of the common medications used as antipyretic and analgesic, paracetamol and ibuprofen, leads to a reduction in discomfort and temperature in a febrile child. This can cause confusion about the role of analgesics/antipyretics and support beliefs that reduction of fever may reduce the severity of the illness. Although professionals may report positive attitudes about the benefits of fever, continuing education in fever management is needed to change the uninformed practice of antipyretic overuse.

Antipyretics are parents' preferred method of managing fever. Of concern for health professionals is that similarly to temperature taking parents' antipyretic administration is often incorrect both in dose or frequency. Underdosing increases health service usage and encourages alternating antipyretics to maintain normal temperature. Overdosing is potentially harmful.

Many parents expect antipyretics to normalize fever and prevent its recurring. As fever does nor normalize body temperature or prevent recurrences of fever, parents' concerns increase leading to increased antipyretic use, including alternating antipyretics, and increased health service use. Alternating antipyretics is an increasingly common practice with parents. Parents alternate the drugs in order to prevent overdosing or unwanted side-effects from one antipyretic; some considered this safer than monotherapy. On the other hand, despite relying on antipyretics to reduce fever, many parents believe antipyretics can cause harm such as liver and kidney damage, unconsciousness or death and stomach irritation. The continued use of antipyretics even though parents believe they may be harmful highlights parental concern about fever and the need to control it.

Many health professionals recommend parents' alternate antipyretics although:

- There is lack of evidence of the safety of this practice.
- The practice can increase parents' fever phobia.
- It also increases the risk of incorrect dosing which is more likely with ibuprofen than paracetamol.
- It increases parental preoccupation with the height of the fever and the need to control it to prevent adverse events. It increases their fears which in turn increase antipyretic and health service use.

Recognition of the need for caution in advising parents to alternate antipyretic is readily available. This practice should only be considered on an individual basis following advice from a health professional who provides parents with written instructions indicating antipyretic preparations, doses and frequency of administration. Alternating is not recommended as routine practice.

Parents need to understand that all drugs, including antipyretics, have potentially noxious side-effects. Those reporting adverse events following ibuprofen administration are fewer as it is a newer drug. However, ibuprofen has been reported to be associated with more adverse drug reactions than paracetamol; it is not recommended as a first-line treatment. There is an urgent need for parents to realize the need for accuracy and caution with the use of these drugs despite their ready availability in many stores. The use of antipyretics and advice about their use should always be directed by competent health professionals.

10.10.4 When to Contact the GP?

Fever remains a common factor influencing parents to seek medical advice. The overuse of health services for self-limiting viral infections has been the impetus for

early fever management education interventions. To ensure parents seek medical advice, it is important physicians educate them about the:

- Beneficial effects of fever.
- Thermoregulation, in particular that fever is well controlled, does not climb up relentlessly and does not damage the brain.
- Benign nature of febrile seizures and that antipyretics cannot prevent them.
- Rational use of antipyretics and that they are not always needed for fever.
- Higher rate of febrile episodes in children compared to adults.

Parents should seek medical advice immediately when the child is:

- Younger than 3 months, unless following DPT immunization.
- Fever is 40.5 °C (105 °F) of higher.
- Crying inconsolably or whimpering.
- Difficult to waken.
- Cries when touched.
- Has a stiff neck.
- Suffers severe headache, neck stiffness or light hurts their eyes.
- Purple spots are present on the skin.
- Having trouble breathing, even after the nose is cleared.
- Unable to swallow and drooling saliva.
- Looks or acts very sick.
- Looks “sick”, pale, lethargic or weak.

Call the doctor in the next 24 h if your child:

- Has fever that is 40 °C–40.5 °C (104 °F–105 °C) especially if the child is younger than 2 years
- Complaints of burning or pain on urination
- Has had a fever for more than 24 h without an obvious source or location of infection
- Refuses to drink
- Persistently vomits
- Has pain
- Shows no improvement in 48 h
- Continues with fever and is under 6 months of age
- Shows signs of drowsiness

Call the doctor during office hours if:

- The child has been febrile for more than 72 h.
- The child had a fever that went away for 24 h or more and has returned.
- The child has a history of febrile convulsions.
- You have any other concerns or questions.

10.11 Fever Phobia and Its Management

Fever, a common occurrence in childhood, is a frightening experience for parents. They believe fever is harmful and brings about febrile convulsions, brain damage, death, dehydration and discomfort and therefore must be controlled. These concerns have been increasing over the past decades resulting in more concerns about brain damage, febrile seizures and frequent administration of antipyretics. These concerns reflect parents' fever phobia. Some health professionals contribute to parents' fever phobia through:

- Continuing reports of febrile convulsions and brain damage
- Recommendation of regular antipyretics, even alternating antipyretics, despite evidence that fever is not harmful and antipyretics do not prevent febrile convulsions
- Unnecessarily advising to reduce fever
- Distributing conflicting information from doctors about illness severity and their proposed management, which increases parents' uncertainty about how to best care for their febrile child

To address parents' fever phobia, health professionals must update their own knowledge about fever and consistently advise parents to:

- Manage fever in an evidence-based manner.
- Manage their febrile children at home including careful observation of the child's interaction with the environment and response to fever.
- Prevent dehydration by encouraging fluids, small, frequent drinks of clear liquid, e.g. water or diluted juice.
- Reduce distressing symptoms such as pain and discomfort with recommended doses of analgesics.
- Observe the child closely, focusing on the child's well-being rather than temperature.
- Maintain an awareness that mild to moderate fever is beneficial and supports the immune system.
- Make the child comfortable, dressing them in light clothing, not overdressing.
- Provide a light blanket for children who are cold or shivering.
- Selectively reduce fever with medications when fever is:
  - Greater than 39.0 °C and associated with discomfort
  - 40 °C or higher
  - In all children who are irritable, miserable or appear to be in pain, irrespective of the height of body temperature

Accurately medicate their child as follows – for children up to 6 years:

- Paracetamol 15 mg/kg every 4 h up to four times a day
- Ibuprofen, always administered with food or milk, check labelling as dosage is age-related until 2 years (ibuprofen is not recommended for all children; check the recommendations for your country) then 10 mg/kg three to four times a day

- Aspirin should be avoided
- Do not continue giving regular medication for more than 48 h without having your child assessed by a doctor.

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Fever and Complementary and Alternative Medicine

11

Core Messages

- CAM = Complementary (practice used in addition to conventional) and alternative (practice used instead of conventional) medicine.
- Practically all human cultures have used some form of CAM.
- There has been little research in CAM on the subject of fever. Trials are needed to assess the effect of herbal antipyretic medicine on the treatment of fever.
- CAM aims to treat the patient as a whole; treatment attempts to stimulate the body self-healing abilities.
- While conventional medicine is largely science-based, CAM is largely based on beliefs. Part of the success may be due to placebo effects.
- More research is needed to determine what practice in CAM is superior to the conventional medicine so that it can be advocated for wider use.
- CAM should be evidence-based and procedures scientifically based.
- Consumers of herbal or homeopathic products are advised to take them only if these are officially licensed, and not for prolonged use. Chinese herbal medicines with complex ingredients are best avoided due to reported side-effects.

Complementary and Alternative Medicine (CAM)

CAM is a group of diverse medical and healthcare practices and products that are not presently considered to be part of conventional medicine. Complementary medicine is used alongside the conventional medicine, while the alternative medicine is used instead of the conventional medicine. Most population in the developing world rely on CAM for health issues using some form of CAM, as discussed in the chapter.

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_11

11.1 Homeopathy

Homeopathy is considered as a holistic system of medicine that uses highly dilute substances in an attempt to stimulate the body's potential for self-healing. It was developed two centuries ago by the German doctor Samuel Hahnemann, who thought the side-effects of the orthodox drugs were unacceptable. He then began to investigate the healing power of natural remedies. His research was published between 1811 and 1821 in six volumes "Materia Medica Pura". The homeopathic practice is based on the principle that if a symptom picture is correctly matched to its compatible remedy, then the patient would be swiftly cured.

Fever is the body's natural way of fighting infection by stimulating the immune system to activate and produce substances capable of destroying the invading organisms. Homeopathy helps fever not by suppressing it but stimulating the body to overcome the infection causing the fever.

The following drugs have been used in the homeopathy to treat fever:

- Belladonna. It is said to be most beneficial in the first few hours of fever. It can cause hallucination and confusion.
- Aconitum napellus (monkshood, also known as Wolfsbane) is effective against fever if it is given for early stage of a febrile illness in association with cold symptoms. It is also used to treat the initial stage of croup. It is poisonous in large quantity, usually after consuming the plant.
- Chamomilla (German Chamomile). This agent has been advocated for young children with teething and for older children with prolonged fever. Its main therapeutic use is for digestive disturbance. It can be rubbed into the painful area of the gum.
- Tanacetum parthenium (feverfew or wild quinine). This herbal preparation is used as a traditional remedy for migraine and fever.

Homeopathy is one of the most controversial methods of complementary medicine, mainly because of the high dilution of the substances used. The effect of homeopathy is often considered to be no more than a placebo effect. What is the available scientific evidence?

- When recent double-blind and/or randomized trials placebo-controlled trials with homeopathy were recently studied, the results of systematic reviews and meta-analysis showed that the clinical effect of homeopathy is not indistinguishable from placebo. Homeopathy show clinical effects on several diseases including influenza, irritable bowel syndrome and allergic rhinitis [1].
- In searching placebo-controlled trials of oscillococcinum for treatment of influenza and fever, this homeopathic medicine was found to slightly reduce the duration of the symptoms [2].
- A placebo-controlled trial in children with recurrent upper respiratory tract infections showed a small but insignificant difference in symptom score in favour of the homeopathic medicines [3].

- In a controlled trial, a homeopathic medicine (Viburcol) was compared with acetaminophen (paracetamol). Viburcol was found as effective as the antipyretic and better tolerated [4].

11.2 Herbal Medicine (Herbalism)

The use of herbal medicine dates back at least 5000 years to the Sumerians. Many conventional drugs are already known to originate from plants, including aspirin (from willow bark), quinine (from cinchona bark), and morphine (from opium poppy). Herbal medicine was challenged over a century ago by the western (conventional) medicine because of lack of scientific evidence. In recent years, there has been a resurgence of the use of herbal medicine due to problems associated with the western medicine, including side-effects of the chemical drugs and increasing drug resistance. In addition, research based on scientific evidence has intensified in search for effective treatment from plants. Recent randomized controlled trials showed adequate management of bronchiolitis using Chinese herbs [5].

Fever is a self-regulated reaction to the infection causing it. The use of herbal treatment against febrile illness aims to support the cleansing process initiated by the body to increase its resistance against the invading organisms. Herbal antipyretics are in thousands. The number of plant species to treat fever and malaria alone accounts over a thousand. The following plants are known to reduce fever:

- Feverfew (Tanacetum Parthenium) is a perennial aromatic herb, which has been used medicinally for a variety of indications, e.g. reduction of fever (hence its name), vasodilatation, sedation and uterine stimulation. It was well known to ancient Egyptian and Greek physicians. Feverfew appears to exert an inhibitory action on prostaglandin production by preventing its production from arachidonic acid. Its extracts inhibit the release of enzymes from polymorphonuclear leukocytes, hence its effectiveness in the management of arthritis. The extracts are effective in treating and preventing migraine. As an antipyretic, feverfew is currently not in use. Feverfew should not be used in children younger than 2 years of age, and it is contraindicated in pregnancy. It also can cause contact dermatitis and mouth ulceration.
- White willow bark (Salix Alba) was used as an anti-inflammatory and analgesic medicine in ancient Mesopotamia, China, and among Native Americans. The white willow is a source of salicin, which was isolated in the 1820s and eventually led to the synthesis of aspirin. It has been used as an antipyretic and in rheumatic diseases. It is not recommended in children because of the risk of Reye's syndrome.
- Anise seed (Pimpinella anisum) is a pleasant-tasting plant, initially native to Egypt, but cultivated in many parts of the world. Anise has anti-inflammatory cytotoxic properties (particularly on colon cancer) and is used to treat fever, bronchitis and sore throat. Anise seed is contraindicated in pregnancy.

- Licorice (Glycyrrhiza glabra) has been used for thousands of years as a treatment for inflammatory conditions through its steroid-like actions. Its strong anti-inflammatory action is utilized to treat pain and fever. Although it is related to steroids, it does not cause gastric or intestinal ulcer. It does not suppress the bone marrow. Prolonged or high dose of licorice may produce mineralocorticoid adverse effects.
- Ginger (Zingiber officinale roscoe) was used in the Middle East for centuries before moving to Europe. It has been used for numerous ailments, ranging from dyspepsia, fever, cholera and malaria. It encourages the body to produce sweat and fight inflammation such as certain types of arthritis. It is currently used for nausea and depression.
- Yarrow (Achillea millefolium) has an anti-inflammatory action and also a cooling effect in fevers by stimulating sweating. A combination of garlic, ginger and lemon is considered by herbalists as the classic remedy for flu.
- Elder flowers (Sambucus nigra) are used in the treatment of many febrile respiratory conditions, particularly those associated with phlegm (colds, flu, bronchitis and sinusitis). Although these flowers are effective against certain pathogens, such as Salmonella typhi and Vibrio cholerae, the clinical relevance of this effect is uncertain. The stems must not be used as they contain cyanide.
- Nigella sativa seeds (black seeds) are commonly used herbs and oil in the Middle East and South East Asia. The seeds have wide therapeutic effects against fever caused by bacteria, viruses and parasites. Seeds are known to support the immune system.

11.3 Aromatherapy

Aromatherapy, meaning treatment using scent, is a particular branch of herbal medicine. The ancient Egyptians are generally regarded as the founders of aromatherapy, and aromatic oils were described on papyri from 1500 BC. The Greeks had a penchant for decorating their heads with fragrant flowers, a form of psychoaromatherapy. Hippocrates advocated daily aromatic bath and scented massage to prolong life. Arab physicians harnessed the power of aromatic oil and floral waters (camphor and rosewater) to purify the air and protect themselves from disease. The crusading knights brought these "Arab perfumes" to Europe. The word aromatherapy was first used in 1937 by the French chemist Rene-Maurice Gattefosse. His research revealed that volatile extract distilled from certain aromatic plants had a good effect on the skin. He also found that essential oils applied to the skin could be absorbed into the bloodstream where they interact with the body's chemistry.

