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Evaluation of Childhood Fever Management

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Since the earliest times of history, fever has been the symptom that has attracted the most attention of mankind among the many symptoms of disease. Ancient civilizations (Egyptian, Mesopotamian, Jinn, Indian and Greek), despite their good knowledge of anatomy and physiology, feared of fever as a punishment caused by evil spirits or as a sign of death. In the history of medicine, it is very difficult to separate the history of febrile diseases from the history of infectious diseases, as most of the diseases that cause the body temperature of living beings to increase are also transmitted from one living being to another. For this reason, since fever as a harbinger of infectious diseases means the onset of the disease, fever is a warning for healthy people. Hippocrates (5th century BC) linked the importance of fever to the pulse rate and made predictions based on what the patient felt. Galen (2nd century AD) stated that there are four qualities in the body: heat, cold, dryness and humidity.

He thought that a person could be healthy if the ratio of those elements was right. In the early tenth century, the Turkish physician Razi argued that fever was not a disease, but a struggle of the body to expel the disease, and applied cold water treatment for febrile diseases. In the eleventh century, Ibn Sina thought that fever was burden in the heart and spread throughout the body through the blood, that this burning disrupted the functions of the body, and the resulting heat caused pain and fatigue. In the seventeenth century, it was thought that fever was caused by the fermentation of chemicals in the blood and was a harmful by-product of infection. In the last 40-50 years, intensive research has been

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conducted to investigate the importance of fever. Despite disagreement, the evidence suggests that fever is generally beneficial, although its effects are complex.

Fever is one of the most important symptoms of infections in childhood. In pediatric emergency department and outpatient clinic admissions. Fever and febrile illnesses account for 10-20%. However, despite being one of the most common symptoms of illness in the childhood, it is a symptom that continues to be surprisingly misunderstood by parents and health professionals and causes anxiety and stress, especially in parents. It is an important symptom that alerts the family that there is something unusual about the child. Parents feel they have important responsibilities to protect their children from illness, one of which is to eliminate the threat of illness; another is their sense of personal control. Giving their children medications that they believe are beneficial, such as fever reducers, can give parents a sense of control and reduce their anxiety and unnecessary use of health facilities. Therefore, it is important to safely reduce fever when necessary.

NORMAL BODY TEMPERATURE

The body is normally able to maintain a fairly constant temperature due to the hypothalamic thermoregulatory center balances excess heat production from metabolic activity in muscle and liver with heat radiation from the skin and lungs. Normal body temperature is influenced by factors such as age, physical activity, time of day, place of measurement and menstrual cycle. The body temperature varies diurnally throughout the day, with the lowest level occurring in the early morning (04.00-06.00) and the highest in the late afternoon (16.00-18.00), and the diurnal variation can be up to 1°C. The normal diurnal rhythm is also observed in febrile patients. Body temperature is higher in the first two years of life than in other age periods. This is due to the larger surface area, body weight ratio and higher metabolic rate of infants and young children. It also rises after physical activity and feeding. Among girls, it also varies with the menstrual cycle and rises slightly after ovulation.

According to the results of many clinical studies, normal body temperature is generally accepted to be 37°C. This value was derived by Wunderlich in the 19th century from studies of over 25.000 people. More recent studies have found slightly lower average body temperatures in healthy people. The latter studies were based on oral or rectal measurements, whereas Wunderlich preferred axillary measurements. Mackowiak et al. found a mean oral temperature of 36.8°C in adults, with the upper limit of normal ranging from 37.2°C at 06.00 am to 37.7°C in the afternoon. However, temperature measurement at a single point does not provide information about the actual body temperature. Depending on the measurement site, body temperature can vary by 1°C or more. Regional variations in temperature do not have a fixed relationship with each other. Although the axillary temperature is lower than the rectal temperature, the absolute difference between the two varies greatly.

The average normal body temperature in the neonatal period is 37.5°C and the upper limit of normal is 38°C. Exercise, overdressing, hot baths, extremely hot weather, hot food and drinks can raise the body temperature of a healthy child up to 38.0-38.5°C.

DEFINITION OF FEVER

Fever is defined as an increase in body temperature above the normal daily periodic change, which is centrally regulated by the body against various pathological stimuli. It is a series of events that usually start with the release of cytokines due to an infection, followed by the release of prostaglandin E_2 (PGE_2) from the anterior hypothalamus and changes in the thermoregulation center in the hypothalamus, where the body temperature is readjusted as if the person were in a cold environment. Although the most common cause is infections, it is also a common finding in hypersensitivity reactions, autoimmune diseases and malignancies. The two main features of fever are an abnormal rise in body temperature and a coordinated physiological response. The first distinguishes fever from normal elevations in body temperature (elevations associated with circadian rhythm) and the second distingusihes it from conditions in which regulatory mechanisms are dysfunctional (such as heat stroke).

High body temperature can be caused by fever or hyperthermia. It is important to distinguish between them, because they have different clinical causes and management strategies. Fever is an abnormal elevation of body temperature that occurs as part of a biological response generated and controlled by the thermoregulatory center in the hypothalamus. It is usually regulated to not exceed 41°C as long as dehydration is absent and an environment is provided to allow heat loss. Hyperthermia is an uncontrolled condition in which body temperature rises above 41°C without a change in the thermoregulation center (set point). The most important causes are heat stroke, neuroleptic malignant syndrome and malignant hyperthermia (Table 1). Characteristics of hyperthermia include delirium, convulsions and central nervous system dysfunction leading to coma.

Table 1. Main differences between fever and hyperthermia

	Fever	Hyperthermia
Clinical findings	Chills, cold skin	Hot, dry, flushed skin
Body temperature	Usually 38-41°C	May exceed 42°C
Hypothalamic set point	Elevated	Normal

The temperature rise that warrants clinical investigation for infection depends on the child's age and clinical conditions (immunodeficiency, sickle cell disease, poor appearance); in most cases, fever is less important than other signs of serious illness (irritability, meningismus). Although fever is generally defined as a body temperature ≥38°C, the definitions of fever for some conditions are given below:

- In a healthy infant younger than three months of age, fever is defined as ≥38.0°C (measured rectally).
- In children aged 3-36 months, fever can be defined as ≥38.0°C (measured rectally) and a body temperature of ≥39.0°C (measured rectally) in fever without a focus is of concern.
- In children >36 months and adults, fever can be defined as 37.8-39.4°C (measured orally) and above 39.5°C is alarming.
- In neutropenic patients, fever is defined as a single oral measurement ≥38.3°C, 38-38.2°C for more than one hour, or two elevations >38°C over a 12-hour period. Fever is defined as a single axillary measurement of ≥37.7°C or ≥37.4°C for more than one hour.

Pathogenesis

Fever is one of the most common findings of infectious diseases, but not all fever is due to infections, nor is fever seen in all infectious diseases. As the duration of fever prolongs, we encounter collagen tissue diseases and malignancies as well as infections. For these reasons, the mechanisms of fever should be well known when approaching the febrile patient.

Normal body temperature is regulated by thermosensitive neurons in the sweat-more regulation center in the preoptic area of the anterior hypothalamus. Information reaching the hypothalamus from the periphery is first interpreted and then regulated via efferent nerves to cause peripheral heat accumulation, loss or heat production. At rest, many organs such as the brain, muscles, viscera, liver, heart, thyroid and adrenal glands contribute to cellular heat production (ATP-mediated). Newborns do not shiver due to the immaturity of their skeletal muscles and rely on brown adipose tissue (containing large amounts of mitochondria) to protect against cold exposure. In older children, the first response to cold is behavioral, such as curling up or wearing thicker clothing. If this response is inadequate, the hypothalamic center is stimulated to generate heat by peripheral vazoconstriction and shivering. The dominant stimulus for shivering is skin temperature rather than core temperature. Heat is lost by evaporation, radiation, convection and convection-duction in response to a rise in body temperature above 37°C (or ambient temperature above 30-31°C). In a hot environment or when body temperature rises (fever), heat loss through evaporation (sweating) is the primary route of heat loss (10% for every 1°C increase in body temperature). This is accomplished by cutaneous vasodilation through acetylcholine-mediated relaxation of vascular smooth muscle. Radiation heat loss occurs when heat is transferred directly between two objects that are not in direct contact. Convection heat loss (12% of heat loss) is the result of the movement of a fluid or gas across the surface of the body. To maximize heat loss, blood flow to body surfaces is increased. Conduction (3% of heat loss) is the transfer of heat between two objects in direct contact and at different temperatures.

The thermoregulation center is stimulated by endogenous pyrogens, which are polypeptides produced as a host response to infection, injury, inflammation and antigenic changes. Substances that cause the release of endogenous pyrogens are called exogenous pyrogens. Toxins, which are products of microorganisms, are the best known exogenous pyrogens. Endogenous pyrogens are released by the action of many exogenous or endogenous substances on monocytes and macrophages. Endogenous pyrogenic substances released by monocytes and macrophages are also called pyrogenic cytokines. Cytokines are hormone-like polypeptides that are produced in response to antigenic stimuli, regulate immune events and are released mainly from macrophages and activated lymphocytes. Cytokines involved in the pathogenesis of fever are IL-1, tumor necrosis factor-α (TNF), IL-6 and interferon (IFN). IL-1α and IL-1 are the most potent EPs known. Tumor necrosis factor-α has similar properties to IL-1. It also induces IL-1 production, causing fever to persist and a second fever peak 3-4 hours later. Tumor necrosis factor-α and IL-1 exert their effects via IL-6. The most potent pyrogenic IFN is IFNα. In animal studies, it causes monophasic fever 80-90 minutes after administration. Other substances considered as potential EPs are IL-2, granulocyte monocyte colony stimulating factor (GM-CSF), immune complexes, uric acid crystals, C3a and C5a (Table 2).

Table 2. Factors that stimulate endogenous pyrogens

Microorganisms (Viruses, bacteria, fungi)
Peptidoglycans (Bacterial wall)
Endotoxins (Lipopolysaccharides)
Enterotoxins (A, B, C, D from staphylococci)
Toxic shock syndrome toxin-1
Group A streptococcal erythrogenic toxin
Capsular polysaccharides
Tuberculin
Antigen-antibody complexes
Complements (C5a-C3a)
Medicines (penicillin, bleomycin)
Pyrogenic cytokines (IL-1, IL-2, TNF, IFN)

In recent years, a very potent endogenous pyrogen called macrophage inflammatory protein-1 (MIP-1) has also been found, which directly stimulates thermosensitive and pyrogen-sensitive neurons through a pathway other than PGE_2.

After pyrogenic cytokines are formed, they enter the bloodstream and reach the preoptic area (thermoregulatory center) rich in vascular structures in the hypothalamus. Here, phospholipase A2 is activated and as a result, plasma membrane arachidonic acid is released and becomes a substrate for the cyclooxygenase pathway. Some cytokines can directly increase the expression of cyclooxygenase and cause the formation of arachidonic acid metabolite PGs, especially PGE_2. Since PGE_2 is a small lipid molecule, it easily crosses the blood-brain barrier and is transported to the hypothalamus for the activation of thermocen cytifying neurons to raise *the set* point.

Once the hypothalamic *set point* is raised, the thermoregulation center perceives the current body temperature as too low and initiates a series of events to raise the temperature to the new set point. Peripheral mechanisms stimulate the sympathetic chain and prevent heat loss through peripheral vasoconstriction via terminal adrenergic efferent nerves, and produce heat through muscle contraction and shivering. In addition, autonomic (decrease in sweating) and endocrine (decrease in vasopressin secretion and decrease in the amount of body fluid to be heated) pathways contribute to thermoregulation. Thus, the increased heat production is maintained within the new limits set by the hypothalamus (Figure 1).

Benefits and Harms

Ancient physicians such as Hippocrates and Rufus of Ephesus used fever to treat certain diseases. For centuries, fever was also the main treatment for syphilis and gonorrhea. However, whether fever is beneficial or harmful is still controversial. In birds and mammals, raising body temperature above 2-3°C leads to a ≥20% increase in energy expenditure. If fever did not have a beneficial role, it would be unlikely that it would have evolved and persisted after it evolved, as it is very costly in terms of energy. This evolutionary history supports the hypothesis that fever is an adaptive host response to infection.

Fever is an integral part of inflammatory response and may therefore play a role in fighting against infections. Fever is effectively controlled by the hypothalamic center and therefore does not rise too high. Temperatures above 42°C are therefore usually caused by hyperthermia, not fever.

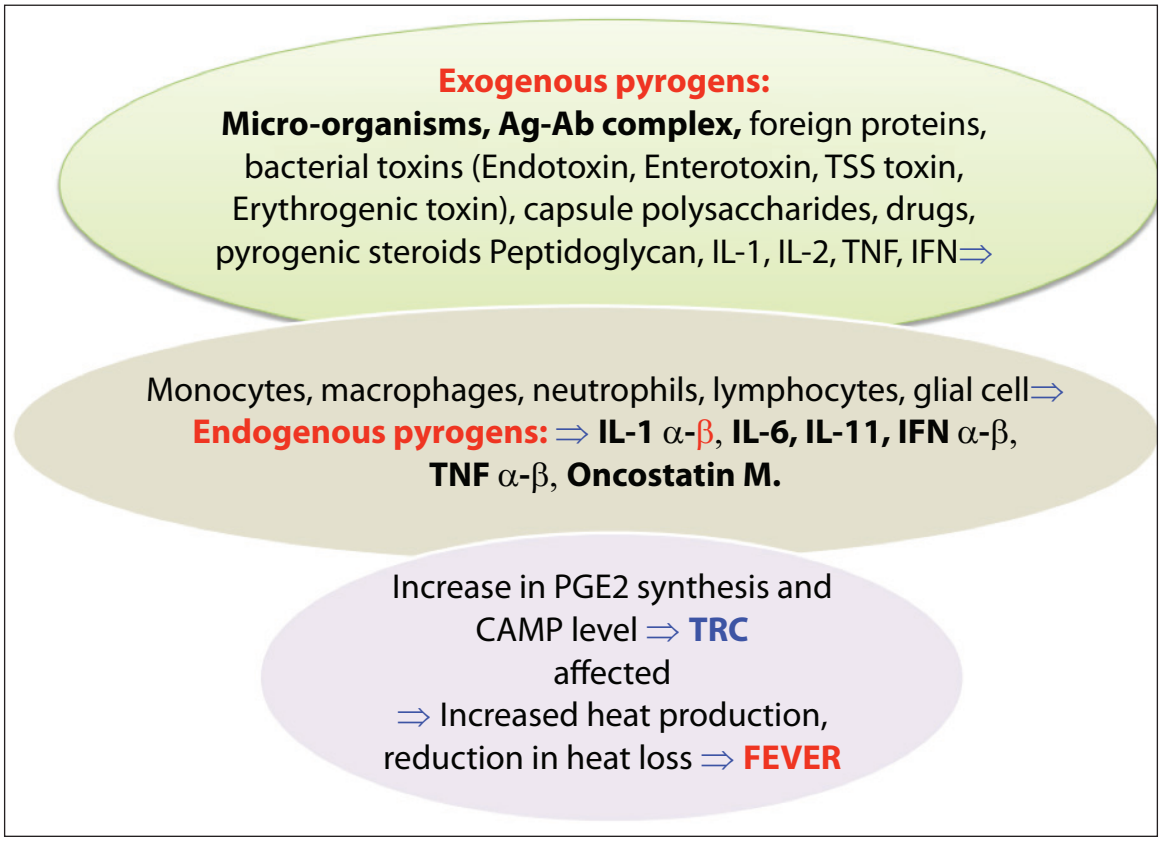


Figure 1. Fever pathogenesis.
TRC: Thermoregulation center.

