CONTINUING MEDICAL EDUCATION

The Febrile Child: Diagnosis and Treatment

Tim Niehues

SUMMARY

Background: Fever accounts for 70% of all consultations with pediatricians and family physicians. Fever without an identifiable cause (<7 days' duration) and fever of unknown origin (FUO, ≥ 7 days' duration) are particularly challenging clinical situations.

Methods: This article is based on a selective literature search for publications containing the term "pediatric fever management," with special attention to meta-analyses and systematic reviews.

Results: The mainstay of diagnosis is physical examination by a physician who is experienced in the care of children and adolescents. The frequency of severe bacterial infection (SBI) is about 10% in neonates, 5% in babies aged up to 3 months, and 0.5% to 1% in older infants and toddlers. The mortality of SBI in neonates is about 10%. Both the degree of the parents' and the physician's concern are important warning signs for SBI. Clinical signs of SBI include cyanosis, tachypnea, poor peripheral perfusion, petechiae, and a rectal temperature above 40°C. Antipyretic drugs should only be used in special, selected situations. More than 40% of cases of FUO are due to infection; in more than 30% of cases, the cause is never determined.

Conclusion: Aspects of central importance include the repeated physical examination of the patient, and parent counseling and education of medical and nursing staff pertaining to the warning signs for SBI. Research is needed in the areas of diagnostic testing and the development of new vaccines.

► **Cite this as:**

Niehues T: The febrile child: diagnosis and treatment. *Dtsch Arztebl Int* 2013; 110(45): 764–74.
DOI: 10.3238/arztebl.2013.0764

Most consultations with pediatricians and family physicians are about fever. In one study, it was found that 70% of all appointments with a family physician concerned uncharacteristic fever (1). Fever in a child is a source of deep concern not only for parents, but often also for the treating physician (2, e1, e2).

Fever is defined as a rectal temperature above 38°C. Fever arises when the hypothalamic set point for body temperature is regulated upward, in a manner similar to the workings of a thermostat (*Figure 1*). The pyrogenic substances that bring this upward regulation about can be either exogenous or endogenous. Recent research has shed much light on the composition and molecular recognition of pyrogens. The macrophages and cells of the reticulo-endothelial system can be activated by bacterial components or molecular patterns of bacterial components on the surface of bacteria, so called pathogen-associated molecular patterns (PAMP), e.g., lipopolysaccharide, as well as by destroyed cells and their cellular components or crystals derived from them (damage-associated molecular patterns [DAMP]). This activation leads to the secretion of interleukin-1β (IL-1β), which is a key cytokine of the inflammatory cascade. Acting like a hormone, IL-1β stimulates the production of prostaglandin E2 (PGE2) by hypothalamic endothelial cells. PGE2, in turn, induces upward regulation of the hypothalamic set point from the normal value of (say) 37°C to 40°C, for example. The body produces additional heat, and actively raises its own core temperature, by a number of mechanisms simultaneously including activation of the sympathetic nervous system (cutaneous vasoconstriction and inhibition of sweating to prevent loss of heat), activation of metabolism (e.g., in brown fat tissue), and shivering (3, 4). Just to raise the body temperature by 2° to 3°C and maintain

Centre for Pediatric and Adolescent Medicine, HELIOS Klinikum Krefeld:
Prof. Dr. med. Niehues

Definition

Fever is defined as a rectal temperature above 38°C. Fever arises when the hypothalamic set point for body temperature is regulated upward, in a manner similar to the workings of a thermostat.

FIGURE 1

The physician can intervene at multiple points. Treatment can be targeted to the cause of the fever, e.g., an infection can be combated with anti-infective drugs or an inflammation can be treated with anti-inflammatory drugs so that no pyrogens (such as gout crystals) can be formed. In autoinflammatory diseases, a genetic abnormality leads to the production of too much interleukin-1 β ; here, cytokine antagonists against interleukin-1 and interleukin-6 can be used. These drugs are not appropriate for treating fever and their use is limited to rare diseases (e.g. fever syndromes). The greatest experience to date is with prostaglandin synthesis inhibitors such as paracetamol and ibuprofen, which inhibit cyclooxygenase peripherally and centrally to block prostaglandin (PGE2) synthesis and thereby interfere with the upward regulation of the thalamic set point for body temperature.