Essential oils are volatile, odoriferous liquid components of aromatic plants. At least 150 essential oils have been extracted for use in aromatherapy. Although essential oils can be used as steam inhalation, aromatherapists tend to favour massage as the most effective way of therapy. Because they are highly concentrated, they must not be swallowed.

The plants are antiseptic (notably eucalyptus), possessing antiviral and antibacterial action. The plants have been shown to reduce body temperature (Table 11.1).

Table 11.1 Some essential oils known to reduce fevers

Essential oils	Clinical effects
Eucalyptus (*Eucalyptus globulus*)	Antiseptic, diuretic and deodorant (should not be used for small children)
Peppermint (*Mentha piperita*)	Remedy for digestive problems, reduces sweating, thus cooling effect on body. It has a stimulant effect, hence not to be used at night
Lemon (*Citrus limon*)	Stimulate the body defences to fight infection, diuretic, laxative
Lavender (*Lavandula angustifolia*)	Relaxing: useful for irritability and low concentration (e.g. for children with ADHD) insomnia analgesic: for headaches, neuralgia, muscular pain, shingles, rheumatism anti-inflammatory: flu, colds

11.4 Safety of Homeopathy, Herbal Medicine and Aromatherapy

The safety of these three forms of alternative medicine (homeopathy, herbal medicine and aromatherapy) remains a concern. Some products are uncontrolled as many countries do not recognize them as medicines. Although the toxicity of certain herbal medicines is well recognized, the incidence of such toxicity is unknown. Herbal products should be free from toxic ingredients and contamination, such as residues of pesticides. Some Chinese medicines contain complex ingredients, which have been associated with serious adverse reactions, such as liver damage by Dictamnus dasycarpus and renal failure by *Stephania tetrandra* and *Magnolia officinalis* (both used as slimming products). Although homeopathic medicines may appear to be too dilute to cause toxic effects, they may however contain toxic metals such as arsenic, cadmium and mercury.

Consumers of these products are advised to take them only if are officially licensed and as directed, and not for a prolonged use. Chinese herbal medicines with complex ingredients are best avoided.

11.5 Acupuncture

Acupuncture was established as part of Traditional Chinese medicine (TCM) prior to third century BCE [6]. The celebrated physician Zhang Zhong Jing (150–219 AD) with his "Treatise on Febrile Disease" categorized and outlined treatment for different types of fever as the disease progressed through the body. Although primarily an herbal text, his work provided the theoretical framework for the acupuncture treatment of fevers. Since the Song dynasty (960–1279), paediatrics has been a recognized subspecialty of TCM with techniques specific to the different clinical realities that children present.

Acupuncture is increasingly common in medical practice today, and among adults, there is substantial evidence supporting its effectiveness in treating such conditions as chronic pain and nausea and vomiting. In particular, there is empirical

Table 11.2 Outcome of evidence-based medicine applied to various medical conditions, which treated by acupuncture [2]

Conclusively positive	Inconclusive	Conclusive negative
Dental pain	Addition	Weight loss
Low back pain	Asthma	Smoking cessation
Migraine	Stroke	
Nausea and vomiting	Rheumatic diseases	

support for the efficacy of acupuncture in treating various conditions of chronic pain affecting particularly the musculoskeletal system [7]. Acupuncture needling releases various transmitters (endorphins, serotonin, norepinephrine), which inhibit the transmission of pain impulses. Applying the rules of evidence-based medicine to acupuncture proves it to be effective for some conditions and ineffective for others [8] (Table 11.2).

In contrast to the large number of trials on acupuncture in adults, there have been relatively few studies in paediatric populations, including only a very small number of trials of acupuncture for pain complaints in children [9]. There is a conventional view that children are afraid of needles, and for this reason, clinicians may hesitate to recommend acupuncture because of concerns regarding its acceptability [10]. However, there is also evidence that at least among children in chronic pain, acupuncture treatment is highly acceptable [11].

Despite the lack of scientific evidence on the treatment of paediatric fevers with acupuncture, there continues to be a rich tradition and abundant empirical evidence for the treatment of such conditions. This tradition includes the recognition that fevers are caused by "external pernicious influences", what we now call viruses or bacteria, and the interplay between these influences and the constitution of the patient determines the kind of treatment that is applied [12]. Fever causes marked release of pyrogenic cytokines IL-6 and TNF-alpha (Chap. 3). Although electroacupuncture in rats has demonstrated a reduction of hypothalamic production of pro-inflammatory cytokines, including prostaglandin-E2, IL-6, IL-1 beta mRNA levels, acupuncture is not usually used clinically to decrease body temperature.

Acupuncture has proved to be very safe and adverse events are extremely rare [13]. Serious adverse events have been estimated to be 0.05 per 10,000 treatments [14]. The most common serious adverse events are hepatitis B and C and HIV infection. It is advisable to ensure that the practitioner is familiar with the treatment of children and uses disposable needles.

11.6 Reflexology

This is a holistic, non-invasive technique aimed to treat imbalances within the body. It is based on the principle that all parts of the body are interdependent and that the body has to maintain a state of balance for optimum energy flow and health. This balance is achieved by applying pressure on certain points (on the feet, hands and ears) that correspond to every organ and gland of the body. By exerting pressure on

these "reflex points", one can stimulate or sedate the nerve pathways linking these points to the corresponding organs. The treatment is said to stimulate the normal function of the organ involved to secrete hormone or enzyme. Reflex areas, which may be used to treat fevers, are:

- Pituitary gland reflex area (hypothalamic/pituitary point) situated in the centre of the great toe. This area is thought to control the autonomic functions as well as the regulation of body temperature.
- Facial reflex area located in the first three toes of each foot. This area is also recommended for teething troubles accompanied by fever.
- Top of the ear. This area is thought to be ideal for any inflammatory condition or any fever. It is said to have a soothing and analgesic effect on the body.

11.7 Massage

For thousands of years, massage has been used to heal and to soothe the sick. Ancient Chinese and Indian texts describe various massage techniques. Greek and Roman physicians used massage as one of the principal means of relieving pain. Hippocrates wrote "The physician must be experienced in many things, but assuredly in rubbing". Massage was almost forgotten during the Middle Ages but was revived in the sixteenth century by the French doctor Ambroise Pare and later at the beginning of the nineteenth century by a Swede Per Henrik Ling (1776–1839).

Massage will not calm a fever. It is not recommended for febrile illness, and it is contraindicated with high fever.

11.8 Shiatsu

Shiatsu means "finger pressure" in Japanese, and it combines massage and acupuncture without the use of needles. It originated in China between 2000 and 3000 BC and was later adopted by the Japanese. It is practiced through a layer of clothing, in contrast to most types of massage.

This method is based on traditional Oriental philosophy and medicine, which believes that everything in existence is a manifestation of energy. The universal energy, called Ki, is required to flow around the human body smoothly in order to maintain optimum health and prevent diseases. Shiatsu practitioners believe that that the body has 12 energy channels (or meridians). Pressure on certain points along these meridian channels is to "unlock energy from being impeded". Certain points are believed to treat fevers, including:

- The end of the elbow flexure (also help to treat cough, sore throat)
- Between the seventh cervical and first thoracic vertebra (also help to treat cold, asthma and headaches)

11.9 Chiropractic

Chiropractic (meaning "done by hand") was founded in 1895 and is based on the belief that the body has an inherent ability for self-healing if nerve impulses are allowed to travel freely between the brain and the rest of the body. This is usually performed by manipulation of the spine. A variety of physiotherapy exercises are used to help relax muscles before manual adjustment is made.

11.10 Osteopathy

This method of healing teaches and practices that the:

- The body is a unit which functions as such.
- The body has its own self-protecting and self-regulating mechanisms.
- Structure and function are reciprocally interrelated.

Diseases according to osteopathy are due to chiefly to loss of structural integrity which can be restored to harmony or equilibrium by manipulation. Practitioners focus on history, observation and palpation. The later involves tissue tone, texture, temperature and moisture. This is followed by manipulation and thrust, such as high-velocity, low-amplitude and muscle energy techniques, which have been the mainstay of osteopathic treatment. Although diseases affecting the musculoskeletal system are the main reasons to use this form of treatment, symptoms, such as fever, are also targeted. Osteopathy may include treatment of nutrition, occupational and physiotherapy, psychotherapy, various types of medicines and spiritual support.

11.11 Spiritual Healing

Spiritual healing is the oldest practiced therapy used in some forms in every culture to treat febrile illness. It is defined as a purposeful intervention by one or more persons aiming to help others by means of focused intention, touch, religious direction or intercessory prayer, without the use of conventional physical or chemical therapy. Spiritual healing is not recommended by medical professionals as an alternative to conventional treatment. However, many support its supplemental usage. In many instances it has been used as a last resort treatment when conventional treatment has had little or no effect.

Practitioners of this method believe that they can penetrate the body through energies that surround the body. Emotional disorders, such as anxiety and depression, often respond to spiritual healing. A literature search to identify studies published between 1999 and 2003 describing the effect of religion on health outcomes showed that religious intervention such as intercessory prayer decreases the

duration of fever in patients with sepsis and the length of hospital stay as well as improves the success rate in in vitro fertilization [15]. Prayer, a special form of meditation, has been found to boost the immune system causing multiple functions including significant increases in antibody titers to influenza vaccine [16].

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Differential Diagnosis (DD) of Febrile Diseases

12

Core Messages

- Establishing a diagnosis from several clinical presentations is a common challenge in paediatrics that needs knowledge and experience to solve. This chapter provides clinicians with a guide to clinical and laboratory means to reach a diagnosis of the most common febrile diseases.
- Infection is the most likely diagnosis in a child with fever, where the fever is usually of short duration and is associated with a focus in about three quarters of cases and without a focus in the majority of the remaining cases.
- Viral infections, affecting mainly the upper respiratory tract (URT), are the cause of fever in about 90–95% of febrile children. It is the physician's primary role to identify the remaining 5–10% of children who have a bacterial infection and who may require antibiotic treatment.
- Nowadays, most cases of tonsillitis, otitis media and pneumonia, during the first years of life, are caused by a viral infection.
- In the tropics, bacterial and parasitic infections are more common than in developed countries and are important causes of mortality of millions of children.
- Pyrexia of unknown origin is considered when fever persists for more than 1 week, and its cause is unknown despite investigation. In contrast to adults, PUO in children is mostly due to infection followed by collagen and vascular causes.
- The diagnosis of fever of non-infectious origin is considered after excluding an infection. This is done by history, physical examination and laboratory tests.
- Persistent and/or insidious fever of a low degree (<39.5 °C), the absence of chills and diurnal rhythm of fever are suggestive of non-infectious fever.
- An important cause of elevated body temperature is heat stroke, which is due to a combination of heat, high humidity, excessive wrapping and lack of fluids.

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_12

12.1 Differentiating Fever of Infectious from Non-infectious Origins

Main causes of fever:

- Infections: bacterial, virus, TB, parasitic and rickettsia are by far the most common cause of fever in children. Infection remains the likely diagnosis in a febrile child until proven otherwise.
- Non-infectious: collagen/vascular, malignancy, drugs, allergy, recent immunization and periodic fevers.

Diagnosis that fever is caused by an infection is supported by:

- Underlying conditions, e.g. immunocompromised status, splenectomy, sickle cell anaemia, neonates and young infants and intravascular catheters.
- Fever of 39.5 °C or greater, presence of chills, diurnal fluctuation of fever.
- A focus for infection (e.g. tonsillitis, pneumonia). In case of fever without a focus, the diagnosis can usually be established by laboratory means (e.g. UTI).
- Short duration of fever, for example, in viral infections.
- Rapid response to antibiotics in bacterial infections.
- Concomitant herpes labialis.
- Leukocytosis >20,000 in bacterial and leukopenia <500 in viral infections.
- High procalcitonin (PCT) levels. PCT is low in viral infections and inflammatory diseases, e.g. connective diseases and neoplasms.

Diagnosis that fever is not caused by an infection is supported by:

- History (e.g. recent vaccination, drug intake).
- Persistent or insidious fever of low degree (<39.5 °C).
- Associated pruritic rash and multiple joint involvement.
- Negative bacterial cultures in blood, stool, urine and cerebrospinal fluid.
- Absence of chills and diurnal rhythm of fever.
- Exclusion of an infection by history, physical examination and laboratory tests.
- Fever not responding to antibiotics but responding to steroids.
- Absence of leukocytosis and left shift and presence of antinuclear factor (ANF).

12.2 Differentiation Between Viral and Bacterial Infections

Viral infections, affecting mainly the upper respiratory tract (URT), are the causes of fever in about 90–95% of febrile children. It is the physician's primary role to identify the remaining 5–10% of children who have a bacterial infection, and who may require antibiotic treatment. Those with viral infection will usually require only symptomatic treatment. With stomatitis, varicella or other readily identified exanthems, the cause of the fever is apparent, and further diagnostic

Table 12.1 Differential diagnosis between viral and bacterial infections

Features that increase the likelihood of viral infection	Features that increase the likelihood of bacterial infection
Many organs are involved at the same time, mostly affecting the URT	Localized to one organ (ears or tonsils)
Attendance of nursery or being in contact with people with similar symptoms	High fever (>39 °C), duration (>3 days) and the presence of rigour, herpes labialis
Well-appearing, playful and interacts well with his parents	Irritable, lethargic child, who looks ill with a weak cry and who is uninterested in the surroundings
Normal CRP and leukocytes (leukocytosis is rare in viral infections with few exceptions, such EBV and CMV.) Leukopenia, lymphocytosis (or lymphocytopenia) and thrombocytopenia. Neutrophilia as an early sign of some infections, e.g. chickenpox Reduced cytokines levels except INF-α level Normal procalcitonin	High CRP, ESR, WBC and absolute neutrophil count. In parasitic infections (malaria, *Leishmania*), initial leukocytosis is often followed by leukopenia, monocytosis, thrombocytopenia and eosinophilia High procalcitonin (PCT)[a] level > 1.2 ng/mL and a higher level (>5 ng/mL) in severe bacterial infections

[a]PCT is a precursor of the hormone calcitonin found in small quantities in healthy subjects (<0.10 ng/mL). It offers higher sensitivity and specificity than CRP and WBC to differentiate between viral and bacterial infection

evaluation may not be required. Patients with impaired immune status (e.g. on chemotherapy), sickle cell disease, human immunodeficiency virus infection or cystic fibrosis should be considered to have a bacterial infection until proved otherwise. Often, however, it is difficult to differentiate viral from bacterial infections. Although high and prolonged fever is more often caused by bacterial than by viral infection, such fever may frequently be caused by respiratory virus infections (Table 12.1).