Benefits

Potential benefits of fever include slowing the growth and replication of certain bacteria and viruses (related to reduced rumen iron) and enhanced immunological function at moderately high temperatures. A body temperature of 38-39°C has direct positive effect on lymphocyte transformation, formation of cytolytic cells, B-cell activity and immunoglobulin synthesis. This process is optimal at high temperature (approximately 39.5°C). Animal studies have shown that the bacterial growth rate in experimental pneumococcal meningitis is significantly reduced at high temperatures. Gram-negative bacteria such as salmonella have been shown to be increasingly susceptible to the bactericidal effects of serum when they grow at temperatures higher than 37°C. A study of 102 children with salmonella gastroenteritis from Finland showed a significant negative correlation between the degree of fever and the time taken for the organisms to be eliminated from the body. Those with a fever higher than 40°C had the shortest and those without a fever had the longest bacteria withdrawal.

Many viruses have been shown to stop replicating at temperatures between 40-42°C. For example, the replication rate of poliovirus at 37°C is 250 times higher than that at 40°C. Some animal studies have shown increased survival in response to fever. However, it is not clear whether this is the result of a direct effect of temperature on the growth of microorganisms or the effect of high temperature on host defense responses.

Harms

Fever can make children uncomfortable. Increased metabolic rate increases the work on the cardiovascular and pulmonary systems by rising oxygen consumption and carbon dioxide production. For a normal child, these stresses have little or no significance. However, for the child in shock or with pulmonary/cardiac abnormalities, the increased demand can be detrimental and override the immunologic benefits of fever. There is no evidence suggesting that a temperature of ≥40°C is associated with adverse outcomes **(**e.g. brain damage). Contrary to popular belief, complications and mortality associated with fever above 40°C are closely related to the severity of the underlying disease, not the level of fever.

TYPES AND CHARACTERISTICS OF CLINICAL THERMOMETERS

Thermometers are devices that objectively measure temperature. The thermoscope developed by Galileo Galilei (1564-1642) to measure heat and cold is the forerunner of the thermometer. The beginning of the measurement of body temperature with a thermometer dates back to the 17th century.

Reinhold August Wunderlich (1815-1877), who conducted numerous observational experiments on this subject, the results of which are still valid today, is considered to be the first person to use the thermometer clinically.

Today, there are a wide variety of thermometers produced in parallel with technological developments. Although mercury thermometers are the most widely used, their use has been discontinued due to the risk of heavy metal poisoning. The most appropriate method for measuring body temperature in children is still unclear. The main features that should be sought in an ideal thermometer are that it measures body temperature accurately and reliably regardless of age and sex, gives results in a short time, does not cause infection during measurement, is not affected by the environmental conditions in which the measurement is made, the device is accessible, inexpensive, easy to use and safe. The main clinical thermometers used today (Figure 2).

Liquid (Mercury, Alcohol) Glass Tube Thermometers

In these thermometers, the liquid (mercury, alcohol) is placed in a capillary glass tube with a reservoir at the bottom; as the temperature increases, it expands and rises in the capillary tube, and as it decreases, it contracts and falls. Designed to measure body temperature, they can measure temperatures between 33°C and 45°C. Mercury thermometers in this group are the most widely used standard thermometers, but they are breakable, and inhalation or contact with the vapors generated by the leakage of mercury can cause heavy metal poisoning in patients and healthcare workers. For this reason, the Ministry of Health of the Republic of Türkiye discontinued their use and production.

Other disadvantages are long measurement time, possibility of infection, the need for disinfection, and time-consuming disinfection.

Electronic Thermometers

Previous analogue electronic thermometers have been replaced by electronic thermometers, which are easier to use and provide fast and reliable results. The working principle is that the resistance of conductors to electrical conduction changes with temperature change. The thermometer tip has semiconductor metal sensors that become more conductive under the influence of temperature and allow a large current to flow. The temperature calculated from the current flow is displayed on the screen. The measuring range is from 32 to 42.9°C, temperature, those lower than 32.0°C is shown as low "L" on the display, and those higher than 42.9°C is shown as high "H" on the display, and the last measured value is saved. Measurement time is short and results are reliable.

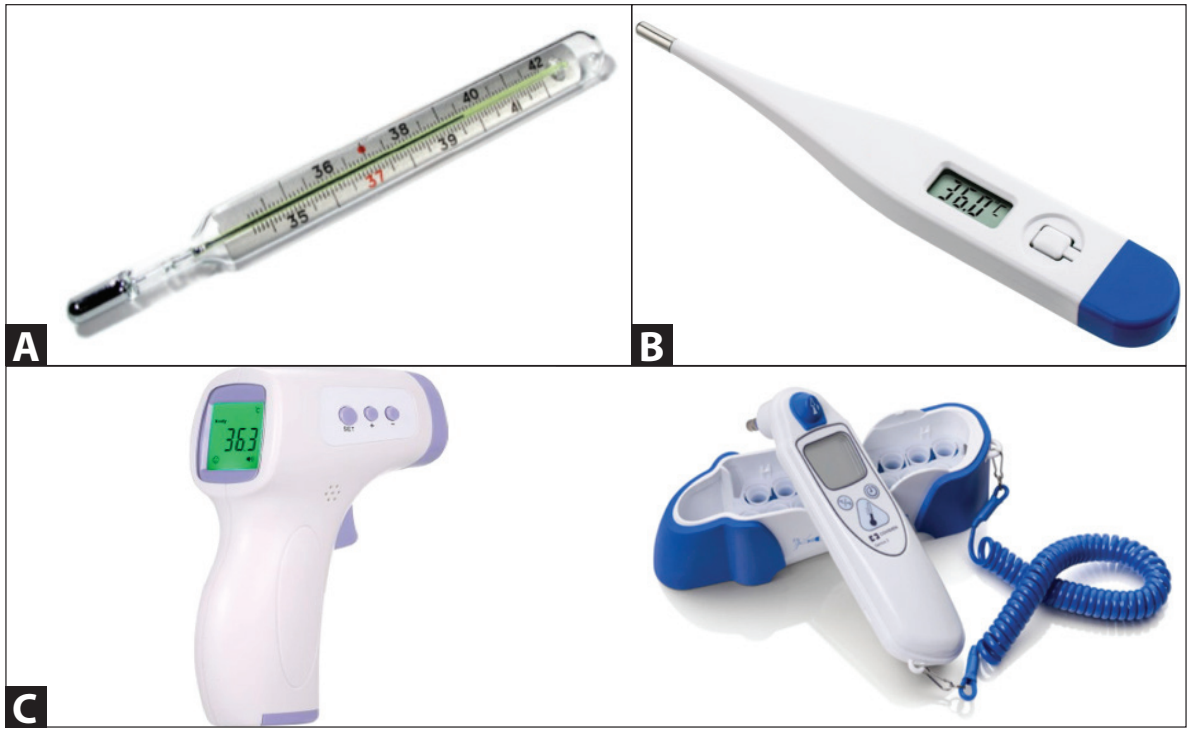


Figure 2. Thermometers.
A. Mercury glass thermometer, **B.** Electronic thermometer, **C.** Infrared thermometers.

Infrared Thermometers

Infrared thermometers measure electromagnetic waves emitted circularly from objects. The energy collected by the lenses is converted into electric current and reflected as a measured value. A new speculum is attached to the infrared tympanic thermometer before each measurement, the external auditory canal is flattened by pulling the ear upwards and backwards if the child is younger than one year old, or downwards and backwards if the child is older than one year, and the thermometer immediately detects the heat produced in the eardrum and surrounding tissue and reads it within seconds. A non-contact infrared thermometer takes measurements from the forehead and temporal artery, and since it is non-contact, no additional apparatus is needed.

Similarly, a thermal camera measures infrared waves emitted by objects and converts them into an electronic image that shows the apparent surface temperature of the object. Initially used in security systems, the thermal camera has been recognized as the most effective method for screening travelers for fever since the SARS outbreak, its use became widespread during the H5N1 and H1N1 outbreaks, and has become even more important during the COVID-19 pandemic.

Chemical Phase Conversion Thermometers

They were developed based on the ability of various mineral salts to change their color at certain temperatures. These disposable strip thermometers can be used for oral and axillary measurements, are easy to use and have no risk of infection. They can be affected by ambient temperature and changes in the skin, and their cost is high because they are disposable.

TEMPERATURE MEASUREMENT ACCORDING TO AGE (USE OF THERMOMETER)

A child may have fever if he or she feels hot, has pink cheeks, sweats or shivers. The only certain way to tell if a child has fever is to use a thermometer. The method used to measure fever is correct.

It should be reliable and applicable in the child's age group. In children, fever can be measured through the skin, mouth, rectal mucosa or tympanic membrane (Table 3).

An electronic or non-contact infrared thermometer should always be used to measure body temperature in children. Mercury thermometers can break accidentally, releasing mercury and causing poisoning. For this reason, the American Academy of Pediatrics (AAP) does not recommend the use of mercury thermometers.

The most commonly used method to measure body temperature is axillary measurement with an electronic thermometer. With the development of technology, non-contact infrared thermometers are being used more frequently in all age groups. While rectal temperature measurement is

Table 3. Types of thermometers to be used according to age

Age	Technique/Type
Newborn-3 months	• Rectal • Axillary (armpit)
3 months-3 years	• Rectal • Axillary • Tympanic
4-5 years old	• Rectal • Oral • Axillary • Tympanic
5 years and older	• Oral • Axillary • Tympanic

appropriate in children younger than three years of age, oral temperature can be measured in children over 4-5 years of age. Rectal measurement has been abandoned because it causes anal injuries. In children, the appropriate thermometer should be selected according to age.

Fever Measurement in Newborns

One of the most important vital signs in newborns is body temperature. Especially preterm infants are prone to heat-related problems due to their large body surface area and immature thermoregulation mechanisms. Therefore, temperature measurement should be accurate, reliable, reproducible and the best reflector of core temperature.

In outpatient and hospital settings, axillary measurement of body temperature using an electronic thermometer is the most commonly used and recommended method in infants <4 weeks. Rectal measurement seems to be the ideal method because it shows core temperature, but it is not a very comfortable measurement in children. Keeping it in the rectal area for a long time causes restlessness in the child.

In tympanic measurement, the thermometer must be placed appropriately in the external auditory canal and the presence of hyperemia or buds in the ear is a significant disadvantage. Uslu et al. have recommended the use of a tympanic thermometer as an acceptable and practical method in newborns.

Non-contact infrared thermometry appears to be a rapid, non-invasive and sterilization-free alternative. Sollai et al. compared non-contact infrared thermometry with electronic axillary and infrared tympanic measurement in term and preterm infants and presented it as an easy-to-apply method.

Fever Measurement in Children

Traditionally, temperature measurement with a rectal thermometer was considered the gold standard. However, due to the risk of rectal perforation, the need for sterilization of the thermometer, and discomfort in children, alternative measurement methods are being investigated. In a systematic review, no difference was found between rectal and axillary measurements in detecting fever in children and young adults, but the axillary temperature was one degree lower. The oral thermometer should be kept in the mouth for 3-4 minutes. For this reason, it cannot be used in young children under five years of age, who may not be able to cooperate and may break it by biting. For accurate tympanic temperature readings with tympanic thermometers, the infrared probe sensor must be inserted deeply into the meatus to ensure that it is directed to the tympanic membrane. In children younger than six months, the diameter of the meatus is small, which can lead to complications. In a meta-analysis by Pecoraro et al. mercury, electronic and infrared thermometers used in children and adults in emergency and inpatient services were compared. The sensitivity and specificity of the temporal infrared thermometer was 76% and 96%, while the sensitivity and specificity of the tympanic thermometer was 77% and 98%, respectively. Bayhan et al. found that non-contact infrared thermometers with low sensitivity and high specificity were suitable for screening in children aged four months and older. Similarly, the results of the comparison with rectal measurements in children showed that the non-contact temporal infrared thermometer was successful in showing rapid temperature changes but was not sufficient in reflecting core heat. In a study from Türkiye, fever values measured simultaneously with an electronic axillary thermometer and a smartphone application were recorded. It was stated that the method of measuring fever with a smartphone application was seen as a reliable method that can be used everywhere and in all age groups. As a result of ongoing studies, it is not possible to say which is the most appropriate fever measurement method.