DAMP, damage-associated molecular pattern; IFN α , interferon- α ; IL1 β , interleukin-1 β ; IL6, interleukin-6; PAMP, pathogen-associated molecular pattern; PGE2, Prostaglandin E2; PRR, pattern recognition receptor; RES, reticulo-endothelial system; TNF α , tumor necrosis factor α .

it at the new level, the body must increase its energy consumption by 20% (5).

Fever is both highly conserved throughout evolution and closely regulated by the central nervous system (CNS). These two facts suggest that fever might confer an advantage on the individual in terms of survival. Conceivably, elevated temperatures might inhibit bacterial and viral replication and strengthen the immune response to pathogens. There is as yet insufficient evidence to support these hypotheses (6).

In normal human physiology, the body temperature is lowest early in the morning and highest early in the evening, with a mean amplitude of variation of 0.5°C (7). Moreover, normal body temperature changes with age (infants are about 0.5°C warmer than older children and adults), with the level of physical activity, and with the menstrual cycle in girls (3).

Learning objectives

This article should enable the reader to

- name the most important steps in the diagnostic evaluation of fever and describe how they vary depending on the age of the child,
- know when fever in a child is associated with a high risk of a serious bacterial infection and how to give antibiotics critically and rationally, and
- state the arguments for and against the use of antipyretic drugs and know when they are indicated.

Methods

A selective literature search was carried out in PubMed with the search term “pediatric fever management,” under the limitations “review,” “controlled trial,” “human,” “<18 years of age,” “publication <5 years,” “systematic review,” and “Cochrane analysis.” The date of the search was 29 August 2013. Particular consideration was given to meta-analyses and systematic

A bodily response conserved across evolution

Fever is not a disease, but rather a bodily response to external or internal stimuli that has been conserved over the course of evolution. It is regulated by the central nervous system.

Normal temperature variation

In normal human physiology, the body temperature is lowest early in the morning and highest early in the evening, with a mean amplitude of variation of 0.5°C.

FIGURE 2

Flowchart of the clinical algorithm for fever in a child

red = step 1: search for focus and critical evaluation
yellow = step 2: counseling / decision on further steps to be taken
green = step 3: assessment / re-evaluation; laboratory / ancillary tests if needed
CRP, C-reactive protein; CSF, cerebrospinal fluid

reviews that were carried out according to the principles of evidence-based medicine. Textbooks of pediatrics and textbooks specifically about fever were also consulted (8–10). The references and citations found in these articles and books were used to find further relevant publications. Case reports were not considered. A search of the AWMF website (AWMF = *Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften*, the Association of

Scientific Medical Societies in Germany) on the term “Fieber” (fever) was carried out on 29 August 2013: this search turned up only a single publication, which was the guideline on fever of unknown origin issued by the German Society for Pediatric and Adolescent Rheumatology (*Gesellschaft für Kinder- und Jugendrheumatologie*, GKJR) (11). Moreover, the Up-To-Date database was also searched on the same day.

Temperature measurement

Rectal measurement of temperature is considered the gold standard. Its superiority over other methods has been documented in systematic reviews (5, e3–e5). Ear thermometry is quicker, easier, cheaper (because it takes up less of the nursing staff’s time), and more pleasant for children, but its sensitivity is inadequate (12). For special classes of patients (e.g., on an oncology service), ear thermometry can be used when care is taken to clean the ear canal thoroughly. Despite the fact that the NICE guideline in England (13) and the guidelines of the Italian Pediatric Society (14, e6) recommend axillary measurement with a digital thermometer in neonates, the most reliable method—i.e., rectal measurement—is to be preferred for neonates, infants, and toddlers.