Diagnosis of viral infection can be made using detection of viral antigen with enzyme immunoassay (ELA), fluorescent antibody (FA) or electron microscopy.

Serologic proof requires demonstration of a significant rise in IgG antibody between acute and convalescent sera or demonstration of virus-specific IgM antibody.

12.3 Periodic Fever (See Also Chap. 1, Sect. 1.2)

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 or quartan when the spike occurs every fourth day) and brucellosis. The differential diagnosis of the hereditary causes of periodic syndrome is shown in Table 12.2.

Table 12.2 Differential diagnosis of hereditary periodic fever syndromes

Disorder	Inheritance	Fever duration	Periodicity	Clinical features	Labour tests/aetiology
FMF	AR	1–3 days	3–6 weeks	Polyserositis (abdominal, chest pain) synovitis, myalgia	↑inflammatory markers, gene mutations MEFV on chromosome 6
Cyclic neutropenia	AD	5–7 d	3 weeks	Pharyngitis, gingivitis, mouth ulcers, lymphadenopathy, cellulitis	Neutrophils <200, mutations of the gene neutrophils elastase (ELA2): chromosome 19
TRAPS	AD	Weeks	Irregular	Muscle cramps, vomiting and diarrhoea, migratory arthralgia, migratory rash, periorbital oedema	↑inflammatory markers
HIDS	AR	4–6	4–8 weeks	Abdominal pain, headache arthralgia, lymph adenopathy, diarrhoea	↑IgD, IgA and mevalonic acid in the urine. TNF and the enzyme MVK are low
PFAPA	Sporadic	3–5 days	3–6 weeks	Aphthous stomatitis pharyngitis, lymphadenitis	Inflammatory marker
MWS/FCUS/ NOMID/CINCA	AD	Irregular	Irregular	Urticaria, conjunctivitis progressive deafness, arthritis, chronic meningitis, skin rash	Mutations in CIASI gene on chromosome 1q44

FMF familial Mediterranean fever, *TRAPS* tumour necrosis factor receptor-associated periodic syndrome, *HIDS* hyperimmunoglobulinaemia 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 syndrome, *AR* autosomal recessive, *AD* autosomal dominant, *GCSF* granulocyte colony stimulating factor, *NSAIDs* nonsteroidal anti-inflammatory drugs

FMF (familial Mediterranean fever) and PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenitis) are the most common causes of PF. Fever is a constant finding, and it may be present alone before other manifestations. Fever is usually greater than 39 °C and may reach 40.5 °C. FMF occurs in individuals from Mediterranean ancestry who usually present with loss of appetite and abdominal pain due to apparent peritonitis. About 6–10 h later, fever occurs and rapid recovery ensues within 24–72 h. While patients with FMF usually respond dramatically to colchicine 0.6 mg hourly for four doses, for those with PFAPA, steroid therapy is very effective in controlling fever and other symptoms within 2–4 h. IgD is elevated in the majority of cases of PFAPA.

TRAPS (TNF-receptor associated periodic syndrome) is rare and occurs in many ethnic groups. Fever usually lasts 2–3 weeks, which distinguishes it from FMF. HIDS is very rare and has been described mostly in Western Europe.

FCUS (familial cold urticaria syndrome) and MWS (Muckle-Wells syndrome) are characterized by recurrent episodes of fever, which starts 1–2 h after exposure to cold and lasts <24 h, occurring before the age of 6 months.

12.4 Unexplained Fever (Pyrexia of Unknown Origin, PUO)

Unexplained fever or PUO indicates the presence of fever without a focus due to a single diagnosis which remains obscure after a week of intense investigation. Although the degree of fever, age of the child and the results of initial screening tests (CRP, WBC) are not in themselves diagnostic, a combination of history, examination and the results of these tests can provide important clues to the underlying diagnosis. Table 12.3 shows the most common diagnoses of PUO.

12.5 Differential Diagnosis of Hyperthermic Conditions

The most important causes of hyperthermia are heat stroke, malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS), serotonin syndrome (SS), drugs and haemorrhagic shock and encephalopathy (HSE). The differential diagnosis of these conditions is shown in Table 12.4. NMS and SS share similar features, but they can be distinguished by the difference shown in Table 12.5. NMS should also be differentiated from the more common adverse drug reaction characterized by the presence of rash (often urticaria), itching, blood eosinophilia, wheezing and usually no fever.

12.6 Unexplained Hypothermia

At rest humans produce 40–60 kilocalories (kcal) of heat per square metre of body surface area through generation of cellular metabolism. The body loses heat through radiation, conduction, convection and evaporation (see Chap. 8)

Table 12.3 Main causes of PUO

Causes	Pattern of fever	Clues to diagnosis
Infection (60–70%)		
TB	Persistent, low-grade fever often lasting for weeks, night sweats	Cough, weight loss, history of contact with an infected person
HIV	Fever occurs in 85% of cases Unexplained, persistent or intermittent for >1 month is common	Mononucleosis-like symptoms with sore throat, myalgia, arthralgia, rash, lymphadenopathy. Lab findings: low WBC and platelets
Cat-scratch fever	Fever occurs in about 30% with a range of 38–39 °C in mild cases; more severe cases present with high and persistent fever	Kitten exposure, papule at the site of inoculation, regional lymphadenopathy, abdominal pain, splenomegaly
Endocarditis	Insidious, low-grade fever, night sweats	Splenomegaly, tender nodes (Osler's node), subungal (splinter) bleeding, pre-existing CHD, heart murmur, anaemia, low platelets
Typhoid fever	Ladder-like increase of fever to reach 40–41 °C. If untreated with antibiotics, the temperature remains continuous at 39–40.5 °C for 2–3 weeks before abating slowly. RB is typical	Abdominal tenderness, delirium and hepatosplenomegaly. At the end of the first week, roseate detected in 20–40%, on chest and abdomen. Lab findings: leucopenia, anaemia, thrombocytopenia and increased liver enzymes
Brucellosis	Incidence in 90–100%, either insidiously over several days or sudden with chills, rising sharply to 40.5 °C and swinging considerably. Pattern is remittent, and often periodic. RB is common	History of direct contact with infected animals or their discharge or through consumption of infected milk or milk products. Arthralgia/arthritis, hepatosplenomegaly. Leukopenia
Q fever	Sudden onset of high fever up to 40.5 °C. There is no typical pattern Diagnosis should be always considered in children with PUO	Persons at risk of infection are those who work with cattle, sheep or their products. Flu-like symptoms, headaches, arthralgia, myalgia, hepatitis, pneumonia
Viral (e.g. EBV, CMV)	Eighty percent have pharyngeal form with lymphadenopathy and 20% present with fever alone (typhoidal form). Fever may last 4 days to 2 or 3 weeks, peaking on the fifth day of illness. Fever is frequently intermittent, with ranges 38.5–39.5 °C, but rarely higher than 40 °C.	Fatigue, periorbital oedema, splenomegaly. Cases with fever alone require blood tests to confirm diagnosis. Leukocytosis with lymphocytosis is often present
Non-infection collagen and vascular (20%)		

Table 12.3 (continued)

Causes	Pattern of fever	Clues to diagnosis
Still's disease	The commonest pattern is intermittent, often hectic, with a daily rise in the evening, then falling to normal in the morning. As the fever continues, the pattern may become double quotidian. Other febrile patterns include continuous and periodic	Leukopenia, rash, generalized lymphadenopathy and splenomegaly. Persistent arthritis for >6 weeks
SLE	SLE may present abruptly with fever, simulating an acute infection, or may develop over months with only episodes of fever, malaise, arthralgia, and weight loss. Fever ranges from moderate to high, occurring in 80–85% and accompanying the facial erythematous rash in about 40% of cases	Butterfly facial rash, leukopenia, renal involvement, anaemia, thrombocytopenia
Malignancy, 5%		
Lymphoma	Fever is either "neoplastic" or infectious (usually >39 °C). Only a few patients during the course of fever have the relapsing Pel-Ebstein fever (high fever for a few days, regularly alternating with a few days or weeks of normal temperature)	Cervical lymphadenopathy, mediastinal and/or hilar mass. Night sweats, weight loss, pruritis
Miscellaneous (10%), e.g. FMF	Fever usually last 48–96 h, peaking within 1–3 days Fever may be the only feature, presents as PUO	Polyserositis, inherited as AR. Symptom-free intervals range from days to months, even longer, rash (erysipelas-like) usually anterior leg
Undiagnosed (10%)		

URT upper respiratory tract, *EBV* Epstein-Barr virus, *MCV* cytomegalovirus, *RB* relative bradycardia

- Decreased heat production
  - Hormonal: hypopituitarism, hypoadrenalism and hypothyroidism. These conditions are considered particularly if patients do not respond to conventional therapy.
  - Metabolic: urea cycle disorders (defects in the nitrogen metabolism), particularly argininosuccinic aciduria (an autosomal disorder of the urea cycle which

Table 12.4 Differentiating common hyperthermic conditions

Condition	Diagnostic clues
Heat stroke	• Infants are at high risk
	• Causes are extreme heat, high humidity, excessive wrapping and lack of fluids. Infants left in unattended in a car. It is the result of exposure to heat and inability to sweat
	• Rapid onset and an increase within few minutes of body temperature to 40 °C or greater
	• Signs: flushed, dry and hot skin, not sweaty, disorientation, headache
MH	• Family history may be positive (multifactorial)
	• Event occurs during anaesthesia, primarily halogenated inhalation and succinylcholine anaesthesia
	• Diagnosis: exposure of biopsied muscle tissue to caffeine or halothane
NMS	• Caused almost exclusively by antipsychotics, including all types of neuroleptics
	• The disorder typically occurs within 2 weeks of the initial treatment
	• First symptom is muscular rigidity, followed by high fever, sweating, unstable BP, tachycardia, confusion, delirium
	• Increase of CPK and metabolic acidosis are usual findings
HSE	• Rare condition, characterized by an acute onset of shock (poor perfusion, low BP), occurring predominately in 3–8-month-old infants. HSE resembles heat stroke

Table 12.5 Differential diagnosis of SS and NMS

Feature	SS	NMS
Mechanism	Serotonin excess	Dopamine antagonism
Cause	SSRIs, antidepressants, drug interaction enhances, serotonin transmission	Typical antipsychotic, haloperidol and atypical antipsychotic (e.g. clonazepam, risperidone)
Onset of symptoms	Minutes to hours	Days to weeks
Fever	Low-grade fever	Higher degree of fever
Neuromuscular	Myoclonus, hyperreflexia euphoria, rapid eye movement	"Lead pipe" rigidity
Gastrointestinal	Diarrhoea, vomiting	Diarrhoea, vomiting
Metabolic acidosis	Rare	Common
Rhabdomyolysis	Rare	Common
Elevated transaminases	Rare	Common

SS serotonin syndrome

is characterized by the triad of hyperammonia, encephalopathy and respiratory alkalosis).
- Transfusion/infusion of cold blood or fluids, gastric lavage using cold fluids or for peritoneal dialysis.
- Hypoglycaemia.
- Severe and overwhelming infection, such as sepsis or septic shock.
- Severe malnutrition and starvation, such as anorexia nervosa.

- Increased heat loss
  - Cold delivery room.
  - Drugs causing vasodilatation.
  - Spontaneous periodic hypothermia, which may be associated with absent corpus callosum (Shapiro's syndrome). There is an absent shivering and profuse sweating. Episodes usually last hours to days. The condition is usually benign.
- Impaired thermoregulation
  - Cerebral bleeding and hypoxic ischaemic encephalopathy.
  - Menkes kinky hair syndrome, an X-linked inherited disorder of copper metabolism.
  - Prader-Willi syndrome. The syndrome is associated with disturbance in thermoregulation, causing unexplained hyperthermia or hypothermia. This risk is high in very cold weather or postoperative period.
  - Drugs: Sedative-hypnotics – benzodiazepines, barbiturates, opiates, antidepressants, antipyretics (rare side-effects of antipyretics) and organophosphate poisoning.

12.7 Pharyngitis/Tonsillitis

The major cause of bacterial pharyngitis is group A beta-haemolytic streptococcus (GABHS), accounting for 10–20% of cases in children. Most causes of pharyngitis are viral including EBV, adenovirus and Coxsackie A viruses (Table 12.6).

Table 12.6 Differential Diagnosis of Pharyngitis

Pharyngitis	Features	Diagnosis
GABHS	School age, absence of symptoms of URTI (e.g. coryza, hoarseness), exudates on tonsils, deviation of the uvula, high fever	Rapid antigen test, throat swab culture, ASO titre. High WBC and CRP
Viruses	Pre-school age, presence of rhinorrhoea, conjunctivitis and cough No response to antibiotics, thus longer duration of fever	Diagnosis is usually clinical. Viral study is not necessary
EBV	Older children and adolescents, grey membrane on tonsils, lymphadenopathy, splenomegaly	Monospot test (sensitive in 90% and 95% specific), IgM for EBV
Herpangina (Coxsackie A virus)	Pre-school age, ulcers on whitish-grey base and a red border on soft palate, high fever	Clinical, diagnostic tests unnecessary
Scarlet fever	Tonsillitis, punctuate, erythematous, blanchable, exanthem, accentuated on skin folds and creases and tongue is bright red, with white coating (strawberry tongue)	Positive throat swab culture for streptococci, ASO titre rising fourfold
KD	Most affect children <5 years, persistent fever, lymphadenopathy	(see diagnostic criteria, Chap. 6)
Peritonsillar abscess	High fever (40–41 °C), toxic appearance, history of tonsillitis with an afebrile period or continuing fever, asymmetric uvula deviation, torticollis	Clinical diagnosis

URTI upper respiratory tract infection, *EBV* Epstein-Barr virus, *KD* Kawasaki disease

12.8 Differential Diagnosis of Pneumonia and Chest Infiltration

Pneumonia is a primary infection of the parenchyma of the lung, which is much less common than secondary bacterial infection complicating an acute bronchiolitis. The diagnosis of pneumonia can only be established with certainty by a chest X-ray. It is important to note that:

- A viral URTI often precedes the onset of bacterial pneumonia.
- Pneumococcal pneumonia cannot be differentiated from other bacterial or viral pneumonias with certainty. Therefore antibiotics are usually administered once a radiological pneumonia is diagnosed.