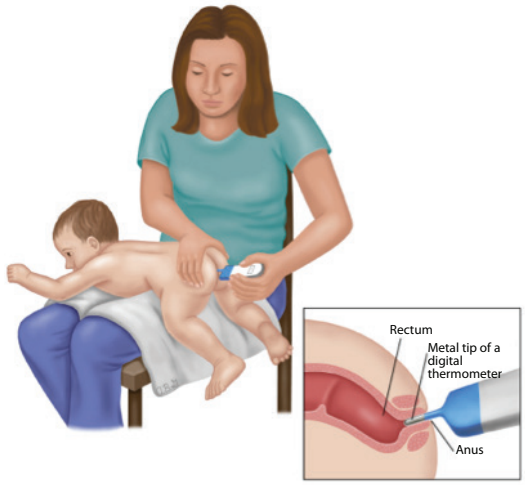
Measurements that are suitable for the age of the patient, economical, practical and fast should be preferred.

Rectal Measurement

The rectal temperature is closest to the body core temperature and the rectal measurement is considered the gold standard. Normally, the rectum is the site where the body temperature is measured the highest. However, changes between rectal temperature and core body temperature are reflected late. For this reason, the rectal region may be preferred as the measurement site in thermally stable patients.

In rectal temperature measurement, after lubricating the chamber of the thermometer, the chamber of the thermometer is inserted 1-2 cm into the rectum while the baby is flexed at the hips and knees and lying prone on the mother's lap, and the reading is usually taken after waiting for 40 seconds (Table 4). During this time, the baby should

Table 4. Important points in rectal temperature measurement



- The rectal route is usually used in children under three years of age but should be preferred especially if hypothermia is to be demonstrated.
- Make sure that the thermometer to be used for measurement is clean and should be cleaned with clean water or alcohol before use.
- Sterile lubricant gel is applied over the electronic thermometer probe and anal opening (e.g. Vaseline).
- The child is placed on the mother's lap with the buttocks up, then
- The buttocks are separated and the thermometer is gently inserted without straining **until the metal tip is no longer visible** in the anal canal (1-2 cm).
- Thermometer by squeezing both buttocks of the child with the hands of the practitioner is stabilized.
- The thermometer is left in the rectum until a beep is heard (measurement time is usually 40 seconds), then the number on the thermometer is read.
- Normal rectal body temperature is between 36°C and 37.9°C.

be held very tightly to prevent any damage to the anus and rectum by the thermometer. In addition, body temperature should not be measured rectally when the child is supine. Because it may cause perforation of the rectum because the angle is not suitable.

Rectal thermometers are commonly used in infants and young children. Most studies determining the risk of serious infection in infants and young children with fever have relied on rectal temperature measurement. Rectal temperature measurement is risky because it is uncomfortable, there is a risk of perforation of rectum in young infants and it is a source of infection. In addition, every child should have his or her own thermometer, because thermometers can transmit intestinal infections from one child to another. It is not preferred in older children due to physical conditions and psychological discomfort. Rectal temperature measurement should not be performed in children with gastroenteritis, rectal bleeding and anal fissure. Rectal thermometry is contraindicated in patients with neutropenia due to the risk of traumatizing and infecting the rectal mucosa. Table 3 summarizes the important points in rectal temperature measurement.

Axillary Measurement

Axillary measurement is a safe, uncomplicated, easy method that can be applied without much discomfort to the patient. However, at the onset of fever, when peripheral vasoconstriction is intense, skin temperature may decrease as the core temperature increases. In addition, sweating and evaporation cause the axillary temperature to be lower than the core body temperature. Normal body temperature is 34.7-37.3°C in axillary measurement. Although rectal measurement shows central body temperature, it is not recommended for routine use in neutropenic patients, newborns and infants. In previous studies, axillary body temperature of 37.2°C and above is accepted as fever. In a study involving a total of 1364 pediatric patients, axillary body temperature of 37.5°C and above in 0-2 months and axillary body temperature of 37.0°C and above in other age groups were determined as fever. However, the correlation between axillary temperature and core temperature is weak. The sensitivity of axillary measurement in detecting fever has been reported to be only 27.8-33%. Because of this low sensitivity, axillary measurement is a method that should not be relied upon to detect fever in children. Therefore, it is not a recommended method for routine fever screening except in neonatal units. In addition, axillary measurement can be performed in neutropenic patients who cannot use an oral thermometer. Table 5 summarizes the important points in axillary fever measurement.

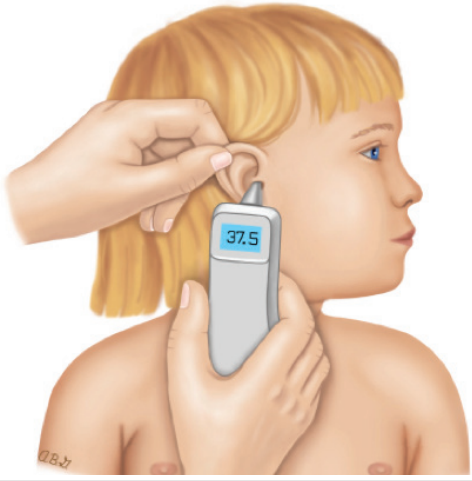
Table 5. Important points in axillary temperature measurement

- Axillary temperature measurement can be used in all children, including newborns.
- After drying the armpit, the tip of the thermometer is inserted.
- The child's elbow is held towards the chest, covering the armpit.
- Requires supervision; otherwise displacement may occur.
- Electronic thermometers are held until a beep is heard (usually takes 40-80 seconds) and the thermometer is read.

Tympanic Measurement

Body temperature can be divided into two parts: external heat and core heat. The core temperature, which indicates the temperature of the internal organs and the brain, is of primary interest. External heat is the temperature of the outer surfaces of the body and is often measured in the axillary region or forehead. The core temperature is the temperature of the center, i.e. the brain, liver or pulmonary artery. The temperature closest to core temperature can be measured in the esophagus. In practice, the closest temperature to core temperature is the temperature measured rectally. The hypothalamus, the center that determines body temperature,

Table 6. Important points in tympanic temperature measurement

	• Measurement is performed with a disposable probe. • The child's head is held in a fixed position for a short time. • The auricle of the child's ear is held at the top and moved backwards and upwards. • The sensor part of the thermometer is placed in the external auditory canal gently until it is closed. • With the thermometer in the ear canal, press the measurement button, wait 2 seconds and then remove the thermometer and read the temperature on the display. • One ear should be used for the measurement. The measurement is repeated twice and the highest reading is recorded. • Normal body temperature is between 35.7°C and 37.8°C when measured tympanically.

and the tympanic membrane are supplied from the same branch of the carotid artery. Therefore, the temperature of the tympanic membrane is assumed to reflect the core temperature (Table 6).

Normally, 60% of total heat loss occurs through radiation in the form of infrared heat rays, a form of electromagnetic energy. This heat loss increases during fever. Tympanic body temperature is obtained by measuring the infrared waves emitted from the eardrum using infrared thermometers. This method of measurement is rapid, has a lower likelihood of interindividual contamination than oral and rectal measurements, and patient compliance is very good. The most important problem encountered with tympanic thermometers is inaccurate measurements due to improper placement in the external auditory canal. Therefore, inaccurate measurement results may be obtained by inexperienced users. In addition, in young children, especially in the first year of life, the reliability of measurements is low due to anatomical differences. It may also be affected by the presence of a bulb or local infection in the external auditory canal. Another disadvantage is the relatively high cost of disposable ear covers, resulting in a high cost of use.

Studies on the reliability of the measurement have varied results. Some studies have concluded that measurement reliability is lower than that of mercury or electronic thermometers. According to a recent meta-analysis, the sensitivity and specificity of rectal thermometry in the diagnosis of fever in children was found to be 70% and 86%, respectively. Discordance is especially common in infants of a few months of age. Tympanic measurement should not be used in newborns and small infants.

According to 2018 measurements in nearly a thousand children, the tympanic thermometer can be a screening tool to detect rectal temperature of 38°C and above. Tympanic thermometry has detected febrile patients with a sensitivity of over 90%, especially in children aged six months to five years. When tympanic temperature of 37.8°C and above was accepted as fever, 95% of all children with fever would be detected, and 83% of children with fever would also be classified as febrile by rectal measurement. The mean difference between tympanic and rectal measurements was 0.05°C. For accurate estimation of the rectal measurement, the 95th percentile limits of the difference of the tympanic thermometer from the rectal were between -0.97 and +1.07°C.

In the measurements made in nearly a thousand adults, tympanic membrane measurements showed the best performance among temporal artery, oral and tympanic membrane measurements in predicting rectal fever of 38°C and above. When 37.5°C and above was chosen as the limit, it was calculated that the sensitivity and specificity of tympanic membrane measurements would be 90%.

According to the most recent review, the ideal limit value for measuring fever with new generation infrared tympanic thermometers in children is 37.8°C. In a study conducted in 1364 children in a single center in Türkiye, the mean tympanic body temperature was calculated as 36.91°C (standard deviation: 0.46°C, minimum: 35.15°C, maximum: 37.9°C). The 99th percentile value of 37.8°C was found on the tympanic thermometer and supported the acceptance of above this value as fever. Table 5 summarizes the important points in tympanic temperature measurement.

Oral Measurement

Oral temperature measurement is preferred in children old enough to comply. It is most suitable for young children (<5 years), patients who are unconscious, mentally retarded, post oral/nasal surgery, mouth breathing, oxygen therapy, patients with oral ulcers,convulsions and intubated patients due to the

Table 7. Important points in oral temperature measurement

	• Suitable for children aged five and over. • Hot baths, exercise and mouth breathing affect the results. Also, the child should not have had any hot or cold liquids or food recently. • Tachypnea causes cooling of the oral cavity and should not be used as it may reveal low results. • Place the tip of the thermometer on the floor of the mouth under the tongue. • Ask the child to place the thermometer on his/her lips, fingers or tongue. • Ask him/her to keep it on the floor and not to bite it. • Tell the child to keep his/her mouth closed and breathe through the nose. • Hold the thermometer for about 40 seconds (electronic thermometer), usually the thermometer emits a beep to signal the end of the reading. • Normal body temperature is between 35.5-37.5°C when measured orally.

need for sublingual placement. Oral temperature is typically 0.6°C lower than rectal temperature due to mouth breathing, which is especially important in tachypneic patients. In addition, oral temperature can be affected by recent intake of hot or cold fluids. Therefore, if you want to measure the temperature of a child who has consumed hot or cold food or drink, wait 30 minutes.

When taking oral temperature, the thermometer should be placed in the sublingual space. Because the sublingual arteries are branches of the external carotid artery and reflect the core heat well. Mercury glass thermometers should be kept in the mouth for 5-7 minutes with the mouth closed for accurate measurement. This may cause problems for patients. There are also risks of mouth injuries, mercury ingestion and infection transmission that may develop as a result of glass thermometers breaking during measurement. It is recommended to use electronic thermometers due to the risk of mercury toxicity. Table 7 summarizes the important points in oral temperature measurement.

Temporal Measurement

Infrared contact and non-contact forehead thermometers measure the amount of heat generated by the temporal arteries with an infrared thermometer that scans the surface from the forehead to behind the ear. The accuracy of such measurements can be affected by sweating or vascular changes. While this device is easy to use, its sensitivity of 66% remains as a problem. Batra et al. reported that temporal artery temperature was measured by rectal body temperature and was better than axillary or tympanic temperature at approximately core temperature.

Erdem et al. found that the difference between temporal artery temperature and axillary temperature was 0.7°C in the third minute and 0.5°C in the second minute. As with tympanic temperature measurement, the results of studies comparing temporal artery and rectal temperatures are contradictory and temporal artery temperatures should not be used in clinical decision-making. The measured temperature may be greater or less than the rectal temperature but can be used to screen for fever in children older than four years.

CORE BODY TEMPERATURE

Temperature can be measured from the outer surface of the skin and subcutaneous adipose tissue that isolates the body center from the external environment. External temperature is often assessed by measuring the axillary region or forehead. Core body temperature is defined as the temperature of the internal organs in the head and trunk. Under normal conditions, core body temperature is higher than the temperature of more superficial tissues such as the skin. The actual body temperature (temperature regulated in the hypothalamus) is practically the same as the aortic blood. The eardrum and esophageal temperatures are closest to the aortic blood temperature. Oral temperature is 0.25°C lower, axillary temperature is 0.9°C lower and rectal temperature is 0.5°C higher. Although it varies during the day; rectal temperature is 37.2-37.6°C, oral temperature is 36.6-37.0°C and axillary temperature is 36.4-36.7°C.

Core body temperature varies about 1°C during the day. The lowest temperature is observed in the early morning, while the highest temperature is measured in the late afternoon. In addition, the measurement of core body temperature varies depending on metabolic activity, blood flow, etc. of the organ being measured.

Since fever is regulated in the hypothalamus, the gold standard method of measuring core body temperature is to measure the temperature of this region. However, in the presence of a hypothermic insult or brain injury, the temperature of this region will deviate greatly from core body temperature. Moreover, implanting a temperature sensor in

the brain is only possible during surgical interventions of the brain.

Intracardiac and pulmonary arterial blood temperature has been suggested to be a good indicator of body core mean temperature. However, it can only be measured invasively using a specialized pulmonary artery catheter. Therefore, this method is only preferable when there is another indication for a pulmonary artery catheter. In a clinical study, it was shown that intra-bladder and intra-oral temperature measurements were closest to pulmonary artery temperature, followed by tympanic temperature and axillary temperature was the lowest. In studies conducted in the following years, this method was abandoned due to the dependence of intra-bladder temperature measurements on urination frequency.

Measurement of esophageal temperature is another invasive method that can be used to demonstrate core body temperature. This procedure, which may cause discomfort in conscious patients, can be performed with a probe inserted through the transoral or transnasal route in anesthetized and intubated patients.

Although theoretically, the tympanic membrane is thought to be an ideal site for measuring core body temperature because it is perfused by an artery that also supplies the body's thermoregulatory center, numerous studies have found that tympanic membrane measurements give highly variable results compared to oral or rectal readings obtained simultaneously. In newborns and infants younger than three months, the measurement may not be reliable due to the sloping external auditory canal. Hyperemia in the ear and the presence of a bulb may affect the tympanic temperature measurement.