Three-step procedure

There is no German guideline for the clinical management of the febrile child. One possible algorithm, based on the present author’s recommendations, is shown in *Figure 2*.

Step 1:

Search for the cause (history and physical examination)

- Physical examination remains the physician’s main tool for determining the cause of fever.
- The duration and pattern of fever must be documented.
- How long has the child been febrile, and what is the maximum temperature?
- Does the temperature vary with the time of day?
- What are the accompanying symptoms (diarrhea, rash, cough, pain)?
- Has the fever persisted for more than a week with no known cause? If so, this is by definition a fever of unknown origin (FUO).

The history, in view of the age of the patient and any prior significant illnesses, is determinative of the further procedure.

A special challenge

Determining whether a child is seriously ill on the basis of a detailed history, precise observation, clinical examination, and further testing is a challenge for all physicians taking care of children.

Temperature measurement

Rectal measurement of temperature is considered the gold standard. Ear thermometry is quicker, easier, cheaper (because it takes up less of the nursing staff’s time), and more pleasant for children, but its sensitivity is inadequate.

Neonates and children with any of the following problems are three times as likely as others to have a severe bacterial infection (SBI) (15, e7):

- acquired immune defects, e.g., immunosuppressive treatment for inflammatory bowel or joint disease
- primary immunodeficiencies, e.g., hypogammaglobulinemia
- asplenia, e.g., post-traumatic
- hematological diseases and impaired function of the spleen, e.g., sickle-cell anemia
- central venous catheters for parenteral nutrition or chemotherapy
- congenital heart disease, e.g., valvular anomalies
- cancer, e.g., leukemia.

The physical examination of the child is performed in order to answer two main questions (*Figure 3*):

- Is there anything abnormal about the child's physical condition?

The child's respirations, pulse, and blood pressure should be checked. His or her behavior, level of consciousness, and reaction to stimuli should be observed, as well as the skin coloration and turgor.

- Can a source of the fever be found?

The throat and ears should be inspected, and the lungs and heart ausculted. If the child is in pain, the site where the pain is felt should be localized.

The need for repeated physical examination at short intervals by the same physician (or by several physicians) may be a compelling reason to hospitalize a child who appears ill and has a persistent fever of as yet undetermined cause.

Step 2:

Critical assessment of the child and decision about the next steps to be taken (hospitalization vs. outpatient care)

The body temperature is measured once again, as precisely as possible, in order to exclude (for example) excessively warm clothing as the cause of elevated temperature. If the subsequent physical examination yields no positive findings, this situation (fever without source) is one that would pose a challenge to any pediatrician (16). The physician's overall impression is still the most important factor in the decision whether or not to hospitalize the child.

A child with fever who does not seem to be

particularly severely affected, as in the vast majority of cases, can be treated on an outpatient basis and does not need to have any blood drawn for testing, as long as the clinical history and physical examination have excluded significant infection of the upper or lower respiratory tract, appendicitis, and meningitis. *Caution:* the clinical signs of meningitis are not reliably present in infants under 15 months of age.

Urinalysis should be carried out, and the child must be evaluated again in one or two days. Thorough explanation of the situation to the child's parents is very important so that they can be sensitized to the warning signs, and so that unnecessary visits to the doctor and unnecessary medication (antibiotics) can be avoided. If the child does, in fact, seem to be unusually severely affected and has positive physical findings (capillary refill time ≥ 3 sec, cyanosis, somnolence, dyspnea, edema, dehydration, oliguria, meningeal irritation, impaired mobility [e.g., the child does not walk any more], seizure, vomiting), or if other risk factors are present (*Box*), then hospitalization is necessary.