In the differential diagnosis of pneumonia:

- Salicylate poisoning. With features of hyperthermia and tachypnoea
- Any illness causing respiratory distress, e.g. bronchiolitis, tuberculosis, congestive cardiac failure, aspiration of a foreign body and atelectasis

Bacterial pneumonia can be diagnosed by the following findings:

- Pneumococcal pneumonia
  - Typical age >4 years of age.
  - A brief URTI is followed by shaking chills, then fever as high as 41 °C, followed by tachypnoea, a dry cough, delirium and abdominal pain.
  - Chest findings include chest retraction, flaring of alae nasi and fine rales on the affected side. Initially, there may be dullness on the affected side. Classic signs of consolidation are noted on the second and third day of illness producing bronchial breathing.
  - Radiological evidence of consolidation.
  - Leukocytosis of 20,000 cells/mm^3 or more.
  - Isolation of the organisms from the blood (positive in 10%) or from pleural fluid aspirate or bronchoscopic washing.
- Mycoplasma pneumonia
  - Onset is insidious with fever, headaches and abdominal pain, followed by cough.
  - May present with similar clinical and radiological features of other pneumonias. However, children with *M. pneumoniae* appear well despite the extent of the X-ray lesions. Chest X-ray often shows peribronchial and perivascular interstitial infiltrates.
  - Diagnosis is made by fourfold rise in antibody titre, a single titre of 128 or more, IgM antibodies and serum cold agglutinins.
  - A high CRP or ESR and a normal WBC are fairly characteristic.
- Staphylococcal pneumonia
  - Occurs most commonly under 1 year of age, often with a history of staphylococcal skin lesions and URTI.

  - Abruptly, the infant's condition worsens rapidly with the onset of high fever, cough and signs of respiratory distress, such as tachypnoea, grunting, sternal and subcostal retraction and nasal flaring.
  - Radiological evidence of non-specific bronchopneumonia early in the illness. The infiltrate soon becomes patchy. Pneumatoceles of varying size are common. Pleural effusion, empyema and pneumothorax.
- *Haemophilus influenza pneumonia* has become very uncommon because of vaccination. Although it may be difficult to distinguish clinically and radiologically from other types of pneumonia, the progression is more insidious and the course is usually prolonged.

Viral pneumonia has the following characteristic findings:

- It is the most common type of pneumonia, particularly in young children most commonly caused RSV.
- It cannot be definitely differentiated clinically and radiologically from other types of pneumonias, particularly mycoplasma pneumonia.
- Most viral pneumonias are preceded by several days of respiratory symptoms, including rhinitis and cough. Onset is usually more gradual than in bacterial pneumonia. Dyspnoea with retractions and nasal flaring is more common in young children. Physical examination is often not diagnostic.
- Temperature usually ranges from 38.5 to 40 °C.
- Radiological findings may mimic those of bacterial pneumonia. Suggestive of viral aetiology is a diffuse infiltrate, especially in the perihilar areas. Several segments of more than one lobe are often involved.
- Leukocytosis is usually under 20,000/mm^3.
- Failure to respond to antibiotics.

12.8.1 Chest Infiltrates

- Diffuse pulmonary infiltrates suggest infection, oedema, haemorrhage and interstitial lung disease. Causes can be confirmed high-resolution CT scan.
- Hilar lymphadenopathy. Bilateral suggests sarcoidosis. Unilateral suggests TB.
- Ground-glass opacities (a hazy increase in lung attenuation through which lung vessels are seen). Acute presentation suggests respiratory distress syndrome, pneumonia, pulmonary haemorrhage or eosinophilic pneumonia.

Chest infiltrates may occur in all types of pneumonia, more characteristically in:

- *Pneumocystis carinii*, which consists of generalized granular pattern and bilateral pulmonary infiltrates. There is a relative paucity of pulmonary findings for the severity of distress. Cough and fever may be absent.
- *Pulmonary tuberculosis*. In primary TB, mediastinal lymphadenopathy, causing partial or complete obstruction of the bronchus. With complete obstruction there is atelectasis of the distal segment, with dullness on percussion and diminished

breath sounds. Rarely is there a classic pulmonary infiltrate with hilar lymphadenopathy. In post-primary TB, the early change shows a well-circumscribed, homogenous shadow, commonly in the apices.

12.9 Differential Diagnosis of Abdominal Pain (AP)

The most common febrile causes of AP include GE, appendicitis, mesenteric adenitis, UTI, referred pain, pancreatitis or intussusception.

The differential diagnosis between gastroenteritis, appendicitis and mesenteric adenitis (Table 12.7) can be difficult. When appendectomy is carried out, 30–40% do not have appendicitis; 20% are found to have mesenteric adenitis. Missed cases of appendicitis occur particularly in young children who may be afebrile (20%) and have often associated diarrhoea.

Presentations of other conditions causing abdominal pain are:

Urinary tract infection: presentation is usually with high fever without focus, particularly in young children, and with lesser degrees of fever and flank pain in older children. Diagnosis is established by urinalysis.

Table 12.7 Differentiating gastroenteritis, appendicitis and mesenteric adenitis

Gastroenteritis	Appendicitis	Mesenteric adenitis
History of diarrhoea in other family members	Fever, ranges 38–39 °C, is present in 80%	History of an URTI or the presence of URTI on examination
Crampy AP	Pain, often crampy, starts in the periumbilical region and moves after a few hours to the right iliac fossa Vomiting and fever follow Examination shows localized tenderness, guarding and rebound in the RLQA. Moving, jumping and coughing worsen the pain	AP is more diffuse than in appendicitis. However, the diagnosis is one of exclusion, particularly appendicitis, and it is often made at laparotomy
Diarrhoea Vomiting is usual in rotavirus GE, rare in *Salmonella* and unusual in Shigella GE	Pain precedes vomiting. Very young children may have diarrhoea, which is usually not pronounced as in gastroenteritis	Vomiting precedes pain
High WBC and CRP in bacterial and usually normal in viral	WBC > 15,000, high CRP	WBC <15,000, normal CRP
	High-resolution ultrasound scan can differentiate conditions mimicking appendicitis and may suggest the diagnosis	CT image often shows the enlarged mesenteric lymph nodes (5–15 mm), with thickened wall of the terminal ileum

RLQA right lower quadrant of abdomen, *URTI* upper respiratory tract infection, *AP* abdominal pain

Intussusception is characterized by paroxysms (every 10–20 min) of colicky AP. The child appears well between these paroxysms. There is usually a palpable mass and a bloody red, currant stools. Pyrexia may occur as a late sign.

Referred pain originating either from a viral URTI or pneumonia. It is characterized by:

- AP, which is usually mild to moderate and diffuse.
- Physical examination of the respiratory system usually reveals the diagnosis.

Crohn's disease: Children usually present with fever, headache, anorexia, oral ulcers, perianal skin tag/fistula, growth failure, vague crampy abdominal pain, often mimicking appendicitis and erythema nodosum. High CRP, anaemia and thrombocytosis are fairly characteristic.

Enteric fever has the following characteristic clinical course:

- The onset is insidious with fever (without shaking chills), present in almost all patients, associated with headache, cough and abdominal pain.
- Symptoms gradually increase over 2–3 days, with constipation, nausea and anorexia.
- The temperature continues to rise in a stepwise fashion to reach 40–41 °C. If untreated with antibiotics, the temperature remains continuous at 39–40.5 °C for 2–3 weeks before abating slowly. In young children the onset of fever is more often abrupt. Sustained or intermittent fevers are more common than the stepwise pattern of fever. In all ages, fever may continue for many days despite antibiotic therapy, and the child does not become afebrile until the end of the therapy.

12.9.1 Pancreatitis

- Risk factors are intake of the anticonvulsant valproate, hyperlipidaemia, biliary tract disorder or family history of pancreatitis.
- Abdominal pain/tenderness (occurs in 80%) which is persistent, radiating to the back.
- Vomiting/retching (incidence about 75%).
- Fever/chills (incidence in about 25%).
- Elevated serum lipase and amylase level.
- Imaging studies: ultrasonography and CT scan.

12.9.2 Amebic Liver Abscess

The common clinical symptoms and signs are abdominal pain (85%), fever and chills (75%) and abdominal tenderness (70%). The location of the abscess is predominantly in the right lobe (75%).

Table 12.8 Differential diagnosis in febrile infectious diarrhoea

Diarrhoea	Fever	Faecal WBC	Likely cause
Watery, no blood or mucus	Variable	Absent	Toxigenic E. coli, traveller's diarrhoea, cholera, clostridium
Crampy, blood and mucus, no vomiting	Usually present	Present	Shigella, *E. coli* 017:H57, *Yersinia*, *Campylobacter*, amoeba (in endemic area)
Watery diarrhoea with vomiting	Variable	Variable, mostly monocytes	Rotavirus and Norwalk virus (in winter), adenovirus, salmonella (in summer/fall)

12.10 Gastroenteritis

Most diarrhoeal diseases in children living in developed countries are mild and self-limited, and do not require hospitalization or laboratory evaluation. In a young child who is ill enough to require hospitalization, laboratory investigation of the stool is indicated to determine the cause of the diarrhoea and those cases in which antibiotics may be needed.

The three major presentations of diarrhoea are shown in Table 12.8. The single most helpful, initial laboratory test is the stool white cell assessment.

12.11 Differential Diagnosis of Jaundice

Jaundice is very common during the neonatal period. It is not discussed here as the causes are almost always afebrile. After the neonatal period, infection remains the most common cause of jaundice worldwide. The incidence of hepatitis A (HA) has declined significantly in developed countries. Jaundice should be differentiated from xanthochromia (carotenaemia), which is due to carotene deposits in the skin; the sclera remains normal. Table 12.9 facilitates the differential diagnosis of jaundice.

12.12 Coma

Children have a reduced conscious level if they score less than 15 on the modified Glasgow Coma Score (GCS) or if they are alert (A), responsive to voice (V), pain (P) or are unresponsive (U) on the AVPU. The main causes are:

12.12.1 Intracranial Infections

Bacterial Meningitis

Children with reduced conscious level but no neck stiffness should be suspected if they have fever and two of the following:

Table 12.9 Differential diagnosis of conditions causing jaundice in older children

Condition	Fever	Distinguishing features	Diagnosis
Acute hepatitis A, B, C, D, E	Common, low grade, appears first; jaundice follows when the fever is normal	Eighty percent of cases: asymptomatic. Presentation with malaise, nausea, anorexia, abdominal pain, dark urine and acholic stools	Abnormal LFT, with high SGPT>SGOT. IgM anti-HA for each virus
Autoimmune hepatitis	Occurs in about 40%	Pallor 100%; jaundice in about 60%	Anaemia, positive auto-antibodies
Drug-induced hepatitis	Variable non-specific pattern of fever	Drugs causing toxicity (e.g. Rifampicin, paracetamol, valproate, INH)	Abnormal LFT, negative IgM for viruses. History of drug intake
Mononucleosis	100% of cases, variable degree	Pharyngitis and lymphadenopathy	Positive EBV-IgM and Monospot
Leptospirosis	High, occurring in almost all cases. Relative bradycardia	Animal exposure, myalgia, subconjuntival bleeding renal involvement adrenal dysfunction, drowsiness	Isolation of organisms and/or fourfold rise in antibody titre
Malaria	High, intermittent	Jaundice is usually mild, anaemia, splenomegaly	Smear for malaria
Typhoid fever	Stepladder rise until the end of the first week, also noted during day	Jaundice appears at the peak of fever, abdominal symptoms	Isolation of *S. typhi* from blood, stool or bone marrow. IgM
Hepatic abscess	High hectic	Right upper quadrant pain and tenderness	Ultrasound scan
Reye syndrome	Mild and infrequent	History of aspirin intake and a flu-like symptoms; decreasing consciousness	See Chap. 10 for diagnostic criteria
Yellow fever (YF)	Sudden high fever for 2–3 days, then remits, followed by second spike, relative bradycardia	In contrast to the gradual onset of hepatitis, jaundice in YF appears 3–5 days of high fever	Isolation of virus or IGM enzyme immunoassay

- Rash
- Irritability
- Bulging fontanelle, neck stiffness in older children

Herpes Simplex Encephalitis (HSE)

HSE should be suspected clinically in a child with reduced conscious level if one or more of the following four are present:

- Focal neurological signs
- Fluctuating conscious level for 6 h or more
- Contact with herpetic lesions
- No obvious clinical signs pointing towards the cause

The clinical suspicion of HSE is strengthened by:

- MRI scan with non-specific features of HSE
- Abnormal EEG with non-specific features of HSE
- CSF positive for herpes simplex virus DNA in PCR

TB Meningitis
Should be suspected in a child with a reduced conscious level and:

- Clinical signs of meningitis (see typical CSF findings Chap. 5)
- Insidious, low-grade fever
- Cranial nerve palsy, particularly the sixth nerve
- Contact with a case of pulmonary TB

Diagnosis is established from a CSF sample by a positive PCR for TB DNA.

Intracranial Abscess
Should be suspected in a child with a reduced conscious level with:

- Focal neurological signs ± clinical signs of sepsis
- Signs of increased ICP

Diagnosis is confirmed by imaging.

12.12.2 Non-Intracranial Infection

Shock
Circulatory shock is diagnosed if one or more of the following signs are present:

- CRT >2 s.
- Mottled cool extremities.
- Diminished peripheral pulses.
- Systolic BP is less than fifth % for age.
- Decreased urine output <1 mL/kg/h.