In clinical practice, body core temperature is best measured with a rectal thermometer. Due to the low blood flow and high isolation of the area, the rectal temperature is higher than other areas and there is low heat loss. The rectal area has no thermal function and is remote from the central nervous system and pulmonary artery. Therefore, it lags significantly behind changes in other central regions, especially during rapid temperature changes such as warming and cooling during surgery, exercise and fever. Inflammation around the rectum and heat-producing activity of external microorganisms can alter the rectal measurement. Rectal temperature measurement is not hygienic. It may pose a risk of injury to the intestinal mucosa, especially in infants and during rectal surgery. It is not recommended in neonates, oncological patients, diarrhea, neutropenia and immunodeficiency. It increases psychological stress and may cause embarrassment, anxiety and physical discomfort. Therefore, its use is not recommended, especially in children.

Sublingual temperature measurement is another method that can be used to determine core body temperature. Sublingual temperature may vary depending on the area measured (anterior-posterior, right-left). In febrile individuals, this difference can reach to 1.6°C. Again, oral temperature measurement may be affected by salivation, previous ingestion of hot or cold food, or rapid breathing through the mouth.

Although temporal or axillary contact temperature measurement methods do not directly reflect core body temperature, they are frequently preferred especially in hospitals and clinics because they are fast, practical and non-invasive.

TREATMENT OF FEVER

Fever is an important clinical symptom and the first step in its management is to determine its cause. Once the cause is known, the main indication for the use of antipyretics is not to lower body temperature but to improve the child's comfort. Many parents are convinced that fever is harmful and that no matter the cause or effects of fever, it must be brought down.

For this reason, it is known that antipyretics are often used at low body temperatures that are not considered fever without consulting a health professional. Unfortunately, about half of parents are known to administer the wrong dose of antipyretics, and 15% give antipyretics in excess of therapeutic doses. Parental education is necessary to change this established practice. Such education should be provided at well-child visits and reinforced at presentations for acute febrile illness. Education should include the topics in Table 8.

Antipyretics

The ancient Egyptians and North American Indians were familiar with the therapeutic benefits of willow bark, which contains salicylates. Hippocrates recommended chewing willow leaves for labor analgesia. Later, with the synthesis of the aspirin molecule in 1853 and its clinical use in 1899, modern analgesic and antipyretic applications began. However, the World Health Organization removed aspirin from the list of essential medicines in 1988 following reports linking it to Reye's syndrome (encephalopathy associated with liver necrosis), especially when used in the management of children with chickenpox or influenza. Aspirin also has adverse effects such as inhibition of thrombocyte function, gastritis/gastrointestinal haemorrhage and asthma exacerbation. Aspirin is also more toxic than paracetamol and ibuprofen in cases of overdose. For these reasons, aspirin is no longer used as an antipyretic. After the restriction of aspirin use, the most commonly used antipyretics in children and adolescents are paracetamol (acetaminophen) and ibuprofen.

Table 8. Major topics in parent education

• Fever is a physiological response, not a disease.
• In healthy children, most fevers are self-limiting and benign (provided the cause is known and fluid loss is replaced); fever does not cause brain damage.
• There is no evidence that fever makes the disease worse.
• Antipyretics do not prevent febrile seizures.
• The first measure to reduce a child's fever should be to ensure extra fluid intake and reduce activity.
• If the child is uncomfortable (decreased activity, decreased fluid intake, etc.), lowering the fever may be considered.
• Whether the fever goes down after taking antipyretics cannot help determine whether the child has a bacterial or viral infection
• Children who are planned to be given antipyretics do not need to be woken up to be given antipyretics.
• Children taking antipyretics should not be given cough and cold suspensions, which usually contain antipyretics; administartion of both medicines may lead to accidental overdose.
• Doses of antipyretics are adjusted according to weight, not age. When recommending the use of antipyretics, it is important to remember that to minimize the risk of over- or under-dosing, the clinician should communicate the dose recommendation in writing and by means of a measurement device such as an appropriately marked syringe (for formulations). These recommendations should include which formulation (or concentration of a liquid formulation) to use, how to measure the appropriate volume (for liquid formulations), how often to give, how to monitor response, when to discontinue, and when to seek hospitalization.
• There is no scientific basis for combining two antipyretics and using both drugs will not have a greater antipyretic/analgesic effect than one drug alone.
• Warm application is unnecessary for children with fever in the presence of antipyretics, because it is simpler to use, more effective in lowering body temperature, and less disturbing to children.
• In therapeutic doses, antipyretics rarely cause side effects.
• Recommendations for safe storage of antipyretics.

Antipyretics reduce fever by normalizing *the* hypothalamic *set point*. They do this through inhibition of cyclooxygenase (COX), the enzyme responsible for the conversion of arachidonic acid to prostaglandins (PG) and leukotrienes. Although many PGs can induce fever, PGE_2 is the most important mediator. It leads to a series of physiological events such as normalization of the hypothalamic *set point*, decreased heat production, increased blood flow to the skin and increased heat loss through the skin by radiation, convection and evaporation. Prostaglandins also have important effects on bronchodilation, gastrointestinal tract and renal medulla. Therefore, expected side effects of these drugs include bronchospasm, gastrointestinal bleeding and renal failure.

Antipyretics do not reduce fever to a normal level, shorten the duration of febrile episodes or affect normal body temperature. They also do not directly affect pyrogen formation or heat loss mechanisms such as sweating. Their effectiveness in reducing fever depends on the level of fever (the higher the fever, the greater the reduction), the rate of absorption and the dose of the antipyretic.

Routine treatment of fever in healthy children is not recommended, but treatment of fever in critically ill patients is important. Therefore, decisions about the need for fever reduction in children should be made on a case-by-case basis, depending on the clinical circumstances (e.g. underlying disease, level of discomfort, desire to follow the fever curve) (Table 9). This is because high body temperature can have adverse physiologic consequences. Fever can increase oxygen demand, worsen existing respiratory distress and exacerbate pre-existing heart disease. There is no evidence that reducing fever reduces morbidity or mortality from febrile illness (except in children with underlying disease and a limited ability to tolerate increased metabolic demand). Current pediatric practice in children with fever is to use antipyretics when the body temperature is higher than 38.5°C or 39°C.

Table 9. Main indications for short-term treatment of fever

• Shock
• Underlying neurological/cardiopulmonary disease or other conditions that increase metabolic rate (burns, surgery)
• Fluid and electrolyte irregularities
• High fever (≥40°C)
• Restlessness
• Major head trauma

However, children with a high temperature may continue to play, whereas those with a lower temperature may be in poorer general condition, so the primary aim of treatment of children with fever should be to improve their overall comfort, rather than to reduce parental anxiety by focusing on temperature readings and lowering body temperature. While children's activity and alertness may improve with a decrease in temperature, the improvement in appetite is less pronounced.

Paracetamol is the first drug recommended by all guidelines when efficacy and risk of side effects are comprehensively considered and should be preferred over ibuprofen. Paracetamol is also both cheaper and has fewer side effects than ibuprofen (Table 10). High-quality evidence shows that both are effective in reducing temperature, but evidence of effectiveness in reducing discomfort is lower. Since the mechanism of action of these antipyretics is inhibition of PGE_2 synthesis, there is no rationale for their combined or alternating use. Moreover, there is no scientific support for this practice. However, it is believed to provide little additional benefit in fever control.

Despite a high level of evidence that antipyretics are associated with a high risk of supratherapeutic doses and have not been shown to reduce discomfort, the rate of combined or alternating use of antipyretics in medical practice is 50-69%. However, since a better response to one antipyretic agent than the other can be achieved, if the fever and the child's comfort do not improve 3-4 hours after the administration of paracetamol or ibuprofen, paracetamol can be switched to ibuprofen or ibuprofen to paracetamol and so on. It should be kept in mind that the response to the drug is not related to the severity of the disease and does not predict the course of the disease.

Paracetamol (Acetaminophen) Treatment

Paracetamol, an active metabolite of acetanilide and phenacetin, is used worldwide as a fever and pain reliever. It specifically inhibits PG synthesis in the brain. Because this inhibition is abolished by peroxide (produced at the site of inflammation), its anti-inflammatory effect is weak. After sufficient evidence of an association between salicylates and Reye's syndrome emerged, paracetamol replaced aspirin as the primary treatment for fever. Oral doses of 10-15 mg/kg paracetamol per dose given every 4-6 hours are generally considered safe and effective. The onset of antipyretic effect is between 30-60 minutes; it is known that body temperature decreases in approximately 80% of children during this time (Table 11).

Although alternative dosing regimens have been proposed, there is no consistent evidence indicating an initial loading dose given orally (30 mg/kg per dose) or rectally (40 mg/kg per dose) improves antipyretic efficacy. The higher rectal dose may be used in intraoperative settings, but cannot be recommended for routine clinical use.

In neonates, organ maturation and body composition may vary according to the patient's age, drug pharmacokinetics and pharmacodynamics may change significantly.

Table 10. Key features of an ideal antipyretic for children

• Provide fast results and reduce fever by at least 1°C
• Suspension and suppository forms should be available
• Have a low rate of side effects at therapeutic doses and a low risk of toxicity when overdosed
• Low incidence of interactions with other drugs and rarely contraindicated in pediatric doses
• Must be safe to use
• Must be cost-effective

Table 11. General properties of paracetamol and ibuprofen

Variable	Paracetamol	Ibuprofen
Temperature drop, °C	1-2	1-2
Time of onset of effect, hours	<1	<1
Peak time of action, hours	3-4	3-4
Duration of action, hours	4-6	6-8
Dose	10-15 mg/kg, every 4-6 hours	5-10 mg/kg, every 6-8 hours
Maximum daily dose	75-90 mg/kg	40 mg/kg
Maximum daily adult dose	4 g/day	2.4 g/day
Lower age limit for use	3 months	6 months

Decreased serum paracetamol concentrations have also been reported in obese patients, possibly due to increased oxidative metabolism limiting efficacy. Intravenous (IV) paracetamol has shown a more rapid decrease in body temperature compared with enteral paracetamol in pediatric patients. In a large-scale retrospective evaluation, it was shown that IV and enteral paracetamol had similar antipyretic effects in the pediatric intensive care population, although the effects of IV paracetamol started earlier. In a retrospective study comparing paracetamol (enteral, rectal and IV) and ibuprofen (enteral), it was found that, in general, fever decreased more rapidly in patients receiving ibuprofen within six hours after a single dose and that patients receiving IV paracetamol became afebrile more rapidly than patients receiving other drugs. Nevertheless, the authors recommended that IV paracetamol should not be preferred to enteral paracetamol when both drugs are available.

Hepatotoxicity has rarely been reported with paracetamol at routine recommended doses. Nevertheless, it should be recognized that glutathione is important for paracetamol detoxification. Malnutrition, interactions with other drugs and alcohol may reduce this detoxification effect, leading to an increased risk of toxic effects. Although paracetamol is safe to use, it has been observed that parents often give the wrong dose due to incorrect weight estimation, calculation errors and the like. A study of one hundred parents showed that 30% used the correct dose, 13% gave the correct dose despite miscalculations, 48% used less than the ideal dose and 9% overdosed.

Hepatotoxicity is most commonly seen in acute overdose situations. In addition, paracetamol-associated hepatitis is also of concern in cases of chronic overdose. The most commonly reported scenarios are those involving multiple supratherapeutic doses (i.e. >15 mg/kg per dose) or the use of single doses at intervals of less than four hours per day over several days, resulting in doses of more than 90 mg/kg per day. The use of adult paracetamol preparations by children may result in the use of supratherapeutic doses. In one case series, half of the children with hepatoxicity were found to be using adult preparations. The effect of paracetamol on asthma-related symptoms is another area of concern. Although asthma has been associated with paracetamol use, a cause and effect relationship has not been proven.

A common practice for controlling fever is the alternating or combined use of paracetamol and ibuprofen. In a survey of two hundred and fifty-six parents or caregivers, 67% reported alternating paracetamol and ibuprofen for fever control, 81% of whom said they followed the advice of their health care provider or pediatrician. Although four hours was the most commonly used interval, parents also reported alternating treatment every two, three, four and six hours. This revealed that there was no consensus on the dosing information of the medications. Paracetamol and ibuprofen are effective, well tolerated and safe when used as single agents. However, available data and case reports suggest that concomitant use may be associated with an increased risk of acute kidney injury and/or hepatotoxicity. Furthermore, paracetamol and ibuprofen have different administration dosages and intervals, increasing the potential for parental confusion and administration errors. Guidelines for the treatment of fever in general also do not recommend combined use.

Cough and cold medicines containing paracetamol should not be used in children as parents may give their child an antipyretic at the same time. In addition, there is no proven efficacy for this class of combination products for children.

Paracetamol is also one of the most common drugs for drug overdose (intoxication) in pediatric emergency departments. In 80% of these cases, the drugs were stored in places accessible to children. It should be emphasized that medicines should be kept out of the reach of children. Rumack Mathew namogram is used in intoxications. There are three stages of intoxication. The most important complication is fulminant hepatitis. The antidote is acetyl cysteine. If started within the first eight hours, it almost completely prevents hepatotoxicity. It can be given intravenously or orally.

Paracetamol is recognized as a safe and effective agent when used in appropriate doses. However, as with all medicines, it should be used with caution to minimize the risk of adverse drug effects and toxicity. Pediatricians and other health care providers should minimize fever phobia when counseling a family on fever management in a child and emphasize that the use of fever reducers does not prevent febrile seizures.

Ibuprofen Treatment

Antipyretic (antipyretic) drugs are among the most commonly prescribed medicines for children. Antipyretics also have analgesic properties and make the child feel better, which is a relief for parents. However, antipyretics are not indicated in every febrile child. If antipyretics are to be given, paracetamol is generally considered as the first choice antipyretic drug. In some cases, patient/parent preference may be an important factor in the choice of antipyretic. Some patients may prefer some antipyretics because of their taste or some types of antipyretics may work relatively better in some patients. These situations may guide the choice of antipyretic. Ibuprofen is a safe and effective drug with many years of clinical experience as an antipyretic. Randomized trials have shown that ibuprofen is slightly more effective than paracetamol in reducing fever and its effect lasts longer.