Step 3:

Re-evaluation and specific laboratory tests and accessory studies, where appropriate

Children whose fever still persists under observation in ambulatory care are re-evaluated so that their clinical course can be assessed and so that any new physical findings can be observed and documented. Children who have been admitted to the hospital undergo diagnostic testing, including repeated urinalysis, differential blood count, C-reactive protein (CRP), and, where indicated, a chest x-ray to rule out infiltrates, effusions, or enlarged hilar lymph nodes. The goal of diagnostic evaluation is to identify the pathogen; both anaerobic and aerobic cultures of blood and urine should be performed. Depending on the child's clinical appearance, a lumbar puncture can also be performed to obtain cerebrospinal fluid for examination. Pulse oximetry is indicated for as long as the child continues to appear severely ill.

In neonates, including preterm infants, the clinical signs of sepsis are highly nonspecific and may also be absent. For this reason, measurement of the interleukin-6 (IL6) concentration has now become routine in pediatric intensive care units, so that important diagnostic clues can be obtained in these febrile newborn infants within the first 24 hours of

Three-step procedure

1. Search for cause (history and physical exam)
2. Critical evaluation of the child and decision on further steps to be taken
3. Re-evaluation and specific laboratory testing and accessory studies

The goal of diagnostic evaluation

The goal of diagnostic evaluation is to identify the pathogen; both anaerobic and aerobic cultures of blood and urine should be performed. Depending on the child's clinical appearance, a lumbar puncture can also be performed.

A selection of clinically relevant findings in the physical examination of a child with fever

CINCA, chronic infantile neuro-cutaneo-articular syndrome;
CMV, cytomegalovirus;
EBV, Epstein-Barr virus;
HSV, herpes simplex viruses;
JIA, juvenile idiopathic arthritis;
PFAPA syndrome, periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis;
RF, rheumatic fever;
SLE, systemic lupus erythematosus

FIGURE 3

illness (17). Physicians should act promptly to initiate antibiotic treatment as soon as a suspect finding is noted. Measurement of procalcitonin (PCT) in the blood is very expensive (more than 20 euros per test, compared to less than 2 euros for CRP); the putatively higher sensitivity of PCT measurement for bacterial infection, compared to CRP, is currently a matter of debate (18, e8–e10). At present, the best way to determine the responsible pathogen is still by blood culture. If the child has already been treated with antibiotics, blood cultures are usually negative; moreover, blood cultures take time and are not part of the routine work-up of viral infection. These considerations increase the attractiveness of multiplex polymerase chain reaction (PCR) testing—a new and still very expensive diagnostic method, at 300 euros per test—for the more rapid detection of pathogens across a wider spectrum (19, e11). The individual or combined testing of IL-6, IL-8, procalcitonin, and/or multiplex PCR currently seems unnecessary and unjustified anywhere but in the intensive-care setting.

Fever without a source: a special challenge

The diagnosis and treatment of fever without a source are age-dependent (*Table 1*).

Neonates—Neonatal sepsis can cause death or permanent damage to the central nervous system (CNS), including permanent mental retardation. Sepsis in neonates and premature infants carries a mortality of up to 16% (20, 21). The rate of positive blood cultures indicating bacterial infection in the first three days of life is 1 per thousand neonates born at term, compared to 19 per thousand live births with a birth weight below 1500 g (9). The clinical history is all-important:

- Did the mother have fever, positive swab tests, or premature rupture of the membranes?
- Was the infant born prematurely?

Fever is rare in neonates; indeed, hypothermia is more common. 10% of febrile neonates have a severe bacterial infection (SBI) (*Table 1*) (e12, e13). The treating physician may have difficulty recognizing sepsis in a neonate, because the otherwise typical signs, such as poor drinking, flaccid muscle tone, and altered (e.g., gray-pale) skin coloration may be absent. If there is even a remote suspicion of infection in a neonate, the child should be hospitalized and a battery of tests for sepsis should be carried out, including a complete blood count with differential, CRP, IL-6,

BOX

Risk factors for severe bacterial infection (SBI)

● According to textbook (8)

- the child appears ill
- physical examination abnormal
- history of previous illnesses
- laboratory findings:
 - <5 or >15 000 leukocytes per μL ^{*1}
 - 10% band granulocytes
 - abnormal urinalysis (dipstick and/or culture)