If shock is present, look for signs of:
Sepsis, trauma (blood loss, tension pneumothorax, cardiac tamponade), anaphylaxis (urticarial rash, wheeze, stridor, swollen lips/tongue) or heart failure (enlarged liver, peripheral oedema, distended neck veins, heart murmur).

Sepsis
Most cases of sepsis present without impairment of consciousness. Occasionally the consciousness is impaired. Sepsis is defined as the systemic response to infection, and sepsis is suspected if two or more of the following four are present:

- A body temperature of >38 °C or <35.5 °C, or history of fever at home
- Tachycardia
- Tachypnoea
- A rise in WBC of 15,000 cu mm or a fall of 5000 cu mm or if there is non-blanching petechial or purpuric skin rash [please check]

Investigation: Chest x-ray, throat swab, urinalysis, LP, PCR from blood for meningococci and pneumococci, coagulation studies (PTT, PT, fibrinogen, fibrinogen degradation products), skin swab (if areas of inflammation are present), joint aspiration (if signs of septic arthritis are present), a thick and thin smear for malarial parasites (if foreign travel to endemic area), intracranial imaging (if no other source of infection is detected).

12.12.3 Afebrile Conditions with Reduced Conscious Level

These conditions include trauma and metabolic illness (hyperglycaemia, hypoglycaemia, hyperammonaemia, non-hyperglycaemic ketoacidosis, drug-related).

12.13 Fever in Diseases Occurring Mainly in Tropics

The list of tropical diseases causing febrile diseases is very large and beyond the scope of this book. The most common causes of febrile diseases in the tropics are those occurring worldwide, e.g. URTI, LRTI (pneumonia), diarrhoea and UTI. Other diseases occurring more commonly in tropics are shown in Table 12.10. Factors that increase the risk of various diseases are shown in Table 12.11.

12.14 A Febrile Child with a Non-blanching Rash

Petechial rash is characterized by extravasation of blood from capillaries, venules or arterioles, which persists after pressure, e.g. by a glass slide or drinking glass. The majority of cases (about 90%) are nonbacterial and non-life-threatening. About 10% of cases have septicaemia, which requires immediate attention and treatment, as a delay in the diagnosis could result in rapid deterioration of the child's condition and death. Bacterial causes should always be considered first. If there is any doubt, the child should be treated with antibiotics without waiting for confirmation of the diagnosis. Common causes of petechial rash are shown in Table 12.12.

12.15 Inflammatory Arthritis (IA)

Polyarthritis (>4 joints involved): main causes are JIA, RF and vasculitis.

Table 12.10 Main tropical febrile diseases, main endemic areas, and diagnostic tests

Agents	Endemic geographical area	Diagnosis
Parasitic diseases		
Malaria	*P. vivax*: India, C. America, *P. falciparum*: Africa, *P. vivax* & *falciparum*: SE Asia	Giemsa stain: Thick thin blood smear
Leishmaniasis	India, Africa, Mediterranean area and South America	Identification of L. in splenic or BM aspiration
Schistosomiasis	Africa, Middle East, South America (*S. Mansoni*)	Finding Schistosome eggs in urine or stool
Bacterial diseases		
Enteric fever	Middle East, India and South America	Isolation of bacteria in blood, stool and urine. PCR available in blood
Brucellosis	Mediterranean area, India, parts of S. America	Isolation of the bacteria in blood, BM. Serum agglutination test
Leptospirosis	Worldwide	Isolation of bacteria, serologic testing
TB	Worldwide, particularly Africa and Asia	FAB identification by culture or ZN stain
Amoebiasis	Throughout the tropics	Stool culture, anti-amoebic antibody test
Viral diseases		
Yellow fever	Central and West Africa and South America	Virus isolation, IgM enzyme immune assay
HIV	Worldwide, particularly Africa, India and China	HIV p24 antigen, IgA and IgG antibody, HIV DNA or RNA by PCR
Dengue fever	South East Asia and West Africa	IgM, IgG in paired sera (>fourfold rise)
Lassa fever	Nigeria, Sierra Leone, Liberia	Virus isolation, IgG in paired sera (>fourfold rise)
Hepatitis	Africa, Asia	IgM antibody
Haemorrhagic fever	Depending on the type of disease (e.g. Omsk Haemorrhagic fever in Romania and Russia)	Virus isolation from throat wash, IgG (>fourfold rise in paired sera)
Rickettsial diseases		
Q fever	Worldwide	Serology: fourfold rise of paired fluorescent antibody titre
Epidemic typhus	Africa, South America	Fluorescent antibody assay, PCR

Table 12.11 Risks factors that may lead to infection occurring mainly in tropics

Risk of infection is increased	Disease
Ingesting unpasteurized milk	Brucellosis, enteric fever, bovine TB, *Salmonella enteritis*
Exposure to mosquitoes	Malaria, dengue fever, filariasis, yellow fever
Ingestion of uncooked meet	Toxoplasmosis
Exposure to area with ticks	Lyme disease, relapsing fever, tick typhus, Q fever
Direct contact with animals or contaminated soil or urine	Leptospirosis

Table 12.12 Differential diagnosis of common causes of petechial rash

Causes	Usual findings
Bacterial: meningococcal septicaemia	High degree of fever, ill-looking, lethargy, headache, peripheral under-perfusion, pallor, mottled skin, prolonged capillary refill time, high CRP, WBC
Viral: CMV, rubella, enteroviruses, HIV, EBV, HHV-6	Low-grade fever, children generally well, normal CRP and WBC
Collagen/vascular: SLE, vasculitis	Children are often not ill-looking, and fever can be as high as in septicaemia, absence of signs of shock. Other organ involvement is common
Malignancy: leukaemia	Ill-looking, anaemia, hepatosplenomegaly, lymphadenopathy, blood and bone marrow tests are diagnostic
Thrombocytopenia: ITP	Well looking, usually afebrile (unless associated with an URTI)
Drugs	Well looking, low degree of fever, pruritic rash, history of drug intake, eosinophilia, rash disappearing 12–24 h after discontinuation of the drug

EBV Epstein-Barr virus, *ITP* idiopathic thrombocytopenic purpura, *HHV-6* human herpes virus, *SLE* systemic lupus erythematosus

- *Juvenile idiopathic arthritis (JIA)* is characterized by arthritis of more than 1 week duration, presenting <16 years of age and unexplained by known causes. Cases of polyarthritis affect at least five joints either from the onset or within the first 6 months of the onset. There is a broad differential diagnosis for IA (see Chap. 6). ESR (and not CRP) is commonly raised suggesting that the arthritis is inflammatory but not infectious.
- *Rheumatic fever (RF)*

- Migratory arthritis, occurring 2–3 weeks following an untreated group A beta-haemolytic streptococcal pharyngitis. Diagnosis is established by Jones criteria.
- *Polyarthritis due to vasculitis* (e.g. Henoch-Schonlein Purpura, HSP, or Kawasaki Disease, KD). HSP manifests with a rash of typical distribution (buttocks, external areas of elbows and knee joints), abdominal pain and nephritis. KD is diagnosed by certain criteria (see Chap. 6).

Oligoarthritis (four or fewer joints including monoarthritis): main causes are septic arthritis, oligoarhritis of JIA, reactive arthritis, Lyme disease, transient synovitis, neoplastic and Tb arthritis.

- *Septic arthritis (SA)*
- This disorder is defined as positive joint fluid culture for bacteria and/or WBC count in the joint fluid of >50,000 cells/mm (predominately polymorphonuclear cells) with or without positive blood culture (positive in about 50%). Negative gram staining does not exclude the diagnosis. Features in support of SA:
  - SA is rare in immunocompetent children. Risk factors include haemoglobinopathy and immune compromise.
  - It is almost always monoarticular involving predominately large joints.
  - Abrupt onset of fever and joint pain.
  - Fever is usually high >39.5 °C.
  - Severe pain and restricted range of joint movement, refusal to walk.
  - Joint aspiration is diagnostic (see the definition).
  - Ultrasound and X-ray often show the presence of periosteal reaction.
  - MRI may show periosteal abscess.
  - Bone scan is positive in the majority of cases.
- *Oligoarthritis of JIA*: diagnostic criteria as in polyarthritis of JIA. In addition, patients commonly have uveitis.
- *Reactive arthritis (ReA)* is an autoimmune arthritis that develops in response to an infection elsewhere in the body, most commonly a viral URT or intestinal infection (Campylobacter, salmonella, Shigella or Yersinia). ReA is one of the most common causes of arthritis. Characteristic features include:
  - History of infection occurring 1–3 weeks prior to the onset of arthritis.
  - Arthritis occurring in weight-bearing joints (knee and ankle).
  - Commonly associated with the human leukocyte antigen HLA-B27.
  - Joint aspirate showing an increased WBC but is sterile to culture.

Post-streptococcal ReA differs from RF in the absence of heart and CNS and skin lesions in addition to poor response to aspirin

- *Lyme disease (LD) arthritis* is characterized by intermittent or chronic monoarthritis or oligoarthritis, particularly affecting the knee. Other clues:
  - Common arthritis in certain part of the world, e.g. the USA.
  - The patient has not received an antibiotic treatment when LD was acute.
  - History of tick bite and erythema migrans.

- *Transient synovitis*
  - Fever is either absent or mild.
  - History of a viral infection in the upper respiratory airways.
  - One hip is usually affected; children are limping but still walking.
  - The child is generally well; symptoms are mild.
  - Self-limiting, usually lasts 1–3 weeks.
  - Normal WBC, CRP and ESR.
  - WBC count in the joint fluid of <50,000 cells/mm.
- *Neoplastic arthritis* (e.g. leukaemia, lymphoma) is uncommon. Diagnostic clues:
  - Presence of lymphadenopathy and hepatosplenomegaly.
  - Presence of anaemia, thrombocytopenia and blast cells on the peripheral blood smear.
  - Pyrexia is usually not severe (<39.0 °C).
  - Bone marrow aspiration is diagnostic.
- *TB arthritis*
  - Lack of response to treatment (antibiotics, NSAIDs, intraocular steroids).
  - Synovial biopsy is diagnostic.

12.16 Postoperative Fever

Infectious causes include wound infection, peritonitis, intravenous line infection, viral infection, pneumonia, urinary tract infection, infectious diarrhoea, bacteraemia and osteomyelitis.

Non-infectious causes include dehydration, haematoma, pulmonary atelectasis, transfusion, drug reaction and warm ambient temperature.

The diagnosis of non-infectious causes should only be considered after excluding infectious causes. Although most postoperative fevers are non-infectious, patients are often treated with antibiotics because the differential diagnosis can be difficult. A significant number of cases of infected patients have no fever. Table 12.13 provides key points for each condition:

Table 12.13 Differential diagnosis of fever occurring during postoperative period

Infectious causes	Non-infectious
Fever usually starts on day 3 or later	Fever day 1–2
Fever height fever >39 °C	Low-grade fever, no chills
Fever pattern may be hectic	Remittent fever
Fever duration 2 day and longer	Duration: 1–2 days
Often ill-looking appearance	Usually well appearing
High CRP, ESR, WBC	Low or mildly increased

12.17 Seizures

The main causes of fever in association with seizures are febrile seizures (FS), meningitis, encephalitis, intracranial abscess, epileptic seizures and cerebral malaria.

12.17.1 Condition: Distinguishing Clinical Features (Diagnostic Clues)

Febrile
FS

- This is the most common cause of seizures, age usually 6 m to 5 years.
- Fever is always present at onset; i.e. absence of fever excludes FS.
- Usually the child was well prior to onset, child neurologically normal.
- Family history of FS is common.
- Duration of seizure and unconsciousness usually brief.
- Normal neurological examination before, i.e. healthy child, and after the seizure (no neck stiffness or bulging fontanelle, normal LP results).

Meningitis

- Child was unwell prior to the onset of seizure, with impaired conscious level, vomiting, headaches, anorexia and lethargy.
- Seizure is a late sign, complex at onset (focal, prolonged and/or multiple) and associated with other neurological features.
- Presence of petechial rash, irritability and bulging fontanelle.
- Diagnosis is established by LP.

TB Meningitis

- Contact with a case of pulmonary TB.
- More insidious onset, dominated by reduced conscious level.
- Lower degrees of fever, more insidious than with bacterial meningitis.
- Diagnosis is established from CSF findings, a positive PCR for TB DNA, staining and culture of the acid-fast bacilli, positive tuberculin test and radiological evidence of previous pulmonary infection.

Encephalitis (Herpes Simplex Encephalitis, HSE)

- Usually due to an acute viral encephalitis, most commonly herpes simplex virus (HSV). In milder form, it is also caused by common exanthem (chickenpox, measles, mumps, rubella) or Lyme disease.
- HSE should be suspected clinically in a child with reduced conscious level if one or more of the following four are present:

- Focal neurological signs
- Fluctuating conscious level for 6 h or more
- Contact with herpetic lesions
- No other obvious cause

The clinical suspicion of HSE is supported by:

- MRI scan with non-specific features of HSE
- An abnormal EEG with non-specific features of HSE
- A positive CSF result for herpes simplex virus DNA in PCR of CSF

Intracranial Abscess
Should be suspected in a child with a reduced conscious level if:

- There are focal neurological signs ± clinical signs of sepsis.
- There are signs of increased ICP.
- Diagnosis is confirmed by imaging.

Epileptic Seizure with Fever

- Known history of afebrile epileptic seizures or epilepsy
- Often associated with neurodisability
- Usually low-grade fever due to a viral URTI provoking the seizure

Cerebral Malaria

- Living in or travelling to endemic malarious areas.
- Persistence of coma >30 min (often >6 h) after the convulsion.
- Seizure is usually generalized (rarely focal), with high-pitched cry.
- Deep respiration due to acidosis.
- Core-to-skin temperature difference is abnormal and often >10 °C.
- The presence of severe anaemia, thrombocytopenia, haemoglobinuria and parasites on blood smear. Normal CSF.