Ibuprofen, a propionic acid derivative, is an antipyretic and also analgesic non-steroidal anti-inflammatory drug (NSAID) that has been available over-the-counter since 1984. Like other NSAIDs, it exerts its antipyretic activity by inhibiting cyclooxygenase (PG synthetase) and disrupts the final conversion of arachidonic acid to PGs, prostacyclins and thromboxanes. In contrast to paracetamol, ibuprofen also inhibits cyclooxygenase enzymes (COX-1 and COX-2) in the peripheral tissues. Thus, NSAIDs such as ibuprofen may be more effective than paracetamol in reducing pain in inflammatory conditions (e.g. systemic juvenile idiopathic arthritis) due to their peripheral anti-inflammatory properties.

Pharmacodynamic and pharmacokinetic properties of ibuprofen in clinical practice

***Modes of administration and age*:** Ibuprofen can usually be administered orally or, more rarely, IV. In Türkiye, there are also oral (syrup or tablet) or IV forms of administration. In our country, based on the short product information (SmPC), as of 2021, the IV form is approved for ages 17 years and older and the tablet form is approved for ages 12 years and older. The syrup is the most commonly used form in children and is approved for children over six months (and >7 kg). However, apart from the antipyretic effect, short-term administration(three doses in 48 hours) as a support for patent ductus arteriosus (PDA) closure in newborns is recommended in neonatal guidelines. It may also be administered for anti-inflammatory purposes to improve pulmonary functions in cases of cystic fibrosis.

The lower age limit for ibuprofen antipyretic administration in the world (three or six months) may vary by country. In some other countries,

May be approved for infants ≥3 months of age weighing >5 kg. Compared to older infants and children in general, infants younger than six months of age may be at potentially increased risk of renal toxicity with ibuprofen administration because they have limited renal function.

***Oral bioavailability, metabolism and duration of action*:** The absorption rate (bioavailability) after oral administration is up to 85%. It is highly (90-99%) bound to proteins. Volume of distribution is 0.1-0.2 L/kg. It is metabolized in the liver, but inactive metabolites are excreted by the kidneys. Peak effect in serum is reached 1-2 hours after normal doses (oral, 4-10 mg/kg/dose). However, peak effect may be delayed up to four hours after toxic doses. In children, the half-life is about two hours, but in overdose the half-life may be prolonged. The antipyretic effect of ibuprofen begins to be observed within one hour after oral ingestion and reaches its peak effect within 3-4 hours, during which a mean decrease of 1-2°C in high fever is observed. Duration of action is 6-8 hours.

Ibuprofen doses: The recommended oral dose of ibuprofen in children aged six months to 12 years may vary according to the indication. For antipyretic, analgesic and anti-inflammatory purposes, there may be slight variations in the dose and duration of administration and dose intervals. The maximum daily dose is generally 40 mg/kg/day (maximum 2.4 g/day). For antipyretic effect, usually 5-10 mg/kg/dose is given every 6-8 hours. For pain relief, a targeted dose of 10 mg/kg/dose (maximum dose 600 mg) is given every 6-8 hours (Table 11). For anti-inflammatory activity, 30-40 mg/kg/day (maximum dose 50 mg/kg/day) is usually given, but in some children with mild disease, the anti-inflammatory dose may be as low as 20 mg/kg/day if the disease can be controlled. It is usually given for a short duration for the antipretic effect, whereas for the anti-inflammatory indication it is given for a longer duration/chronic administration.

There may be commercial forms of ibuprofen with different ingredients, either ibuprofen alone or in combination with other drugs. Some sources may also have a fixed dosing schedule for ibuprofen for different age groups, but in children, as a principle, it is preferable to adjust the dose per weight for each patient. When adjusting the dose of ibuprofen, the physician should calculate/adjust the dose in mg according to the weight of the patient and briefly explain to the family.

Oral ibuprofen is usually recommended as a first-line treatment in children >6 months of age where combined antipyretic and anti-inflammatory activity is desired (e.g. children with juvenile arthritis) and who are well hydrated.

***Use of ibuprofen in cystic fibrosis*:** Although there are limited data, ibuprofen may be used to slow the progression of lung disease in mild disease (FEV_1 ; if >60% of age-expected values) at 6-17 years of age, oral 20-30 mg/kg/dose, twice daily. The target serum level in this respect is 50-100 mcg/ml and the dose may be adjusted to achieve these levels. When given in cystic fibrosis, pancreatic enzymes should not be taken for two hours after the ibuprofen dose. Serum samples for measurement of ibuprofen blood levels are taken 30, 45 and 60 minutes after oral suspension dosing and one, two and three hours after oral tablets.

***Use of ibuprofen for PDA closure in premature infants*:** Cyclooxygenase inhibitors (indomethacin, ibuprofen) decrease PG synthesis by inhibiting COX-1 and 2. Thus, they stimulate constriction and closure of the ductus. For this reason, prophylactic treatment is recommended for infants at high risk for PDA within the first 12-24 hours of life, before symptoms of PDA develop. Standard dose therapy consists of an initial oral dose of 10 mg/kg/dose followed by two additional doses of 5 mg/kg/dose administered at 24 hour intervals (total of three doses). In high-dose treatment for the same indication, the initial dose is 20 mg/kg/dose, followed by 10 mg/kg/dose at 24 hour intervals, again three doses. Ibuprofen is administered through an N/G catheter

and then the catheter is washed with approximately 1 ml of distilled water. In infants with renal failure or in cases of renal failure or anuria/oliguria (<0.6 ml/kg/h urine output) after the first dose, active bleeding, thrombocytopenia (<50.000), necrothrombocytopenia, necrotizing enterocolitis, gastrointestinal malformations or risk of bleeding, ductus-dependent congenital heart disease (such as pulmonary atresia, tetralogy of Fallot, severe coarctation of the aorta), ibuprofen is contraindicated.

Use of ibuprofen in hepatic impairment: The manufacturer's labeling does not indicate any adjustment for dose modification, but caution should be exercised if liver function deteriorates and discontinuation of treatment should be avoided unless absolutely necessary.

Use of ibuprofen in renal failure: It can be used safely in a child/infant with normal renal function or a GFR >60 ml/min/1.73 m^2 and no dehydration. If the GFR is 30 <60 ml/min/1.73 m^2, ibuprofen should be avoided if there is concomitant disease that increases the risk of acute kidney injury. It is not recommended if GFR < 30 ml/min/1.73 m^2.

- ***How to use ibuprofen;*** ibuprofen is well tolerated, it is useful to administer it with food or milk to reduce discomfort in patients with gastro intestinal complaints. The suspension should be shaken well before use.

For intravenous administration; in pediatric patients, doses are infused over at least 10 minutes; in adults, doses are infused over at least 30 minutes. Extravasation should be avoided. Ibuprofen should not be administered through the same IV line as TPN. When ibuprofen and TPN must be given together, TPN is cut for 15 minutes before and after ibuprofen administration, and the serum set is washed with dextrose or saline and kept open.

- ***Storage;*** ibuprofen is generally stored at 15-30°C (IV form and tablets preferably at 20-25°C). The intravenous form does not contain preservatives. The intravenous form should be reconstituted prior to administration and it is recommended to infuse within 30 minutes after reconstitution. Intravenous ibuprofen can be infused in SF, 5%D and RL. However, ibuprofen reconstituted in 5%D, SF, and RL is stable for 24 hours at 20-25°C.

Clinical evaluation of fever response to ibuprofen: The response to oral ibuprofen against fever is expected to begin within one hour. The response peaks within 3-4 hours. If the fever does not go down and the child's discomfort does not improve 3-4 hours after ibuprofen (or paracetamol) administration, some experts may recommend switching from ibuprofen to paracetamol (or from paracetamol to ibuprofen). There are no published studies to assess the safety or efficacy of this practice, but theoratically, in some children, fever may respond better to one antipyretic agent than another.

The effect of combined or alternating ibuprofen and paracetamol in antipyretic treatment was evaluated in a meta-analysis of six randomized trials (915 patients). Accordingly, it was stated that combined or alternate administration slightly increased the antipyretic effect, but there was insufficient evidence to suggest this in routine practice. The American Academy of Pediatrics, in its recommendations on the use of antipyretics in children, suggests that combined administration with paracetamol and ibuprofen is not appropriate, drug toxicity may develop more easily in combined administration and combined administration may contribute to fever phobia in families. Similarly, the Italian Pediatric Association and the UK suggest that the simultaneous use of paracetamol and ibuprofen is not appropriate except in special cases.

Duration of administration of ibuprofen for antipyretic purposes: Antipyretics are recommended in clinical practice mainly for the initial treatment of febrile infectious diseases. In a patient with fever, the cause of the fever should be determined and treatment should be directed towards the diagnosis. In this context, unless there is a special condition, treatment of fever for more than 2-3 days is not recommended, while the etiology is determined and targeted treatment planning is made. If fever persists for more than three days in a patient with a suspected infection, the patient should be completely re-evaluated in terms of diagnosis, treatment and possible complications.

Undesirable side effects of ibuprofen: Undesirable side effects of ibuprofen are most commonly caused by gastrointestinal tract irritation. Gastrointestinal irritative side effects may occur in 10-30% of children. In fact, these side effects are not significantly different from the side effects following paracetamol administration. When Ibuprofen is used in lower doses and for short-term analgesia or antipyretic effect, the incidence of unwanted side effects is lower, with approximately 14 percent of patients experiencing side effects such as gastrointestinal symptoms, asthma exacerbation or renal side effects. When administered in appropriate doses and taken with food, these side effects are not expected and ibuprofen is generally considered safe. NSAIDs, including ibuprofen, may rarely trigger the development and/or more rapid progression of necrotizing fasciitis due to group A streptococcus in children with chickenpox. However, a review of five prospective studies did not show such a correlation. In patients with aspirin-induced asthma, other NSAIDs should also be avoided. Ibuprofen should be monitored more carefully in high-risk children for adverse effects.

Ibuprofen toxic doses: Ibuprofen overdose is generally easier to manage than paracetamol overdose. The toxicology of ibuprofen in mild to moderate overdose (<400 mg/kg/dose) is generally characterized by gastrointestinal irritation and clinical manifestations of renal and thrombocyte dysfunction.

In high doses (≥400 mg/kg/dose), neurotoxicity, hypotension, hypothermia and metabolic acidosis may also occur. Adverse effects develop more easily and may be more serious in high-risk children (children with volume depletion conditions including heart failure, gastrointestinal, liver and kidney diseases, SLE).

In most cases of acute overdose/toxicity, the child is asymptomatic, with no significant findings on physical examination. Symptoms usually occur within four hours of oral ibuprofen ingestion. Symptomatic manifestations may include nausea, vomiting, abdominal pain, headache, drowsiness, blurred vision, tinnitus, ataxia and dizziness. In children with high doses of ibuprofen (e.g. >200 mg/kg/dose) and symptomatic children, a single dose of activated charcoal may be useful if the child presents within the first hour. Symptomatic children who develop symptoms are given symptomatic treatment (such as gastroprotectors, antiemetics, antacids). The patient is monitored for cardiac, neurologic and renal symptoms/complications and kept under observation.

The patient is usually asymptomatic in toxic ingestions of <100 mg/kg/dose. These children can be safely discharged after 4-6 hours of observation without the need for laboratory testing.

In toxic ingestions, usually <200 mg/kg/dose, severe symptoms are not expected and laboratory tests are usually not required except for observation.

Life-threatening toxicity due to ibuprofen is rare, deaths have rarely been reported and usually occur at toxic intakes of >400 mg/kg/dose. Apnea, bradycardia, dysrhythmias and prolonged QT interval, hypothermia, anion gap, metabolic acidosis, renal failure, polyuria, ataxia, tinnitus, coma and/or convulsions are signs of severe toxicity. In this case, in addition to a detailed physical examination, it is also appropriate to order laboratory tests. These include blood glucose, serum electrolytes, blood urea nitrogen (BUN) and creatinine, lactate, blood gas, complete blood count and platelet count, urinalysis, ECG (for QRS or QTc or arrhythmia), ibuprophen (including serum levels of paracetamol and aspirin if combined medication is used and if necessary). It should also be borne in mind that ibuprophen serum levels may not always correlate well with the level of toxicity or clinical findings. Nomograms using serum drug concentrations do not provide insight into the severity of toxicity and are not useful in the management of overdoses. There is no antidote for ibuprofen toxicity.

KETOPROFEN AND OTHER NSAIDS

The most commonly preferred antipyretic agents in children are paracetamol and ibuprofen. Aspirin has been abandoned due to its association with Reye syndrome, especially in influenza and varicella infections. Ketoprofen, an NSAID of the 2-arylpropionic acid class like ibuprofen, has been in clinical use as an anti-inflammatory drug since 1973. Its use as an antipyretic is more recent. Ketoprofen exhibits analgesic, antipyretic and anti-inflammatory properties through non-specific COX-1 and COX-2 inhibition. In the literature, studies on the use of ketoprofen in children have often been conducted on its pain relief properties in the post-operative period.

These studies reveal that the bioavailability is high and the incidence of side effects is low in the use of the drug in children. Although the effects of the drug are thought to be mostly peripheral, recent studies show that ketoprofen also has central effects.

In a study comparing the antipyretic effects of ketoprofen and acetominophen, the percentage of fever reduction of ketoprofen and the rate of temperature reduction in patients with fever between 39.0°C and 39.9°C were significantly higher than acetominophen. In the same study, it was observed that the antipyretic effect of ketoprofen started earlier and lasted longer than acetominophen. The finding that this effect is more pronounced especially in high fever above 39°C may make ketoprofen an important choice in the treatment of patients with high fever.

When the antipyretic effect of ketoprofen was compared with acetominophen and ibuprofen in the study by Çelebi et al., it was observed that these three drugs were similar in terms of efficacy, side effects and patient compliance within 48 hours after treatment. These results suggest that ketoprofen can be used as an alternative antipyretic to acetominophen and ibuprofen. In the study, unpleasant taste of ketoprofen and vomiting in the early period after drug intake were slightly more prominent, but the difference was not statistically significant.