● Relevant perinatal factors

- mother: pathological CTG (cardiotocography), premature rupture of membranes >18 hrs. (neonates); >12 hrs. (preterm infants), maternal fever >38°C sub partu, uterine tenderness, foul-smelling amniotic fluid, fetal tachycardia
- neonate: neonatal asphyxia, immature neutrophilic granulocytes >20%, CRP >2 mg/dL ^{*2}, elevated IL-6/IL-8 values

● According to meta-analysis^{*3} (15, 34, 35)

- strong red flags^{*4}
 - degree of parental concern
 - physician's clinical instinct
- red flags^{*4}
 - cyanosis
 - tachypnea
 - poor peripheral perfusion
 - petechiae
 - temperature above 40°C
- to exclude severe bacterial infection:
 - CRP <0.8 mg/dL
 - procalcitonin <2 ng/L

^{*1} Beware: erythroblasts

^{*2} Physiologically elevated in neonates 24–36 hours after birth

^{*3} Meta-analysis of approximately 4000 studies, selection of appropriately designed studies in the outpatient setting with subjects aged 1 month to 18 years

^{*4} None of these parameters is sufficiently informative by itself to reliably confirm or exclude a severe bacterial infection

Atypical presentations

Fever of unknown origin is more likely to be due to an atypical presentation of a common disease than to a typical presentation of an exotic disease.

Fever in a neonate

Fever is rare in neonates; indeed, hypothermia is more common. 10% of febrile neonates have a severe bacterial infection. Beware of sepsis!

TABLE 1

Infections without identifiable cause in neonates, infants, and toddlers (adapted from [8, 9, 28])

Age group	Frequency of fever ^{*1}	Pathogens in order of frequency ^{*1,2}	Frequency of SBI ^{*1}	Treatment/procedure
Neonates ≤ 3 days	rare	GBS, <i>E. coli</i> , <i>Staphylococcus aureus</i> , klebsiellae, enterococci, streptococci (A + C), <i>Listeria monocytogenes</i> , fungi, herpes simplex virus (from maternal rectovaginal flora)	ca. 10%	always hospitalize! empirical treatment with IV antibiotics, e.g., ampicillin + cefotaxime +/- aminoglycoside (such as tobra-/gentamycin)
>3 days		coagulase-negative staphylococci, <i>Pseudomonas</i> , <i>Enterobacter</i> , <i>Citrobacter</i> , <i>serratiae</i> , klebsiellae, <i>Salmonella</i> , <i>Haemophilus influenzae</i>		If initial treatment fails, or in case of nosocomially acquired infection: ceftazidime + vancomycin meropenem + vancomycin ceftazidime + netilmicin
Infants up to 3 months	common	RSV, influenza A, (winter), <i>Enterobacter</i> (summer), GBS, <i>Listeria monocytogenes</i> , <i>Salmonella enteritidis</i> , <i>E. coli</i> , <i>Neisseria meningitidis</i> , pneumococci, <i>Haemophilus influenzae</i> b, <i>Staphylococcus aureus</i>	ca. 5%	hospitalization if there are risk factors for SBI (Box): IV antibiotics, e.g., cefotaxime (empirical treatment)
Infants and toddlers from 3 months to 6 years	very common	viruses, pneumococci, <i>Haemophilus influenzae</i> b, <i>Neisseria meningitidis</i> , <i>Salmonella</i>	<0.5% – 1%	

* Frequencies are not given with greater precision because there is great variability in reported frequencies of fever (depending on definition and method of measurement), pathogens (depending on patient group and setting—practice, emergency room, or hospital), and SBI (depending on prior treatment in peripartal period, vaccination status)

^{*2}The frequency may differ in other countries

SBI, severe bacterial infection; RSV, respiratory syncytial virus; GBS, group B streptococci

acid-base status determination, and urinalysis. Blood, urine, cerebrospinal fluid, and (where indicated) stool should be sent for culture, and empirical intravenous treatment with antibiotics should be initiated.