Afebrile

- Epileptic seizure, seizure and loss of consciousness usually longer than in FS.
- Metabolic disorder

History of Fever

13

Core Messages

- Fever as the most ancient hallmark of disease dates back as far as civilization itself.
- The oldest civilizations (Egyptian, Mesopotamian, Chinese, Indian and Greek) demonstrated extensive knowledge of anatomy and physiology, but they tended to view fever as being induced by evil spirits.
- Many ancient physicians, fostered mainly by the Greeks, believed in the beneficial effects of fever (ancient concepts).
- By the eighteenth century, fever was thought to be "a harmful by-product of infection" (the medical renaissance concept). Antipyretics were introduced, and their extensive use has since then been considered beneficial.
- Over the past 40–50 years, intensive research has been carried out to investigate the role of fever. Although there is still disagreement, evidence now indicated that the effects of fever are complex but overall beneficial (current concepts).

13.1 Introduction

Of the many symptoms and signs of diseases, fever has received the most attention throughout medical history. For most of the history, fever was feared by ordinary people as a manifestation of punishment, induced by evil spirits or a marker of death. However, for medical scholars, the biological role of fever in disease was considered as beneficial, particularly so among Greek scholars. This concept underwent a radical transformation in the nineteenth century, and scholars began to regard fever as harmful. The use of antipyretics was considered beneficial. With the introduction of fever therapy in the twentieth century, renewed interest in the role of fever began. Currently, there is no consensus as to whether fever is beneficial, neutral or harmful. This chapter summarizes the knowledge about fever and the changing concepts of its role in diseases from ancient cultures to our present time (Table 13.1).

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_13

Table 13.1 The three evolving concepts of fever

1.	Ancient concepts (about 3000 BC to AD 1800s: Fever is beneficial
	Ancient civilization (especially Greek civilization)
	Medicine of the Middle Ages
	Early period of European medicine
2.	Medical renaissance concepts (1800s–1960): Fever is harmful
	Scholars such as Boerhaave, Bernard, Osler
3.	Current concepts: Fever is controversial, predominately beneficial

13.2 Ancient Civilizations

13.2.1 Egyptian Medicine

Egyptian medicine is known to us mainly from medical texts written on papyrus. The most valuable papyri are the *Edwin Smith Surgical Papyrus* and the *Ebers Papyrus*, written about 1700 years BC [1]. These papyri, the oldest known medical texts, contain a description of various infectious diseases such as erysipelas, hepatitis, bilharziasis, ankylostomiasis, gonorrhoea and trachoma. Ancient scholars used splints, bandages, compresses and other appliances. Specialists existed even at that time as "physician of the belly", "physician of the eyes", "guardian of the colon" and "healer of the teeth". The ancient Egyptians recognized that local inflammation was responsible for fever and that the pulse underwent acceleration during physical exercise and fever.

The *Edwin Smith Surgical Papyrus* [2] lists 48 medical cases. Local inflammation was differentiated from general fever, the latter usually meaning high fever: "A diseased wound in his breast inflamed (nsr-y*),* high fever (smmt-t) comes forth from it". The word "srf" indicated a lesser degree of fever (Fig. 13.1) [3].

Palpation was used to compare high and mild fever. Cold and warm compresses were prescribed for local inflammation, as well as willow leaves, which is the earliest known example of external application of salicylic acid.

13.2.2 Mesopotamian Medicine

Early Sumerian writings in the form of pictograms and later cuneiform (2500–3000 BC) indicates that fever as a clinical entity was clearly distinguished from local inflammation [4]. The Sumerian of Umma (referring to fever) underwent a progressive transformation 2500 to from about 2500 to 500 BC.

The main source of information about Mesopotamian medicine is a cuneiform writing from about 500 BC. This writing was found on the 30,000 or so tablets recovered from Nineveh in present-day northern Iraq in 1845 from the ruins of the library of Assurbanipal (668–625 BC). Of these, about 1000 were medical texts, which

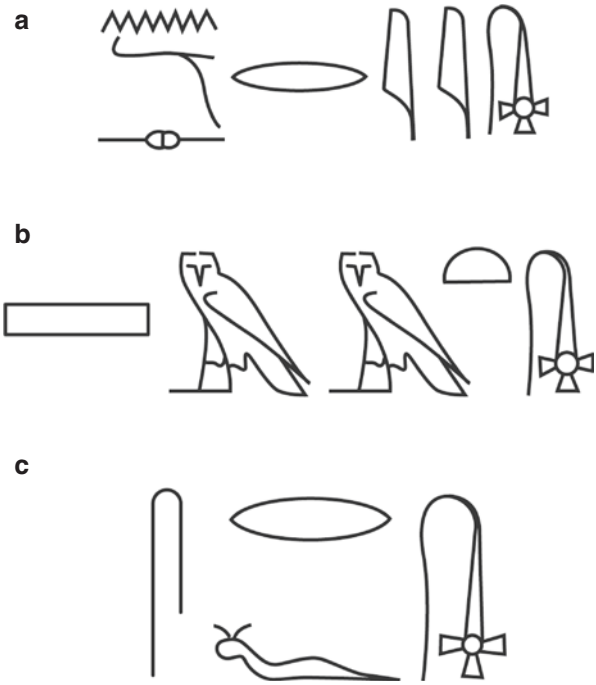

Fig. 13.1 The three words for fever used by the ancient physicians in Egypt were (**a**) nsr-, (**b**) smm-t and (**c**) srf. (Redrawn from *Edwin Smith Surgical Papyrus* [3])

contain lists of medicine ingredients, diagnoses and prognoses of various febrile illnesses [5]. Otitis media, for example, was recognized as fire that extends into the interior ear and dulls the hearing [6]. Pneumonia, with its main symptoms of fever, chest pain, cough and sputum production, was described. Inflammation was related to fever as early as the sixth century BC. As with many ancient concepts, evil spirits played a major role. Nergal, the god of pestilence, and Ashaka were believed to infest mankind with fever. Priests used exorcism to 'expel' the fever.

13.2.3 Chinese Medicine

The Chinese scholars believed that the soul possessed two antagonistic elements, good and evil, and that health and disease depended upon their balance [7].

The greatest medical Chinese classic is the Canon of Medicine by Nei Ching, written about 3000 years ago [8]. Although the method of examination was detailed, palpation focussed on the pulse only, on which the diagnosis, including that of fever, and the prognosis were based [9]. In typhoid fever, a superficial pulse was considered a good sign, while a thin, thready pulse indicated a bad sign.

Chang Chung-Ching was known as the Hippocrates of China. In the second century AD, he wrote an essay on typhoid, which is a treatise on various forms of fever. This work, which appeared in 16 volumes, described symptoms of diseases, physical signs, clinical course, methods of treatment and action of drugs.

Treatment of fever by antipyretic drugs and the use of cold applications were also described. Branches of peach trees were used to strike febrile patients to expel the evil spirit and the fever. Watermelon and material from deer horns were prescribed to treat febrile illnesses.

13.2.4 Hindu Medicine

During the earliest period of Indian civilization, medicine was also characterized by belief in magic and demons. Fever was feared since it was begotten by the wrathful fire of the god of destruction, Rudra, hence his name, "destroyer of created beings" [10]. The fire demons, Takman and Yakshma, were also believed to cause various fevers. When the fever was intermittent, the time interval between the peak periods of fever provided the key to prognosis.

The highest development in early Hindu medicine was achieved during the Brahman period (800 BC to AD 1000) [11]. One of the greatest exponents was Sushruta, who wrote the Physiology of Sushruta. Like the Greek scholars (it remains debatable which culture influenced the other), he believed that the human body contained three humours: bile, air and phlegm. Diseases were thought to be due to the disturbance within these humours. Different types of fever were described: some were caused by a disturbance of air and phlegm, others by air and bile. Intermittent, remittent, double quotidian, tertian and quartan fevers were defined. For treatment of fever, fasting, purging and drinks from diluted barley gruel were advocated.

13.2.5 Greek Medicine

Greek scholars believed that the body was composed of four humours (or fluids): phlegm, blood and yellow and black bile [12]. Health was maintained when these humours were in equilibrium, while diseases, and most especially fevers, were caused by a disturbance of the four humours. This theory of humoural equilibrium in health, and disequilibrium in disease, which persisted until the middle of the nineteenth century, was the first organized concept of thermoregulation. The present concept also envisages equilibrium between temperature production and loss.

Knowledge about fever was extensive in Greek medicine compared to other ancient cultures. Fevers were divided according to their patterns into continuous (from excess of fire) or intermittent in the form of subtertian and tertian (from excess of water), quotidian (from excess of air) or quartan (from excess of earth). Other classifications described 5-day, 7-day, 9-day, nocturnal and diurnal fevers [13]. Most fevers encountered at that time (e.g. continued, quotidian, tertian and quartan) were also thought to be caused by excess of yellow bile because at that time many infections were associated with both fever and jaundice. Each of these fevers was studied according to the characteristics in its nature and in spacing of the paroxysms. The prognosis for each was determined. The Greek scholars knew that diseases were responsible for producing fever.

The Hippocratic writings characterize many febrile illnesses with such accuracy that diagnosis can be made from the descriptions. Malaria is evident, with its paroxysms of fever, and mumps with its soft, nonsuppurative swelling and absence of high fever, complicated sometimes by orchitis [14]. Hippocrates also observed that febrile convulsions occurred in children up to the age of 7 years. Typhoid fever, a classical example of continuous fever with its ladder-like rise in body temperature during the first week, was also well described: "The worst, most protracted diseases were the continued fevers, these showed no real remissions; they began mildly but continually increased paroxysm carrying the disease a stage further". "Shivering fits and sweat were least frequent and most irregular in these patients". It is remarkable that these observations were made by palpation only.

The Hippocratic writings also contain evidence that fever was thought to be beneficial to the infected host, 'fever was beneficial in ophthalmia' and it cured it [15]. Since Hippocrates believed in the benefit of fever, he placed little emphasis on the treatment of it. When a disease was caused by an excess of one of the four bodily humours, the excess humour was then "cooked" by the fever, "I separated and eventually removed". He considered that nature provided the best medicine, a concept that influenced physicians until the beginning of the twentieth century. The best treatment for fever, if any, was dietary and consisted of starvation, accompanied by cool drinks. Acutely ill patients were usually given barley gruel or barley water, supplemented with hydromel (honey with water) or ioxymel (honey with vinegar). The purpose of the relative starvation and fluid regimen was to reduce the amount of bile and blood in the body.

Rufus of Ephesus, a surgeon who lived at the beginning of the second century AD, strongly advocated the beneficial role of fever. He was the first physician to recommend the use of "fever therapy", such as by malarial fever, to treat epilepsy. He said: "fever is a good remedy for an individual seized with convulsion, and if there were a physician skilful enough to produce a fever it would be useless to seek any other remedy against disease" [16].

About eighteen centuries later in 1917, Wagner von Jauregg treated neurosyphilis with malarial fever, for which he received the Nobel Prize 10 years later [17].

Although considerable progress took place in the interval between the third century BC and the second century AD, Galen (AD 130–200) retained the Hippocratic humoural theory. Fever, according to Galen, could result from either excess of yellow bile, black bile or phlegm (a condition which he called a cacochymia) or from an excess of blood, a plethora. To restore a healthy balance, Galen advocated bloodletting.

13.2.6 Hebrew Medicine

The roots of Hebrew medicine can be traced to the Bible (compiled between 1500 and 300 BC) and the Talmud (a book of rules and precepts completed between 70 BC and the second century AD) [18]. Magic, incantation and mystics appear to be less significant than in other cultures. Certainly, the biblical record

contains no indication that fever was caused by demons or evil spirits. In the Old Testament, fever was part of God's punishment for sins. The Creator of heaven and earth, Yahweh, states "but break my covenant, then be sure that this is what I will do: I will bring upon you sudden terror, wasting disease and recurrent fever" (Leviticus 26: 16; Deuteronomy 28: 22). Fever is also mentioned on several occasions in the New Testament, always without comment on causation. The first time, Jesus saw in Peter's house "his wife's mother laid and sick of a fever. And he touched her hand and the fever left her" (Matthew 8: 14–16, Mark 1: 29–34, Luke 4: 38–41). Elsewhere, Jesus healed the official's son with his words (John 4: 49–52), and the apostle Paul prayed to God and placed his hands on Publius, who was then healed of fever and a bloody flux, meaning dysentery (Acts 28: 8).

In summary, the oldest civilizations (Egyptian, Mesopotamian, Chinese, Indian, Greek) demonstrated extensive knowledge of fever but tended to view it as being induced by evil spirits. Hence exorcism was used in many ancient cultures (to a lesser extent in Greek medicine) in the treatment of fever. Many ancient physicians however, fostered mainly by the Greeks, believed in the beneficial effects of fever, but early Jewish and Christian writers regarded it as a punishment from God.

13.3 Medicine in the Middle Ages

With the beginning of the Middle Ages (ca. 400–1400 AD), science and medicine became less important than theology and philosophy [19]. Galen's writings remained a great influence on medicine during the Middle Ages. He had a philosophy embracing body, mind and soul, which was highly acceptable to the religion of the developing church [20]. The central development of medicine was in anatomy learned mainly from animal dissections, but a few were performed on humans. Anatomical studies began at Bologna (ca. 1150 AD) and Padua University (ca. 1222 AD). Physiology and pathology were still based upon the four humours (blood, phlegm, yellow and black bile). All diseases were characterized as hot, cold, moist or dry. "Hot diseases" were treated by cooling and "moist diseases" by drying. Bloodletting was widely practised in febrile illnesses, as Galen and some of the ancient physicians had done. This was based on the notion of plethora, a theory that attributed disease to part of the body being overfilled with blood. Apart from bloodletting, other methods used in the attempted cure of acute fevers included cooling, emollients and laxatives.

With the destructive epidemics of the Black Death, which killed as much as one third (reportedly 25 million) of the European population in the fourteenth century (with a peak in 1348), fever became a marker of death. Medicine was not helpful in preventing or treating the illness. The wrath of fever was still attributed to demonic possession and therefore required exorcism to expel it in line with evolving theological doctrine. The belief that fever constituted divine punishment also prevailed, particularly among the devout.

13.4 Arabic Medicine in the Middle Ages

Unlike this "dark period" in European medicine, Arabic medicine reached its golden age in the ninth and tenth centuries. The writings of both Hippocrates and Galen were carefully translated from Greek into Syriac and Arabic. Two scholars were outstanding in this period. Abu Ali Husayn ibn Abdulla ibn Sina (AD 980–1037), latinized as Avicenna [21], was, like Galen, a philosopher and physician. His best work, Qanun fit-Tibb or *The Canon of Medicine*, was a vast encyclopaedia.