Pharmacologic studies have shown that ketoprofen can be administered orally, rectally, intramuscularly or IV and the duration of action can be as long as sex hours. After oral administration, the highest plasma level is reached after 0.5-1 hour and the absolute bioavailability is approximately 70-80%. There is also no difference in the bioavailability of a single intramuscular and oral dose of ketoprofen. Therefore, the oral form may be preferred in children who can take orally. Oral bioavailability has been reported to be similar to the rectal route. Ketoprofen binds to plasma proteins with high affinity (99%) and is excreted by the kidneys as unstable esters after primary glucuronidation. Studies have shown that the half-lives of the drug are similar regardless of the route of administration. In the light of these findings; ketoprofen can be given orally every 6-8 hours or by other routes.

Pharmacokinetic studies show that drug exposure after a single IV dose is similar in children and adults (after dose normalization) and therefore a similar mg/kg body weight dose can be used in children and adults. The recommended oral and IV dose of ketoprofen for fever reduction and pain control indications is 0.5-1 mg/kg/dose, rectal 12.5-25 mg/dose in infants aged ≥6 months-36 months, 3-13 years; 25-50 mg dose. There are no pharmacokinetic data in young infants and therefore extreme caution should be exercised when ketoprofen is used in neonates or infants under six months of age.

Available pediatric data suggest that in infants and children ≥6 months, the antipyretic effect of ketoprofen syrup administered at a dose of 0.5 mg/kg is similar to that observed with ibuprofen 5 mg/kg and acetominophen 15 mg. Ketoprofen has been reported to be safe and effective at higher doses (3-5 mg/kg/day) for pain control after adenoidectomy. Ketoprofen doses can be given every 4-8 hours, up to a maximum of 5 mg/kg over a 24-hour period.

Ketoprofen has a small molecular weight and is highly lipophilic in the unionized form. Therefore, it can cross the blood-brain and blood-cerebrospinal fluid barrier and exert central effects. However, this effect is observed to be especially pronounced at doses above 1 mg/kg. Since they are highly protein-bound, they may increase plasma levels of other protein-binding drugs (such as anticoagulants, antihipertensives, diuretics, cardiac glycosides, lithium, cyclosporin, corticosteroids or quinolone antibacterials).

Ketoprofen is generally well tolerated in pediatric patients. The most commonly reported adverse effects in studies were mild to moderate GI upset, particularly diarrhea and vomiting, and transient low body temperature measurements. However, NSAIDs may cause an increased risk of serious cardiovascular thrombotic events. This risk may occur early in treatment and may increase with duration of use.

Because of this feared side effect in adult patients, ketoprofen is contraindicated in the presence of coronary artery bypass graft surgery. Similarly, NSAIDs can cause serious GI side effects such as bleeding, ulceration and perforation of the stomach or intestine. These effects can occur at any time during use and without warning. The risk is increased in the elderly, patients with a history of peptic ulcer disease and/or GI bleeding.

Aspirin and other NSAIDs are contraindicated in the presence of signs of hypersensitivity (such as urticaria, bronchospasm and severe rhinitis). This group of drugs should be used with caution in children with renal dysfunction, hypovolemia or hypotension, coagulation disorders, thrombocytopenia or active bleeding for any reason and in children with impaired liver function. There are cases of photoallergic dermatitis with topical ketoprofen in the literature. Ketoprofen is not recommended for use in infants younger than six months and IV form of ketoprofen is not recommended for use under 12 years of age. Similarly, topical ketoprofen is not approved for use in children.

In the literature, data on the use of other NSAIDs as antipyretics in pediatrics are quite limited. The use of metamizole-dipyron, which was used as an antipyretic in the past, is not recommended especially in children because it has serious side effects such as agranulocytosis, shock, toxic epidermal necrolysis, cyanosis and respiratory distress.

Physical Cooling Methods

High fever, which is frequently seen in children in the course of infectious diseases, continues to be unsettling not only for families but also for healthcare professionals. Although the application of antipyretic treatments dates back to ancient Assyrian, Egyptian and Greek civilizations, the scientific recognition/identification of antipyretic molecules took place in the 1700s. On the other hand, the use of physical cooling methods as antipyretic treatment has been going on since the early periods of history. Despite advances in the understanding of the pathophysiology of fever and the pharmacology of antipyretic drugs, physical cooling measures sa well as environmental cooling are still practiced worldwide.

Today, the main aim of fever treatment is to eliminate the discomfort caused by fever in the child. Physical cooling methods include lowering the ambient temperature, reducing clothing, massage with warm/cold cloth, warm/cold shower, massage/bath with vinegar/alcoholic water.

Warm (30°C)/cold water baths or massage methods themselves also cause discomfort in the child. When physical cooling methods are applied, the peripheral temperature decreases by conduction, convection and evaporation, but they have no effect on the core temperature, which is our main target.

This mismatch between the hypothalamic set point and the skin temperature leads to a peripehral vasoconstriction and metabolic heat production, which leads to shivering and increased discomfort, which we do not want in a febrile child. On the other hand, there is sudden cardiometabolic response to maintain body temperature, which increases energy and oxygen requirements as well as heat production. Warm/cold application may lower body temperature more rapidly than acetominofen or paracetamol treatment, but this effect is limited to the early period of the first 15-30 minutes after treatment. For longer periods, physical cooling has been shown to be ineffective. In a study planned to compare treatment efficacy, children who received only antipyretic medication were compared with children who received

cold application in addition to antipyretic medication. It was found that the body temperatures of children who received both methods decreased faster, but at the end of the two-hour follow-up period, body temperatures were similar in all children, and in the same study, it was concluded that cold application caused restlessness in children.

Before 1950, it was common practice to use isopropyl alcohol or ethyl alcohol as part of physical cooling methods. However, since alcohol applied to the skin can be inhaled and the amount inhaled can easily reach toxic levels, especially in young children, this practice is now known to be harmful and should not be practiced. Alcohol poisoning can have significant adverse consequences such as low blood sugar, coma and even death.

In summary, the effectiveness of physical cooling methods in the treatment of fever has not been demonstrated in scientific studies. In particular, methods such as showering with warm/cold water or applying a warm/cold towel/sponge have no effect on eliminating the feeling of discomfort in the child, which is the primary goal of fever treatment, and sometimes they may cause more discomfort than the fever itself. Keeping in mind that their antipyretic efficacy is limited, the comfort of the febrile child can be increased by lowering the temperature depending on the course of the fever, removing excess clothing on the child, allowing the child to play with warm water or warm shower.

Again, even if there is not enough evidence, when the pathogenesis of fever is considered, the discomfort of the child can be reduced by reducing the energy required for fever formation by keeping the child warm while the fever is rising. In this process, when the child warms up to the feet and starts sweating, the clothes can be carefully removed one by one. The only indication for physical cooling methods is limited to cases of hyperthermia, a condition in which anti-pyretics are thought to be inadequate (because the hypothalamic set point has not changed).

FEVER MANAGEMENT IN SPECIAL CASES

The use of antipyretics has an important place in daily pediatric practice, so these antipyretics should be both effective and safe. Safety is an important consideration in the choice of antipyretics and both paracetamol and ibuprofen have been associated with safety issues for which there is no evidence. Even if there is no evidence of harm from antipyretics, it is not a good idea to give them to every febrile child as they can increase confusion and fever phobia, together with interactions with other medicines. If the decision is made to give an antipyretic, even though it is not usually necessary, paracetamol and ibuprofen are considered to have similar safety and tolerability profiles in childhood.

In this section, recommendations for reducing fever in some specific situations will be discussed;

- ***Reduction of fever in malnourished children;***

Malnutrition causes glutathione depletion, which affects the body's drug detoxification mechanisms. Prolonged fasting may reduce glucuronic acid formation by altering the glucuronidation and sulfation mechanisms involved in paracetamol metabolism, thereby inducing decreased drug elimination and increased N-acetyl-p-benzoquinonimine (NAPQI), a potentially hepatotoxic metabolite. It is therefore possible that the risk of paracetamol-induced liver injury in malnourished children at normal doses is increased, particularly during the stabilization phase due to reduced metabolic function in the liver. Physical cooling may be considered as an alternative to paracetamol in these children. However, in children with high fever (≥38.5-39°C) or malnourished children, especially those who are restless, malnourished or disturbed by fever, antipyretics may be given at standard doses. Caution should be exercised when using these drugs because of a small risk of renal toxicity (ibuprofen) or hepatotoxicity (paracetamol), especially in children with Kwashiorkor, but in general this low risk can be ignored if there is a greater benefit from reducing fever when given at the appropriate dose.

- **Reducing fever in children with asthma;**

Aspirin-induced asthma is a well-recognized clinical condition affecting 5% of asthmatic children aged 10 years and older, peaking in the third decade of life. Symptoms of asthma and rhinitis ocur approximately 30 minutes to 3 hours after taking aspirin or other NSAIDs. Asthma attacks are severe and can even be life-threatening, so aspirin is not recommended for fever reduction in both pediatric and adult asthmatic populations. Although only a direct link to aspirin exposure can be made because of the name, another issue of concern is cross-sensitization to all other classes of NSAIDs. The mechanism of sensitization is thought to be related to COX-1 inhibition, which promotes lipo-oxigenase activity, indirectly leading to an increase in the production of leukotrienes and subsequent bronchoconstriction. However, despite this potential association between ibuprofen and asthma, evidence suggests a low risk for asthma associated with ibuprofen use in children.

Ibuprofen is therefore not expected to exacerbate asthma in children without a history of aspirin sensitization. A safety concern in fever reduction is the effect of paracetamol on asthma-related symptoms. Although asthma has also been associated with paracetamol use but causality has not been established, paracetamol and ibuprofen should be avoided in febrile children with documented paracetamol or NSAID-induced asthma.

- **Reducing fever in newborns;**

Paracetamol is the most commonly prescribed drug for pain or fever in neonates. Some studies in preterm and term neonates have also evaluated the use of paracetamol and its prodrug proparacetamol, but in these patients it was used for analgesic rather than antipyretic purposes. Paracetamol clearance is markedly reduced, especially in preterm infants (0.7 L/s × 70 kg^{-1}, 5 L/s × 70 kg^{-1} in term neonates) and is approximately 40% of the paracetamol clearance in adults. Compared to older children and adults, the newborn has a lower risk of drug-induced hepato-toxicity, probably due to reduced activity of oxidative enzymes (CYP2E1) and increased glutathione turnover. On the other hand, due to decreased drug clearance and short time to gastric emptying, the dose should be reduced depending on gestational age. Another important potential group at risk of ibuprofen-associated renal toxicity are infants younger than six months due to developmental differences in ibuprofen pharmacokinetics and renal function. Although ibuprofen can be used for other indications in neonates, available data are insufficient to support a specific recommendation for the use of ibuprofen for fever or pain in infants younger than six months. Paracetamol is the only agent recommended for use as an antipyretic in the newborn and is recommended for use in all febrile newborns due to the high risk of complications.

- **Reducing fever in children with liver disease;**

After sufficient evidence of an association between salicylates and Reye's syndrome emerged, paracetamol replaced aspirin for the reduction of fever. Although hepatotoxicity is rare with paracetamol at recommended doses, hepatoxicity is seen after acute overdose. Even if paracetamol levels are not in the toxic range, paracetamol toxicity should be kept in mind in any child who has taken paracetamol with signs of acute hepatic dysfunction. It is important to remember that children with a family history of hepatotoxicity to paracetamol are at increased risk of developing toxic reactions. Furthermore, in children with underlying liver disease, a potential increase in the hepatotoxicity of paracetamol has been demonstrated, possibly due to hepatic glutathione depletion leading to accumulation of the hepatotoxic intermediate metabolite NAPQI. However, it remains unclear whether liver injury from underlying causes, such as viral infections or metabolic diseases, is exacerbated by paracetamol.

Ibuprofen is considered less hepatotoxic than other NSAIDs. However, possible effects on platelet function and the risk of gastrointestinal bleeding should be considered, especially in febrile patients with chronic hepatitis.

- **Reduction of fever in dehydrated children;**

Although prostaglandins are unlikely to have much effect on children with normal circulating volume, in children with fluid loss, PG synthesis becomes an increasingly important mechanism to ensure adequate renal blood flow. Inhibition of prostaglandin synthesis leads to uncontrolled vasoconstriction of the afferent arteriole and reduced GFR leading to renal ischemia and acute tubular necrosis. NSAIDs have been associated with the development of acute kidney injury, which is thought to be associated with COX inhibition leading to changes in hemodynamics and acute interstitial nephritis. Therefore, caution should be exercised when using ibuprofen in children with dehydration or complex medical illnesses. In several case reports, children with febrile illnesses have been reported to develop renal impairment when treated with ibuprofen or other NSAIDs. However, it is not possible to determine the true incidence of ibuprofen-associated renal impairment after short-term use. However, reversible renal failure in children with dehydration treated with ibuprofen or other NSAIDs has been reported in rare case reports. In conclusion, in clinical practice, renal problems caused by ibuprofen in short-term use (<7 days) in febrile children are an unexpected event; however, caution should be exercised when administering any agent that may interfere with renal function in a dehydrated or multi-organ dysfunctional child.

- **Reduction of fever in children with hypotension;**

During fever, heat loss is tried to be reduced by peripheral vasoconstriction. Antipyretics may cause a decrease in both systemic vascular resistance and blood pressure because they prevent the vasoconstriction that maintains heat when *the set point* is normalized. However, given that heart rate also increases with temperature, the hemodynamic effect of antipyretics may be complex. Some reduction in blood pressure has been associated with paracetamol use in critically ill adults. Parenteral paracetamol use is considered to provide more effective analgesia compared with oral use and is considered desirable when rapid onset of analgesic effect is desired. Although the mechanism of paracetamol-induced hypotension has not yet been fully elucidated, it may be independent of the route of administration. Because NAPQI, the intermediate metabolite of paracetamol, may increase the activity of neuronal voltage-gated Kv7 potassium channels (Kv7.2 and Kv7.3) in the dorsal root ganglion and spinal dorsal horn neurons, decreasing arterial tone and causing a decrease in blood pressure. However, a randomized controlled study showed a trend towards an increased incidence of hypotension following parenteral paracetamol administration compared with enteral paracetamol in intensive care unit patients. It has been reported that this relationship may be due to a decrease in cardiac output due to the diuretic effect of mannitol present in IV paracetamol preparations. In conclusion, in critically ill patients who are hemodynamically unstable, fever reduction may be considered after normalization of blood pressure. Parenteral paracetamol should not be preferred in children who can take orally unless necessary.