Children aged 1 to 3 months—The likelihood of an SBI is lower in this age group (about 5%) (e14), for which the main causes of fever are viral illnesses: respiratory syncytial virus (RSV) and influenza viruses in winter, enteroviruses in the summer and fall. Urinary tract infections are common (prevalence 2% to 20%, depending on sex and circumcision status) (22). Infants who appear ill must be hospitalized for the immediate initiation of intravenous treatment with antibiotics, e.g., ceftriaxone or cefotaxime (23) (Table 1).

Children aged 3 to 36 months—Viral infections are by far the most common, while the rate of SBI is relatively low: it is estimated to be <0.5% to 1% (9, e15). The spectrum of pathogens is similar to that of children aged 1 to 3 months, except that perinatally

acquired infections no longer play a role. Because increasing numbers of children are now being vaccinated against type b *Haemophilus influenzae* (Hib) and pneumococci, the incidence of infection with these pathogens has declined by about 90% and 30%, respectively (e16, e17).

A special challenge—fever lasting longer than seven days: fever of unknown origin (FUO)

The procedure to be followed for children with FUO has been set down in a guideline issued jointly by the German Society for Pediatric and Adolescent Medicine (*Deutsche Gesellschaft für Kinderheilkunde und Jugendmedizin*, DGKJ), the German Society for Child and Adolescent Rheumatology (*Gesellschaft für Kinder- und Jugendrheumatologie*, GKJR), and the German Society for Pediatric Infectious Diseases (*Deutsche Gesellschaft für Pädiatrische Infektiologie*, DGPI) (11). Meticulous and thorough history-taking and repeated physical examination are markedly more efficient means of

Fever in an infant

Infants who appear ill must be hospitalized for the immediate initiation of intravenous treatment with antibiotics, e.g., ceftriaxone or cefotaxime.

Fever of unknown origin (FUO)

The physician should ask systematically about family history, contacts with animals, travel, antibiotics, prior surgery, and long-term medications. Children with FUO and their parents will inevitably be questioned multiple times.

establishing the diagnosis than scattershot laboratory testing and accessory studies. In taking the history, the physician should systematically inquire about family history, contacts with animals, travel, use of antibiotics, prior surgery, and any medications that the child is taking on a long-term basis. When a child has an FUO, the patient and his or her parents will inevitably be questioned multiple times. Documentation of prior hospitalizations and other contacts with physicians must be obtained and read. Invasive procedures such as laparotomy (e.g., in suspected appendicitis), laparoscopy, and biopsy are very rarely necessary. 18 studies on children with FUO (a total of 1638 patients) were recently analyzed in a systematic review (Table 2) (24).

In 10% to 30% of all cases, the cause of the fever can never be determined. Most of these children defervesce without any further complications after symptomatic treatment (9, 24, e18). Empirical antibiotic therapy (initiated after blood cultures, swabs, etc., have been taken) is indicated whenever there is clinical evidence of systemic bacterial infection, so that major infectious complications can be prevented. Empirical steroid therapy, on the other hand, should be avoided as long as possible and should only be given when an autoimmune disorder seems the likeliest diagnosis after the patient has been ill for several weeks and malignant disease has been definitively excluded.

Education and counseling about withholding antipyretic drugs

The parents of a febrile child often think of fever, not merely as a symptom, but as a worrisome disease in itself. Parents and medical staff (practice assistants, nurses, and doctors) need to be continually educated about fever. The goal of parent counseling is to enable parents to observe the child effectively, paying close attention to potential signs of severe illness (e.g., with respect to the child's breathing, skin, behavior, and level of consciousness), rather than being concerned merely about defervescence. The routine use of antipyretic drugs to treat fever in children without any other signs of severe illness is no longer recommended in Germany, England, the USA, or Italy (13, 14, 25, 26, e6).