The second great scholar was Abu Bakr Muhammad Zakariya Al-Razi (AD 864–923, latinized as Rhazes) who was the first scholar to differentiate measles from smallpox with his original treatise on the two diseases [22]. On smallpox he wrote: "The eruption of the smallpox is preceded by a continued fever, pain in the back, itching in the nose and terror in sleep. There is redness in both cheeks, a redness of both eyes, a heaviness of the whole body, distress of the whole body, distress and anxiety". Rhazes' best-known medical work, Kitabul-Hawi Fit-Tibb, or Contents of Medicine, appeared in 25 volumes. The books contain his views on fever and febrile illnesses. He noted that, for example, "exercise excites fever and fuels it like blowing into fire" and that fever in tuberculosis is mild and blunt.

One of Rhazes' remarkable observations was his differentiation of fever (elevated central thermoregulatory set-point) from heat stroke (normal central thermoregulatory set-point): "there is another fever with a higher core temperature than the common fever, where patients are much thirstier and the body feels hot all over" [23]. Rhazes was probably the first scholar to distinguish between the two terms, fever and hyperthermia in the form of heat stroke, often equated even nowadays.

13.5 European Medicine

The concepts of fever in European medicine have gradually evolved over several centuries:

- Towards the end of the sixteenth century, medicine achieved an important milestone with the invention of a means to measure body temperature when Galileo (1564–1642) reinvented the thermoscope. The first thermoscope had been invented by Heron of Alexandria in the second century BC [24]. Galileo's thermoscope (1592) was an air-filled bulb with an open-ended stem inverted over a container of water. The level of water in the stem varied with ambient temperature but was influenced by the pressure. In 1644 Ferdinand II of Tuscany sealed the neck of the flask, thereby eliminating the air pressure variable. Santorio Sanctorius (1561–1636) added thermal graduation to the thermoscope, thereby producing the first thermometer [25]. Temperature was measured by allowing the individual to grasp the bulb of the thermometer. The rate at which the fluid subsequently fell was used as an indicator of body temperature.

- During the seventeenth century, fevers were classified as continued (such as typhus), intermittent (such as malaria) or eruptive (such as smallpox). The most prevalent febrile disease in England at this time was malaria, notably the benign tertian form, which was described at that time as the annual spring epidemic of intermittent fevers. Two scholars were outstanding during this period:
  - For Thomas Sydenham (1624–1689), the writings of Hippocrates remained the principal source of medical knowledge [26]. He emphasized, however, only one humour, namely, blood. In this he had possibly been influenced by the discovery of the circulation of the blood by William Harvey (1578–1657). The other humours, Sydenham thought, were either contained in or derived from the blood. Sydenham believed that these spring fevers were attributed to the warmth of the sun acting on humours accumulated in the blood during the winter. He advocated as a treatment a low-calorie diet without meat, with a mild purgative on the day of intermission. He clearly regarded fever as beneficial as witnessed by his remark "fever is a mighty engine which nature brings into the world to remove her enemies".
  - Hermann Boerhaave (1668–1738), professor of medicine at Leyden, was one of the most well-known physicians of his time. He described the prime symptom of fever as an accelerated pulse and heartbeat, arising, from stagnation of the blood at the ends of capillaries and accompanied by an irritation of the heart. He maintained that a rapid pulse was pathognomonic of fever and strongly advocated the measurement of body temperature by means of an alcohol thermometer held in the patient's hand [27].
- During the eighteenth century, fever became divided into symptomatic (such as pneumonia or wound infection) and idiopathic or essential. The concept of fever most widely accepted by British physicians was that of William Cullen (1710–1790) [28], of the University of Edinburgh from 1773 to 1790. Cullen divided fevers into a simple inflammatory fever without delirium and those fevers accompanied by delirium or stupor, which he called "typhus". Although he thought of fever as a general disease that might assume various forms, he believed that the common underlying pathophysiology was a spasm of the arteries.
- By the mid-1800s, the ancient humoural theory began to disintegrate and with it the concept that fever was beneficial. The belief that fever could result from inflammation also evolved further during this century. Francois Broussais (1772–1838) recognized the relationship between the two and suggested that the usual seat of inflammation was the stomach and the intestines.
- In 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 [29]. 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 identifi-

cation of the typhoid bacillus in 1880 and the discovery of the tubercle bacillus in 1882. These discoveries relegated fever to a sign of disease. Great scholars of this period include:

- Claude Bernhard (1813–1878), the great French physiologist, recognized that body temperature was regulated in healthy organisms by the balancing of heat production and loss. He demonstrated that animals died quickly when the body temperature exceeded the normal level by 5–6 °C, thus suggesting that fever may be harmful and that antipyretics, which were introduced later, may be beneficial [30].
- Carl Liebermeister (1833–1901), a German physician, elaborated the theory that fever is well controlled by the same mechanisms as in normal body temperature, only at higher set-point.
- William Osler declared that "the humanity has three enemies, fever, famine and war, but fever is by far the greatest".
- Billroth (1829–1894) in 1868 attempted to confirm this ancient observation by injecting pus into animals, thereby producing febrile response [31]. His attempt to prove that fever resulted from activity in the host cells themselves failed because the injected material was contaminated with endotoxin, a product of Gram-negative bacteria that induces fever.

Finally, Beeson in 1948, using aseptic techniques to exclude endotoxin, isolated a fever-inducing substance from the host leucocytes, leucocyte pyrogen [32]. This later became known as an endogenous pyrogen identical to interleukin-1.

13.6 History of Fever Therapy

Throughout the history, a variety of diseases have been treated by fever, including:

- Cancer. The *Edwin Smith Surgical Papyrus*, written about 1700 BC, contains the use of increased temperatures to treat cancer. In the nineteenth century, Dr. Coley treated cancer patients with bacterial toxins extracted from erysipelas lesions, which caused high fevers. This was based on observation that some cancers decreased in size or resolved after infection with erysipelas. Malignant tumours were then treated with injection of toxins or erysipelas bacteria. In 1898 Dr. Westermark, a Swedish physician, described local hyperthermia to successfully treat cervical cancers. Research has shown that malignant cells of certain animal and human tumours are more susceptible to elevated temperatures in the range of 41–44 °C than normal tissue.
- Infectious diseases. Hippocrates cited hyperthermia in the form of cauterization using a hot iron to treat various ailments. A few centuries later, Rufus of Ephesus became the first physician to recommend the use of malarial fever to treat illnesses. Although a variety of diseases have been treated during the past two centuries, it was Wagner von Jauregg in 1917 who gave an enormous impetus to fever as a therapeutic agent by treating neurosyphilis with malarial fever, for

which he won the Nobel Prize. Infection diseases have historically been treated by fever. 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 or about 50 h administered in several sessions.

- Other diseases. Treatment with fever was also practiced in patients with rheumatoid arthritis and asthma.

13.7 Present Concepts: Fever May Be Beneficial

Only in the past four decades has there been successful research into the role of fever in disease. 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.

Theoretically, fever could benefit an illness mainly in two ways: It could adversely affect the infecting organisms and/or could enhance the host defences. The accumulated data now suggest that fever has a protective role in promoting host defence against infection, rather than being a passive by-product (see details in Chap. 9: Is Fever Beneficial?).

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Glossary of the Term Fever

14

Fever (pyrexia) is defined as a body temperature of 1 °C (1.8 °F) or more 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, which is fever as measured in the axilla.

Aden Fever (see Dengue Fever).

African Haemorrhagic Fever refers to Marburg and Ebola virus infections (see Crimean-Congo Haemorrhagic Fever).

Algid Pernicious Fever (pernicious malaria) is a severe malarial attack caused by falciparum malaria in which the patient presents with collapse and shock. Fever may be mild or absent.

American Mountain Fever (see Colorado Tick Fever).

Autumn Fever has a variety of definition and meaning. One form is caused by leptospirosis autumnalis that occurs in Japan, also known as hasami disease.

Absorption Fever is a fever occurring shortly after birth caused by absorption of uterine discharge through the vaginal wall.

Behavioural Fever is an acute change of body temperature of ectothermic animals (such as fish) by behavioural means, e.g. moving away from cold to warmer environment to raise body temperature.

Black Fever means kala azar, or dumdum fever, which is a Hindi name given by the physicians in India to refer to the hyperpigmentation of the skin during the disease. It is the most severe form of visceral leishmaniasis.

Blackwater Fever is the passage of the dark-red urine (haemoglobinuria) due to intravascular haemolysis following infection with falciparum malaria. The condition is occasionally seen in association with haemolysis due to G6PD deficiency. Other features include chills, fever, anaemia, jaundice and hepatosplenomegaly.

Boutonneuse Fever (see Mediterranean Spotted Fever).

Breakbone Fever (see Dengue Fever).

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_14

Cabin Fever is a state of anxiety caused by long confinement below deck, e.g. due to bad weather.

Cat-Scratch Fever (cat-scratch disease) is a benign infectious disease caused by Gram-negative bacteria (*Bartonella henselae*), which are transmitted to humans by scratch or bite of a cat (or more likely kittens). Symptoms usually appear after 1–2 weeks and consist of tender regional lymphadenopathy and mild fever. The condition usually resolves in 2–5 months. In immunocompromised patients the condition is life-threatening.

Central Fever is the presence of sustained fever resulting from damage of the thermoregulatory centre of the hypothalamus.

Chikungunya Fever is a mosquito-borne disease caused by chikungunya virus causing fever and debilitating arthritis in Africa and the Indian Ocean. Most people recover within a week.

Childbed Fever (puerperal fever, puerperal septicaemia) is a bacterial infection, usually caused by *Streptococcus pyogenes*, of the genital tract occurring in the post-neonatal period. The localized infection (puerperal sepsis) can lead to a blood-borne spread of infection (puerperal septicaemia).

Colorado Tick Fever (also Mountain Fever, American Mountain Fever) is a tick-borne, febrile illness caused by arenavirus, occurring in the Rocky Mountain area of the USA, mostly in May–June months. The virus is transmitted by the wood ticks (*Dermacentor andersoni*). Three to 6 days after the tick bite, there is a sudden onset of fever, myalgia, arthralgia, headaches, weakness and photophobia.

Crimean-Congo Haemorrhagic Fever (Congo Haemorrhagic Fever, Central Asian Haemorrhagic Fever) is caused by CCHF virus (Nairovirus) which is transmitted by ticks (ixodid). The disease is characterized by sudden onset of fever, myalgia, headaches, back pain, haemorrhagic tendency and lymphadenopathy. The disease is primarily a zoonosis, but outbreaks can affect humans causing high mortality.

Congo Haemorrhagic Fever (see Crimean-Congo Haemorrhagic Fever).

Continuous Fever (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. Examples of this pattern of fever are typhoid fever and malignant falciparum malaria.

Dandy Fever (see Dengue Fever).

Deerfly Fever (see Tularemia Fever).

Dengue Fever is a disease caused by arbovirus which is carried by mosquitoes. The disease is prevalent in Africa. Features include high fever, myalgia, chills, arthralgia and rash (petechiae). Severe cases are called dengue haemorrhagic fever.

Double Quotidian Fever (see Quotidian Fever).

Drug Fever is a febrile reaction caused by a therapeutic agent, such as antibiotic or cytotoxic drugs.

Dutton's Relapsing Fever referred to Dutton disease, which is an African tick-borne disease caused by *Borrelia duttoni* and spread by ticks.

Dumdum Fever is a Hindi term given to kala-azar disease. Dum Dum is a town not far away from Calcutta or a soft-nose bullet.

Ebola Haemorrhagic Disease (see next Ebola Haemorrhagic Fever).

Ebola Haemorrhagic Fever (currently known as Ebola Haemorrhagic Disease) is a severe and often fatal disease in 25–50%. The disease occurs as outbreak in Central and West Africa.

Elephantoid Fever is a lymphatic inflammation caused by filariasis. Features include chills and fever associated with painful swelling of the affected areas (lower legs). The overlying skin may be red.

Enteric Fever is a systemic febrile illness with enteric symptoms caused by *S.* Typhi (typhoid fever) and *S.* Paratyphi (paratyphoid fever). The term was used to differentiate typhoid fever from typhus.

Epidemic Haemorrhagic Fever is an acute infectious disease characterized by fever, purpura and vascular collapse, caused by viruses of the genus *Hantavirus* (see Haemorrhagic Fever with Renal Syndrome).

Eruptive Fever (see Mediterranean Spotted Fever).

Factitious Fever is a creation of fever by manipulation (usually thermometer manipulation). This is occasionally encountered in the differential diagnosis of PUO, occurring in about 2% of mainly adult cases. Sweating and tachycardia are absent.

Familial Hibernian Fever (FHF) is the former name for TRAPS (TNF receptor-associated periodic syndrome). FHF resembles the FMF (Familial Mediterranean Fever) and is characterized by recurrent fever with localized myalgia and painful erythema. In contrast to FMF, the FHF has a benign course without amyloid formation.

Familial Mediterranean Fever (FMF) is a hereditary (autosomal recessive) disorder characterized by periodic episodes of fever and painful serositis (pleuritis, peritonitis) lasting 24–72 h. The disease is prevalent among the Eastern Mediterranean population.

Haverhill Fever is the bacillary form of rat-bite fever, caused by *Streptobacillus moniliformis* and transmitted through contaminated milk and dairy products.

Fever Blisters (cold sores) are labial herpetic lesions caused by herpes simplex infection in association with febrile illness.

Fever Phobia is exaggerated fear that parents have when their children have fever leading to overuse of fever-suppressing drugs.

Fever of Unknown Origin FUO (or pyrexia of unknown origin PUO). In paediatrics, this term is applied when fever without localizing signs persists for 1 week during which evaluation in the hospital fails to detect the cause. In adults, PUO requires fever duration of at least 3 weeks and uncertainty of diagnosis after a 1-week investigation in the hospital.

Five-day Fever (see Trench Fever).

Glandular Fever (infectious mononucleosis) is a viral infection caused by Epstein-Barr virus. The illness manifests as a febrile illness, sore throat and lymphadenopathy. There are often hepatic dysfunction and splenomegaly.