FEBRILE CONVULSIONS AND FEVER MANAGEMENT

Febrile convulsions (FC) are defined as seizures that occur during fever in children between the ages of six months and five years, provided that there is no central nervous system infection or other causative agent. Febrile seizures are the most common cause of convulsions in the childhood and are the most common cause of convulsions in children under five years of age.

It is known to occur in 2-4% of patients. Although the majority of patients with febrile seizures are in this age group, it may rarely occur in younger and older ages.

Simple FCs, defined as generalized seizures lasting less than fifteen minutes and not recurring within 24 hours, represent the majority of febrile convulsions. Although there is a risk of recurrence in about one-third of children in early childhood, it is usually a benign phenomenon and is associated with a risk of future epilepsy that is only slightly higher than in the general population.

The generally accepted criteria in the definition of febrile convulsion are as follows:

- Convulsion with a temperature higher than 38°C
- A child older than six months and younger than five years
- No central nervous system (CNS) infection or inflammation
- Absence of acute systemic metabolic abnormality that may cause convulsions
- No previous history of afebrile convulsions.

Risk Factors

Febrile convulsions are an age-related phenomenon associated with the vulnerability of the developing nervous system to the effects of fever, possibly with an underlying genetic predisposition. In addition to age, the most commonly identified risk factors include high fever, viral infection, recent vaccination and a family history of febrile seizures.

***Age*:** Most febrile convulsions occur between six months and three years of age, with the highest incidence at 15-18 months. Approximately 6-15% occur after the age of four, and it is not common after the age of six.

Children in this age group are more prone to frequent infections. The reason for the age-specificity is the sensitivity of the maturing brain to increases in body temperature.

High fever: Although this is controversial, the rate of rise in fever, rather than the maximum temperature, may be the main risk determinant for the development of FC. This has been demonstrated in animals and confirmed in clinical studies. Most febrile convulsions occur early in a febrile illness and are often the first manifestation. In children with FC at relatively low body temperature (<38.9°C), the initial seizure is more likely to be focal or recurrent during the same febrile illness.

The key to modulating the effect of fever is the seizure threshold, which varies according to the individual, age and maturation. In infants, the seizure threshold is lower. In addition, some medications and fluid and electrolyte imbalances, especially hyponatremia, may also alter the threshold.

Infants and young children are frequently exposed to infections. These infections are mainly upper respiratory tract infections accompanied by high fever, which, combined with a relatively low seizure threshold, lead to the common occurrence of FCs. Occasionally, an immunoglobulin deficiency has been reported in some children with FC, which may cause fever or FC. Other investigators have reported a possible immunologic imbalance in the cytokines and IFN axis in FC. This may play a role in the pathogenesis of FC.

Viral infections are usually associated with FCs, whereas bacterial infections are rare. Febrile convulsions are not thought to be a virus-specific condition; instead, it is believed that temperature rise is more rapid in viral infections. In particular, viral infections with high fever, such as human herpes virus type 6 (HHV-6) and influenza, are found to pose the highest risk. In the United States of America, HHV-6 has been shown to be the causative agent in 1/3 of children up to two years of age who had their first episode of FC. In a study conducted in Europe, HHV-6 was isolated in 35%, adenovirus in 14%, respiratory syncytial virus in 11%, herpes simplex virus in 9%, cytomegalovirus in 3%, and HHV-7 in 2% of children with FC.

HHV-6 is associated with very high fever, which is the reason why it causes frequent FC. In infants with primary HHV-6 infection, mean fever is 39.5°C or higher, and the incidence of FC associated with this infection in the 12-15 month group was found to be 36%. However, the actual prevalences may be estimated to be much higher, as the incidence of PCs associated with this infection in children with lower fevers was not included in these studies. Influenza A and adenovirus are also frequently detected pathogens in FCs. The recurrence of FC due to infections is not well explained. In HHV-6, convulsion recurrence is explained by viral activation and a mild, transient encephalitis.

***Vaccination*:** Seizures that occur after vaccination, especially in the first 48 hours after diphtheria, pertussis, and tetanus (DBT) vaccination and 7-14 days after measles vaccination, tend to be febrile and occur in response to temperature elevation. The decision to revaccinate children who experience FC within a few days of vaccination should be made on an individual basis based on a risk-benefit assessment. Generally, the benefits of vaccination outweigh the risks.

Although a definite mode of inheritance has not been established, genetic predisposition has been accepted in cases of FC for many years. Among first-degree relatives (mother, father and siblings) of children with febrile convulsions, 10-20% have a history of FC. The higher the number of relatives, there are the higher the risk. In cohorts of children with febrile convulsions, the risk of FC in siblings was calculated as 10-45%. When one sibling has a history of FC, the risk of another sibling having FC is 1/5, whereas this risk is 1/3 in those whose both parents and the previous sibling have had FC. Studies finding a higher concordance rate in identical twins compared to fraternal twins also prove a genetic relationship.

Susceptibility to febrile convulsions has been identified in different family models at chromosome 8q13-21 (FEB1), chromosome 19p (FEB2), chromosome 2q23-24 (FEB3) and other loci. This trait is inherited as an autosomal dominant form with reduced penetrance or as polygenic or multifactorial models.

In some patients and families, a propensity for FC is also an early manifestation of generalized epilepsy with FC + generalized epilepsy (GEFS+), a genetic type of epilepsy in which several causal mutations have been identified. Severe myoclonic epilepsy of infancy (Dravet syndrome) is another genetic epilepsy type well known for episodes of FC in early childhood. Hippocampal abnormalities are described in some patients and families with febrile seizures and may be linked to genetic factors and future risk of temporal lobe epilepsy. Developmental abnormalities of the hippocampus, including hippocampal malrotation, have also been reported in 10.5% of children presenting with febrile status epilepticus (FSE).

***Others*:** Many studies have found an increased risk in those with underlying brain disease. There is also controversial evidence that premature birth, prolonged stay in the neonatal intensive care unit (>30 days) and growth retardation indicate suboptimal brain function, which in turn is associated with FC.

The factors listed above are trigger factors rather than risk factors. Children with two of these factors have a 28% risk of having at least one episode of FC. Approximately 30% of children who have had one episode of FC will have a recurrence, and 10% will have more than three episodes.

Clinical Features

Febrile convulsions occur in children between six months and five years of age, with the majority between 12-18 months. FC has been reported in children over five years of age, but unlike in young children, FC in older children should be considered a diagnosis of exclusion. In most children, FCs occur on the first day of illness and in some cases are the first sign that the child is ill. The degree of fever associated with febrile convulsions is variable and depends on the child's threshold convulsive temperature. While the measured temperature is most commonly 39°C or above, about 25% of seizures occur when the body temperature is between 38 and 39°C. Seizures usually occur when the temperature rises rapidly.

Although most febrile seizures are generalized, they may be tonic (contraction), clonic (tremor-pulses), atonic (collapse mushiness) and rarely myoclonic (jumping). Seizures usually last less than five minutes. A postictal period resembling a period of deep sleep may be observed after the seizure. Febrile seizures are typically of two types, simple and complex (Table 12).

Simple FC includes generalized tonic-clonic activity that lasts less than 15 minutes, does not recur within the following 24 hours, resolves spontaneously, and has no focal features. It is the seizure type seen in 80-85% of cases. Rarely, atonic and tonic seizures are also seen. Facial and respiratory muscles are frequently involved. By definition, the duration of simple FC can be as long as 15 minutes, but most simple FCs are much shorter, with a median duration of three to four minutes.

Children typically rapidly return to normal after simple FC. Confusion or agitation and lethargy-like signs are absent in the postictal phase, as seen in afebrile convulsions. Prolonged sleepiness is not typical of simple FC and an alternative etiology (e.g. meningitis, structural brain patology) or ongoing convulsive activity should be considered. Similarly, the presence of constantly open and rolled eyes is an important clinical feature of ongoing seizure activity.

Complex FC is defined on the basis of one or more of the following characteristics:

-Focal onset or focal features during the seizure

-Long duration (more than 10-15 minutes)

Table 12. Characteristics of simple and complex febrile convulsions

Simple Type Febrile Convulsion	Complex Type Febrile Convulsion
Seizures are generalized.	Seizures are focal.
It takes less than 15 minutes.	It takes more than 15 minutes.
It does not recur within 24 hours.	Repeats within 24 hours.
It does not cause neurologic findings after seizure.	There may be post-seizure symptoms such as Todd's paralysis (temporary paralysis of one half of the body lasting 1-4 hours).

Recurrence within twenty-four hours or during the same febrile illness.

The term complicated is also used instead of complex. These seizures constitute 15-20% of all FCs and, in contrast to the basic FCs, they may have postictal focal neurologic findings. Less than 10% of children with febrile convulsions have prolonged convulsions and less than 5% have focal findings. Initial simple FC may be followed by complex FCs, but most children who develop complex FC have this condition from the first seizure. However, the presence of an initial complex FC does not necessarily mean that all subsequent convulsions will be complex.

Transient hemiparesis (Todd's paresis), which usually follows a complex or focal type of FC, is rare and is seen in

It develops in 0.4% to 2% of children. Children with complex FCs are usually younger and more likely to have abnormal development.

Febrile status epilepticus: Some patients present with febrile status epilepticus (FSE) as continuous or intermittent seizures without neurologic improvement. Historically, FSE was defined as seizures lasting 30 minutes or longer; this definition was updated in 2015 to include continuous seizures lasting five minutes or longer.

It is thought that in approximately one-third of cases of febrile status epilepticus, the actual duration of the seizure is underestimated in the emergency department. The most important clinical clues that a convulsive seizure has ended are the presence of closed eyes and deep breathing. Children with persistently open and deviated eyes may be having an ongoing focal seizure even if convulsive motor activity has stopped.

The clinical circumstances in which febrile status epilepticus develops do not differ from those of shorter FIs. The degree of fever may be slightly higher and most patients have an identified viral or bacterial infection. There is also a higher than expected family history of epilepsy in these children.

By definition, FSE does not include episodes of status epilepticus that may develop in children with meningitis-associated fever, but the distinction may not be made based solely on clinical features at the time of initial presentation. Therefore, lumbar puncture (LP) should be considered in these patients.

Differential Diagnosis

The differential diagnosis of febrile convulsions includes non-epileptic events or movements, convulsions caused by CNS infection (e.g. meningitis or encephalitis) and rare genetic forms of epilepsy in which convulsions are common, especially with fever.

Involuntary movements such as trembling and jumping may sometimes occur in sick children and may be mistaken for convulsions. Concussive tremors are usually easily distinguished from convulsions. Tremors are common and characterized by fine rhythmic oscillatory movements around a joint. Rarely, they may also involve the facial or respiratory muscles during FC. In addition, tremors usually affect both sides of the body at the same time and are not accompanied by loss of consciousness, unlike children with generalized seizures. Therefore, bilateral symptoms without significant loss of consciousness strongly suggest that the movements are not epileptic.

Central nervous system infection: Convulsions from meningitis or encephalitis are the main concern in a child presenting with fever and convulsions. A thorough evaluation by an experienced clinician will almost always identify a child with meningitis. In 40% of particularly young infants who have convulsions as the first sign of meningitis, there are other symptoms and signs (e.g. altered consciousness, petechial rash) that strongly suggest a correct diagnosis, despite the absence of meningeal signs.

Detection of bacterial meningitis on the basis of routine evaluation of cerebrospinal fluid (CSF) after every simple FC is extremely rare. The only indication for lumbar puncture is meningitis, which is found in less than 1% of patients with FC, and in less than half of these cases bacterial meningitis is present. Meningitis itself has become increasingly rare due to widespread and routine *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) immunization. However, children with status epilepticus and fever may be more likely to have bacterial meningitis than those with simple FC.

Genetic epilepsies with febrile convulsions: The most common phenotype of generalized epilepsy with FC + generalized epilepsy (GEFS+), a genetic type of epilepsy, is the association with persistent FCs or tonic-clonic seizures without fever over the age of six years, in contrast to typical FCs. The phenotypic spectrum is initially much broader and may include only focal seizures. The diagnosis may be delayed because the first seizures are like FC. This epilepsies typically resolves in mid-adolescence, but can persist into adulthood.

Severe myoclonic epilepsy of infancy (Dravet syndrome) is a rare genetic epilepsy that can resemble complex FCs in the first year. Mutations in SCN1A, which encodes the alpha subunit of the sodium channel, are present in 70-80% of patients. Patients with Dravet syndrome typically present with prolonged, often febrile, generalized clonic or hemiclonic convulsions in the first year of life, when they have normal cognitive and motor development. The most common triggers of seizures in children with Dravet syndrome are fever/illness and vaccination. However, at the time of the first seizure, at least one-third of patients are fever-free.

Most patients have refractory seizures and a progressively worsening neurodevelopmental prognosis. They are therefore easily differentiated from patients with FCs over time.

Diagnostic Evaluation

Febrile convulsion is a clinical diagnosis based on the features described in the introduction of this article. Diagnostic tests are unnecessary in most well-evaluated children with a typical history of simple FC. Assessment should focus on evaluation and diagnosis of the underlying febrile illness and education of the parent or caregiver about the risk of recurrent FC and the low risk of future epilepsy. Children presenting with prolonged or focal FCs require a more individualized approach, especially in the first seizure, as the likelihood of an alternative etiology such as meningitis or an underlying structural or metabolic cause is higher (although still quite low).

Electroencephalography (EEG) and magnetic resonance imaging (MRI) may help to further assess the risk of future epilepsy in children with complex FCs, but are not usually necessary in the acute setting. The approach to outpatient evaluation of complex FCs is not standardized and a tailored plan should be developed for each patient by the treating clinician, usually in consultation with a paediatric neurologist for interpretation of abnormal test results.

Children under twelve months of age require special consideration as they have a higher incidence of meningitis. The threshold for performing LP should be lower in these patients, especially if *H. influenzae* type b (Hib) and/or *S. pneumoniae* vaccination is incomplete or vaccination status cannot be confirmed.

History: In a child presenting with febrile convulsions, the main elements in taking a history of convulsions are the characteristics of the seizure, the duration of the seizure, and the questioning of focal signs (e.g., shaking limited to one limb or one side of the body). If possible, a witness to the seizure should be interviewed, bearing in mind that convulsions are frightening for many parents and that eliciting details of the seizure, including its exact duration, may be difficult or unreliable.

The time of onset of fever and possible sources and degree of infection should also be learned. The recent use of antibiotics should also be questioned for the possibility of an incompletely treated meningitis. Information should also be obtained about whether the patient has had seizures in the past, his/her neurological development, whether he/she has developmental delay, and other factors that may cause seizures (such as trauma, poisoning). With a careful history, any underlying medical or neurologic condition that increases the risk of serious infection or underlying structural abnormality should be investigated. The history should include an assessment of immunization status, personal or family history of seizures and a history of neurological problems or developmental delay. A child with a known neurologic condition is more likely to have a febrile convulsion that would not be classified as a simple FC.

Physical examination: In addition to routine examination, rapid evaluation of the patient's neurological status, looking for signs of meningeal irritation, and checking for trauma or toxicity are the primary issues. Vital signs should include state of attention, state of consciousness or presence or absence of signs such as meningismus, tense or bulging fontanelles, muscle tone and strength, focal differences during normal movements. The presence of any of the pathologic findings should prompt consideration of an alternative etiology, such as meningitis or an underlying structural abnormality. Similarly, children with FCs typically look well. Postictal drowsiness usually resolves within 5 to 10 minutes, depending on the duration and type of seizure. Anything beyond this time should raise suspicion for encephalopathy, possible CNS infection or severe systemic infection. Children presenting with complex FCs, including febrile status epilepticus, may require close monitoring to detect ongoing or recurrent focal seizures. In well-appearing children with no obvious source of infection, noting abnormal signs and symptoms such as tachypnea or hypoxemia, oropharyngeal lesions or viral exanthema may help to identify a specific etiology, which is most often viral.

Lumbar puncture: The decision to perform an LP and CSF examination to exclude the diagnosis of meningitis or encephalitis in children with febrile convulsions is often based on clinical findings. Approximately 25% of children with meningitis have convulsions at or before initial presentation, but almost all have other signs and symptoms of meningitis (e.g. altered consciousness, nuchal rigidity, petechial rash). LP is unnecessary in most children who return to baseline consciousness after febrile convulsions and appear well. The American Academy of Pediatrics (AAP) recommends LP in cases of FC in the presence of the following conditions

- LP should be performed when there are meningeal signs or symptoms or other clinical features suggestive of possible meningitis or intracranial infection.
- LP should be considered in infants between 6 and 12 months of age whose immunization status for Hib and/or *S. pneumoniae* is inadequate or undetermined.
- Since antibiotic treatment may mask the signs and symptoms of meningitis, LP should be considered before starting antibiotics.

LP should also be considered when FC develops after the second day of illness or when the clinician remains concerned about possible CNS infection based on history or physical

examination. The presence of febrile status epilepticus is another possible indication for LP. LP yield has been found to be very low in children presenting with simple FC. LP yield is slightly higher in complex FCs.

The finding of pleocytosis in CSF in a patient with febrile convulsions should be considered as a sign of bacterial meningitis until proven otherwise and further evaluation with empirical antimicrobial therapy may be necessary until culture or PCR results are available. Although pleocytosis in the cerebrospinal fluid may be associated with epileptic seizures in some cases, this is rare in FC and should be considered as a diagnosis of exclusion.

Other laboratory tests: A complete blood count and measurement of serum electrolytes, blood glucose, calcium and BUN are of very low yield in patients with simple FCs; these parameters are valuable only if the patient has a history of vomiting, diarrhea and abnormal fluid intake or if there are signs of physical dehydration or edema. If the decision is made to perform a lumbar puncture, blood culture and serum glucose determination should be performed simultaneously. In children presenting with complex FCs, hyponatremia is more common and has been associated with the risk of recurrent seizures during the index disease. Therefore, aggressive hydration with hypotonic fluids should generally be avoided in children with FCs.

Brain imagings: Brain imaging with computed tomography (CT) or MRI is not necessary for children with simple FCs. The incidence of intracranial pathology in children presenting with complex FCs is also very low. Urgent neuroimaging (contrast-enhanced CT or MRI) should be performed in children with macrocephaly, especially those with focal findings, abnormal neurologic examination findings, or signs and symptoms of increased intracranial pressure.

Although not required in the emergency setting, high-resolution MRI in children with focal or prolonged FCs, especially if there is a history of abnormal development, is usually obtained in the outpatient setting, as these children are at high risk of developing feverless convulsions.

Electroencephalography: EEG after febrile convulsion is not a routine examination. It does not give an idea about recurrence of febrile seizure and prognosis. However, it may be performed to exclude other conditions in the differential diagnosis of FC. If indicated, it is usually ordered after 20 days. Since abnormal EEG findings cannot be used to identify children who may later develop epilepsy, they should not be used to decide which children should be started on anticonvulsant drugs.

Routine EEG is not necessary in a neurologically healthy child, especially with simple FCs. In children with complex FCs, the need for EEG depends on several factors and clinical judgment. A brief, generalized seizure repeated twice within 24 hours is complex by definition, but does not require an EEG unless the neurological examination is abnormal. A prolonged convulsion or convulsion with focal signs requires an EEG and neurological follow-up, as the risk of future epilepsy (recurrent FIs) is higher. The optimal timing of electroencephalography is not well defined, but a study using recordings performed within 72 hours of FSE suggests that this may be a useful time interval for prognostic purposes. In rare cases, it is at the physician's discretion to order an early EEG. However, since some transient disturbances may be seen in early EEG, patients with such findings should have a repeat EEG after a short period of time.

Genetic testing: Genetic testing is not recommended in most children with febrile convulsions, even if family history is positive. However, genetic testing may be useful if the child has these convulsions before 12 to 18 months of age with multiple prolonged focal FCs, as this may suggest an alternative diagnosis such as Dravet syndrome.

Approach and Treatment in Acute Period

The majority of febrile convulsions have spontaneously resolved by the time the child is first evaluated and the child rapidly returns to normal baseline. In such cases, active treatment with benzodiazepines is not necessary. Fever should be treated symptomatically with antipyretics.

If the child arrives during an acute attack, maintaining airway patency, turning the child to the side to prevent aspiration, monitoring vital signs and other supportive care are the pillars of management. If seizures persist for more than five minutes, IV administration of diazepam (0.1-0.2 mg/kg) or lorazepam (0.05-0.1 mg/kg) should be considered. Many seizures end with this treatment. If convulsions persist, an additional dose may be given. Meanwhile, the respiratory and circulatory status of the child should be carefully monitored and if the respiratory status becomes inadequate, advanced airway intervention (e.g. bag-mask ventilation, laryngeal mask airway, artificial airway) should be performed.

When intravenous access is not possible or unavailable, oral midazolam is also an effective alternative (typical dose

0.2 mg/kg, maximum dose is 10 mg). Since diazepam is rapidly absorbed, the rectum can be used as an alternative to the IV route.

Rectal diazepam vials are available in 5 mg for children aged 4-24 months and 10 mg for older children. If a rectal preparation is not readily available, the undiluted IV preparation can be drawn into a small syringe and administered through a polyethylene tube pushed 4-5 cm into the anus. This method has been found effective in transitioning acute seizures at home and in hospital settings.

Patients with prolonged or recurrent seizures despite initial benzodiazepine administration (i.e., FSE) should be treated immediately with additional anticonvulsant drugs, as in other status epilepticus patients. The most commonly used drug in this situation is phosphenytoin (20 mg phenytoin equivalent/kg, IV). Routine convulsion medications such as benzo-diazepines and valproic acid may also be given. Efforts should be made to reduce fever with antipyretics and warm application. Febrile status epilepticus rarely stops spontaneously and often requires more than one drug for control. FSE is more common in young children and seizures are focal in two-thirds of cases.

Indications for hospitalization: Most children with simple FCs do not require hospitalization and can be safely discharged home once they have returned to normal and their parents and caregivers have been educated about the risk of recurrent FCs. Children with focal or prolonged convulsions may require a longer observation period, especially if there is a delay in recovery with initial or postictal focal signs. The normal duration of the postictal phase is not well defined, but studies suggest that return to baseline consciousness typically occurs within five minutes. Failure to return to normal within five minutes or the presence of focal postictal weakness (Todd paralysis) will delay recovery. Todd's paralysis can last up to 24 hours.

Furthermore, children with focal or prolonged convulsions have a higher risk of multiple seizures during the index disease period. In one study, the cumulative probability of early recurrence was found to be 9% within six hours, 13% within 12 hours and 16% within 24 hours. 90% of recurrences ocur within the first 24 hours. Risk factors for early recurrence are focal seizure and prolonged seizure (>15 minutes).

Additional factors to consider when making the decision to hospitalize include lack of confidence that outpatient monitoring (for focal or prolonged convulsions) can be arranged, the comfort level of parents or caregivers, and the severity of the underlying febrile illness (e.g. hydration status, ability to take oral fluids).

Recurrent Febrile Convulsions

Children with febrile convulsions are at risk of developing recurrent FC with other illnesses in early childhood. The overall recurrence rate is approximately 30%-35%. However, these values vary with age. In children younger than one year of age at the time of the first FC, the risk is 50%-65%, while in older children it drops to 20%.

After the first FC, the risk of recurrence within the first year after a seizure is more than half. Risk factors that increase the likelihood of seizure recurrence include:

1. First seizure before 12 months of age,
2. History of FC in a first-degree relative,
3. Short interval between the fever before the seizure and the seizure,
4. Seizures with low-grade fever.

Children with all four risk factors are much more likely to have recurrent FC than those with none (≥70% versus ≤20%). Having complex FC was not associated with the risk of recurrence. Other factors identified in different studies include abnormal development before the first FC, recurrence of seizures fort he same illness and the number of subsequent febrile illnesses. Another risk factor is a history of an unprovoked seizure after an FC, which puts such children at significant risk of having a FC. However, FSE in a healthy child does not appear to significantly increase the risk of future febrile seizures or epilepsy.

Benzodiazepine treatment at home: In children with a long history of FI, including febrile status epilepticus, diazepam rectal gel (0.5 mg/kg) can be administered at home by parents or caregivers if the episode lasts longer than five minutes. Parents and caregivers can be taught to administer the drug safely at home and a single rectal dose does not cause respiratory depression. Children with multiple risk factors for recurrent FIs and long-term FIs should be considered for rectal treatment at home if necessary.

The role of preventive treatment: Prophylactic anti-convulsive drugs may reduce the risk of recurrent FC, but given the benign nature of most seizures, the risks of side effects generally outweigh the benefits. Therefore, indications should be well defined.

Intermittent diazepam prophylaxis, which can be administered both orally and rectally, is effective in protecting against FC. Although seizures may occur before fever is recognized, administration of diazepam suppositories or oral solutions with the onset of fever may prevent recurrence of convulsions. This practice has been reported to reduce the convulsion rate from 27% to 12%. To prevent recurrence, oral administration of diazepam at a dose of 0.3 mg/kg at eight-hour intervals during the febrile illness (2-3 days) is recommended. Side-effects are usually minimal, but symptoms of lethargy, ataxia and restlessness can be reduced by adjusting the dose. Carbamazepine and phenytoin are not effective in FC and there are no published data on the efficacy of lamotrigine, topiramate and other newer antiepileptic drugs on FC.

Although usually a very frightening picture for parents, FCs are benign events. According to meta-analyses, treatment with phenobarbital, valproate or intermittent oral or rectal

diazepam is associated with a reduced risk of recurrent seizures in the short term (six months to two years), but 30% to 40% of these children also develop side effects. The use of chronic anti-seizure medication or prevention of recurrent febrile seizures is not associated with a reduced risk of epilepsy.

Recent guidelines conclude that neither continuous nor intermittent anticonvulsive therapy is recommended for children with one or more episodes of simple FC. Furthermore, the guidelines recognize that recurrent episodes of FI may cause anxiety in some parents, caregivers and affected children and therefore appropriate educational and emotional support should be provided.

Children with complex FC should be evaluated differently. In such cases, treatment decisions should be individualized according to the underlying risk factors and should be addressed with further investigations (EEG, MRI, etc.) when necessary.

The role of antipyretics: The effect of antipyretics in preventing recurrence of febrile seizures has not been proven. However, they may be used to reduce the child's fever and relieve symptoms. There are several possible physiologic reasons why antipyretics do not prevent febrile seizures. Antipyretics facilitate heat loss, but they cannot delay the rise in temperature during the initial phase of fever that triggers convulsions or lower the convulsive threshold. Heat production cannot be inhibited by antipyretics, but heat distribution is enhanced by increased peripheral blood flow and sweating. Both paracetamol and barbiturates cause a drop in body temperature by suppression of the central thermoregulatory mechanism. Phenobarbital inhibits heat production during the pyrogenic phase of fever, whereas paracetamol facilitates heat loss during the peak or decline of fever. The mechanism by which phenobarbital reduces recurrence of FC may be related to both its antipyretic and anticonvulsant effects.

Prognosis

The prognosis for children with febrile convulsions is good. Neurological sequelae, including new neurological deficits, intellectual impairment and behavioral impairment, are extremely rare in cases of FC. Epilepsy is more common in children with FC than in the general population. In a normal child with simple FC, the risk ranges from approximately 1-2%, only slightly higher than the general population. For children with complex FCs, a history of abnormal development or a family history of epilepsy, the risk is closer to 5% to 10%. Simple FCs have also been shown not to cause temporal lobe epilepsy.

In the presence of febrile status epilepticus, it is known that the risk of future feverless seizures increases as well as recurrent FCs. However, the degree of this increased risk is not well defined.

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