Hay Fever (allergic rhinitis) is an acute nasal catarrh consisting of swelling of the nasal mucosa, causing sneezing and itching, associated with conjunctivitis and lacrimation. It is either seasonal (pollen) or perennial (nonseasonal). The illness has

actually nothing to do with fever; in the past patients who suffered from hay fever thought that they had febrile illness until the association to plant pollen became known in 1873.

Haemorrhagic Fever is a severe viral infection seen mainly in the tropics, usually transmitted to humans by arthropod bites or contact virus-infected rodents. Common features include fever, haemorrhagic tendency, thrombocytopenia, shock and neurological disturbance.

Haemorrhagic Fever with Renal Syndrome (HFRS) includes several related infections (epidemic haemorrhagic fever, haemorrhagic nephrosonephritis, Songo fever, Korean haemorrhagic fever, haemorrhagic fever and nephropathica epidemica) caused by *Hantavirus* and transmitted by rodents. In addition to fever, myalgia and abdominal pain, there is interstitial haemorrhage, renal failure and shock.

Hepatic Intermittent Fever (or Intermittent Hepatic Fever) is an intermittently occurring fever resulting from intermittent impaction of stone in the bile duct, which is causing choleangitis.

Herpetic Fever (see Fever Blisters).

Hospital Fever = epidemic typhus (see Jail Fever).

Humidifier Fever is an illness characterized by fever, cough and myalgia, caused by inhalation of air contaminated by fungi and blown from humidifiers or air conditioners.

Katayama Fever is an acute manifestation of schistosomiasis (bilharzia) caused by contact with fresh water that harbours snails infected with *Schistosoma mansoni* or *Schistosoma japonicum*. Acute manifestations (about 6 weeks after contact) include fever, urticarial rash and hepatosplenomegaly.

Kenya Fever (see Boutonneuse Fever).

Intermittent Fever involves temperature that peaks in the afternoon and returns to normal each day, usually in the morning. This is the second most common type of fever encountered in clinical practice. Examples are malaria, lymphoma and endocarditis.

Jail Fever = endemic typhus caused by *Rickettsia prowazekii*. Apart from fever, patients develop myalgia, weakness and headaches.

Korean Haemorrhagic Fever is an infection caused by viruses of the group *Hantavirus* and characterized by fever, haemorrhagic tendency, shock and renal failure (see also Haemorrhagic Fever with Renal Syndrome).

Lassa Fever is a viral infection (arenavirus), with rats being the natural host, seen usually in West Africa. The disease is characterized by fever, myalgia and chest, abdominal and back pain, complicated by haemorrhagic tendency, seizures and shock. Mortality is high (around 40%).

Malignant Catarrhal Fever is cattle-associated illness that has been reported from many countries, including Central Europe. It is caused by a virus related to the herpesvirus. Symptoms include persistent fever, necrosis of the nasal and oral mucosae and lymphadenopathy.

Malta Fever (see Undulant Fever = brucellosis).

Maternal Fever denotes fever occurring in term labour, which is often associated with chorioamnionitis.

Mediterranean Spotted Fever (Boutonneuse Fever) is an acute febrile, zoonotic disease caused by *Rickettsia conorii* and transmitted to humans by the brown dog tick *Rhipicephalus sanguineus*. It is prevalent in southern Europe and central Asia. Features include high fever, myalgia, arthralgia and a distinct mark: tache noire (black spot) at the site of the tick bite.

Mountain Fever (see Colorado Tick Fever).

Metal Fume Fever is an acute allergic reaction caused primarily by inhalation of zinc, magnesium or copper fumes from welding. A few hours after exposure, workers experience flu-like symptoms with low-grade fever (usually 38–38.5 °C), chills, myalgia and headaches. Symptoms usually last 4–24 h, and recovery occurs within 24–48 h.

Mud Fever is a dermatitis which affects the skin of the heels and back legs of horses, caused by invasion of bacteria (*Dermatophilus congolensis*) when the skin is damaged and exposed to mud and wet conditions.

Nodal Fever = erythema nodosum is painful and tender erythematous nodules localized on the shins. Drugs and streptococcal throat infection are most common causes.

Omsk Haemorrhagic Fever is caused by a *Flavivirus*, transmitted to rodents from the bite of an infected tick. The disease mainly occurs in Siberia. Symptoms include fever, severe myalgia, haemorrhagic symptoms, pneumonia and meningitis.

Oroya Fever (the name refers to an area near La Oroya, Peru) is the potentially fatal form of bartonellosis, caused by the bacteria *Bartonella bacilliformis* and transmitted by sand flies. The disease occurs mostly in the Andes Mountains of western South America. Manifestations include haemolytic anaemia and fever.

Paratyphoid Fever is an enteric fever caused by *Salmonella* Paratyphi (see Typhoid Fever).

Parrot Fever (psittacosis, ornithosis) is an infectious disease caused by *Chlamydia psittaci* and transmitted to humans by pet birds, including parrots, parakeets, lovebirds and budgerigars. Humans catch the infection from infected birds by inhaling the organisms from shed features. Symptoms develop 5–12 days after exposure and include fever, myalgia, cough and, in severe cases, pneumonia.

Pel-Ebstein Fever, described by Pel and Ebstein in 1887, was originally thought to be characteristic of Hodgkin's disease. Only a few patients with Hodgkin's disease develop this pattern, which 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 is unknown but may be related to tissue destruction or associated haemolytic anaemia.

Periodic Fever is characterized by episodes of fever recurring at regular or irregular intervals, and each episode is followed by one to several days, weeks or months of normal temperature. Examples are seen in malaria.

Pharyngoconjunctival Fever: this disease is associated with type 3 adenovirus infection. It is characterized by fever (usually high and lasts 4–5 days), pharyngitis causing sore throat, rhinitis, conjunctivitis and posterior cervical lymphadenopathy.

***Phlebotomus* Fever** (also called Sandfly Fever) is a febrile viral disease caused by an arbovirus, which is transmitted by sand flies. It is characterized by influenza-like symptoms, including fever, myalgia and headaches. The disease occurs mostly in the Balkans and southern Europe.

Pontiac Fever is a mild form of Legionnaires' disease, caused by bacteria *Legionella*. Symptoms include flu-like illness with fever. In contrast to Legionnaires' disease, Pontiac fever does not cause pneumonia. Both forms of legionellosis are caused by breathing mist that comes from a water source (such as air-conditioning cooling towers) contaminated with the bacteria. While Legionnaires' disease may cause mortality, Pontiac fever is self-limited.

Pretibial Fever is an infection caused by *Leptospira* bacteria. Characteristic features include an abrupt onset of fever of 39–40 °C, abdominal pain, myalgia and a rash on the pretibial region of the legs.

Protein Fever is fever arising from injection of foreign protein such as milk into bloodstream.

Prolonged Fever describes a single illness in which duration of fever exceeds that expected for this illness, e.g. more than 10 days for a viral URTI.

Puerperal Fever (see Childbed Fever).

Pyogenic Fever is an invasion of the bloodstream by bacteria (mainly staphylococci), which are capable of producing pus.

Q-Fever is a zoonotic disease caused by *Coxiella burnetii*. Cattle, sheep and goats are the primary reservoirs. People working with animal products are at greatest risk of contracting the disease. Common features are fever (39–40.5 °C), myalgia and pneumonia, as well as hepatitis and endocarditis (usually involving the aortic valve).

Quotidian Fever, caused by *P. vivax*, denotes febrile paroxysms which occur daily, while the **Double Quotidian Fever** has two spikes within 12 h (12-h cycles). Examples are kala azar, gonococcal arthritis, juvenile rheumatoid arthritis and some drug fever (e.g. carbamazepine).

Rat-bite Fever is an infectious disease caused by *Streptobacillus moniliformis* and *Spirillum minus*, which is Gram-negative spirochaete. In the USA, rat-bite fever is primarily caused by the former bacteria, while the latter are the cause of the disease in Asia and Africa. Symptoms occur 2–10 days after a rat bite and include abrupt fever, chills and myalgia.

Recurrent Fever is an illness involving the same organ (e.g. urinary tract) or multiple organ systems in which fever occurs at irregular intervals. An example is Familial Mediterranean Fever.

Relapsing Fever describes fever alternating with afebrile periods. Examples are tertian or quartan malaria and brucellosis.

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 paediatric practice and is not specific to any disease. Diurnal variation is usually present, particularly if the fever is infectious in origin. Most viral or bacterial diseases present with this pattern.

Rheumatic Fever is an inflammatory systemic disease of the connective tissue, due to an infection by group A of haemolytic *Streptococcus*. The disease affects the

joints, heart, central nervous system, skin and subcutaneous tissue. Fever is a minor criterion for the diagnosis and occurs in about 90% of cases.

Rift Valley Fever is a zoonosis, primarily affecting animals, but occasionally humans, caused by a virus which belongs to the *Phlebovirus* and transmitted by mosquitoes. Common manifestations include sudden onset of fever, myalgia, headaches and signs of meningeal irritation. Most cases are mild, resulting in full recovery. In severe cases there is involvement of the eyes (causing visual impairment), meningoencephalitis and haemorrhagic tendency, which may cause death.

Rocky Mountain Spotted Fever is a serious systemic disease caused by *Rickettsia rickettsii*, transmitted by dog bite. It is mostly prevalent in southeastern areas of the USA (Virginia, Georgia). Patients usually suffer from sudden high fever (39.0–40.5 °C), headaches, myalgia and chills. The associated rash appears as small spots which begin on the wrists, ankles, palms and soles. Complications include renal failure, shock and occasionally death.

Roman Fever is malignant deadly strain of malaria (tertian or falciparum) which affected Rome historically.

Rose Fever is the spring-time equivalent of hay fever (see Hay Fever).

Ross River Fever is epidemic polyarthritis caused by arboviruses and transmitted by mosquito bites. It is most common in Australia.

Sandfly Fever (see *Phlebotomus* Fever).

Scarlet Fever is a bacterial disease caused by a toxin produced by group A haemolytic streptococci. It usually involves high fever and a characteristic rash, accompanied by tonsillitis.

Sennetsu Fever (human ehrlichial infection) is rare infection caused by different strains of *Ehrlichia* bacteria (*Neorickettsia sennetsu*). Common symptoms include sudden high fever, myalgia and headaches. The illness occurs mostly in Southeast Asia and is thought to be caused by eaten raw fish.

Septic Fever (or hectic fever) occurs when remittent or intermittent fever shows a very large difference between the peak and the nadir. Examples are Kawasaki disease and pyogenic infection.

Sindbis Fever is an infection caused by Sindbis virus and characterized by arthralgia, rash and malaise in addition to fever. It mainly occurs in Africa and Australia. The virus is transmitted by mosquitoes *Culex*.

Snail Fever (schistosomiasis or bilharzia) is a parasitic infection caused by an intermediate snail hosts which release parasites known as cercariae.

Songo Fever (see Haemorrhagic Fever with Renal Syndrome).

South African Tick-Bite Fever (see Tick-bite Fever).

Splenic Fever (anthrax) is a rare and highly lethal infectious disease of humans and animals that is caused by the bacterium *Bacillus Anthracis*. Human is infected by ingestion of infected meat, by inhalation or by cutaneous route.

Spotted Fever (See Rocky Mountain Spotted Fever).

Steroid Fever refers to a fever caused by elevated concentration of certain pyrogenic steroids, such as etiocholanolone.

Swamp Fever is a viral disease which affects horses, mules and donkeys and is transmitted by horse flies or mosquitoes. The disease is mainly found in the USA.

Thermic Fever refers to heatstroke.

Three-day Fever refers to roseola infantum or exanthema subitum caused by human herpes-6.

Therapeutic Fever refers to pyrotherapy or therapy by heat.

Tick-Bite Fever is usually a benign disease caused by *Rickettsia* and is transmitted by tick bites. Five to 7 days after the bite, there is a characteristic black bite mark (eschar or tache noire), associated with severe headaches and lymphadenopathy. It is common in South Africa (caused by *R. conorii*).

Tobia Fever (see Rocky Mountain Spotted Fever).

Trypanosome (or trypanosomiasis) Fever is caused by parasitic protozoan trypanosomes. The disease, which includes African trypanomiasis and Latin America Chagas disease, is characterized by lymph node swelling, haemolytic anaemia, haematuria, myalgia and arthralgia, in addition to fever.

Trench Fever is caused by *Rickettsia quintana*, transmitted by body lice, typically attacking the army. Characteristic features are intermittent fever, aches and pain (particularly in the shins), chills, skin rash and inflamed eyes. There are often multiple relapses.

Tularemia Fever (Deerfly Fever or rabbit fever) is a rare infection caused by bacteria *Francisella tularensis* in rabbits that can be transmitted to humans through insect bites or direct contact with infected animals. Apart from fever symptoms include lymphadenopathy, joint stiffness and respiratory and pneumonia.

Typhoid Fever is an enteric infection caused by *Salmonella* Typhi, chiefly involving the lymphoid follicles of the ileum. Characteristic features are fever, which gradually rises during the first week, relative bradycardia, headache, abdominal distension, splenomegaly and maculopapular rash.

Undulant Fever describes a gradual increase in temperature, followed by a period of high fever for a few days, then a gradual decrease to a normal level. A classical example causing this fever pattern is brucellosis.

Valley Fever refers to coccidioidomycosis, which is caused by a soil-borne fungus. The infection mainly occurs in Southern California and characterized by nonspecific symptoms of fever, chest pain and cough.

West Nile Fever (WNF) is caused by the West Nile virus, which belongs to the genus *Flavivirus*. Mosquitoes transmit the virus from birds (where it is mostly maintained) to humans. WNF is found in Africa and occasionally reported in some European countries. It is characterized by high fever, influenza-like symptoms, disorientation, tremors and coma.

Yangtze Valley Fever referred to *Schistosomiasis japanicum*, which occurs in the Far East.

Yellow Fever is a tropical disease caused by a viral infection (*Flaviviridae*), which is transmitted by infected mosquitoes (*Aedes aegypti*). Mild cases present with flu-like symptoms. Severe forms are life-threatening and present with high fever, myalgia, chills, headaches leading to shock, bleeding and renal and hepatic failure.

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A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9