In my experience, febrile children can be made to feel better even without antipyretic drugs as long as they are given enough fluid by mouth (50–80 mL/kg body weight) or intravenously as a saline or glucose

TABLE 2

Causes of fever of unknown origin*

	n (%)	Most common diagnoses
Infections	275 (42%)	urinary tract infection/pyelonephritis (n = 33) EBV infection (n = 31) osteomyelitis (n = 25) tuberculosis (n = 22) pneumonia/respiratory infection (n = 22) viral infection (n = 17) bartonellosis, brucellosis, typhus (n ≤ 10) sepsis, meningitis, abscess, sinusitis (n ≤ 10)
No diagnosis at time of publication	202 (31%)	
Miscellaneous	72 (11%)	inflammatory bowel disease (n = 12) unclear autoimmune disease (n = 11) drug fever (n = 7) factitious fever, immunodeficiency (n ≤ 2)
JIA/collagenoses	62 (10%)	juvenile idiopathic arthritis (JIA), systemic lupus erythematosus, unspecified collagenoses (no precise numbers; given in decreasing order of frequency)
Malignant diseases	38 (6%)	leukemia, lymphoma, neuroblastoma, Wilms tumor, myelodysplastic syndrome (no precise numbers; given in decreasing order of frequency)

EBV, Epstein-Barr virus; JIA, juvenile idiopathic arthritis

* Eight studies (USA, Spain, Germany, 649 children total) taken from a meta-analysis of 18 studies from industrial countries and emerging economies (USA, Spain, Germany, India, Poland, Tunisia, Serbia, Georgia, Argentina, Kuwait, 1638 children total) (24)

solution (about 100 mL/kg body weight in infants, or up to 200 mL/kg body weight in neonates). Additional fluid losses of 10% to 15% are to be expected for each 1°C elevation of temperature: for example, the fluid requirement is 30% higher if the child has a temperature of 40°C (27).

Restricted use of antipyretic drugs

Antipyretic drugs are now used only in the following situations (25, 28): when the child

- seems severely ill,
- has a very high fever (>40°C),
- takes in only small amounts of fluids,
- is in a special situation, such as shock or an underlying illness that increases the body's energy consumption—for example, a chronic heart or lung disease, acute stroke, or bronchiolitis.

Antipyretic drugs should be given only if the child . . .

- is severely affected
- has a very high fever (>40°C)
- is taking in very little fluid
- is in a special situation, as mentioned in the text

The dosage of antipyretic drugs

Antipyretic drugs should be dosed by body weight, not by age.

Antipyretic drugs should be dosed by weight and not by age. They should be stored in a safe place. A single dose of either paracetamol or ibuprofen has been shown to reduce fever more effectively than placebo (e19, e20).

Paracetamol is the antipyretic agent of first choice, because longstanding clinical experience has shown that it is safe. It should be given orally at a dose of 10–15 mg/kg every four to six hours. It takes effect in 30–60 minutes. It can also be given as a suppository or intravenously. Rectal administration is useful for children who are vomiting or have impaired consciousness; intravenous administration is useful if rapid entry into the central nervous system is needed, e.g. intra- or perioperatively (when paracetamol is used for its analgesic effect). Paracetamol, when dosed appropriately, has almost no side effects. Hepatotoxicity has been described in only a few individual case reports (29). On the other hand, a paracetamol overdose, whether accidental or deliberate with suicidal intent, can be fatal. Paracetamol is associated with the development of asthma, but no causal relationship has been established, and the association itself is debated (30).

Ibuprofen is given at a dose of 10 mg/kg body weight every six hours, with a maximum daily dose of 40 mg/kg. Its main effect sets in within three to four hours and lasts only slightly longer than that of paracetamol—six to eight hours, rather than four to six hours. There is no scientific evidence indicating any significant superiority of ibuprofen over paracetamol (3, 25, 31, e21, e22). As for its side effects, there have been individual case reports of gastritis and of gastric and duodenal ulcers (32) developing under treatment with ibuprofen, as well as nephrotoxicity (33). Caution should therefore be exercised if the child is suffering from dehydration or from any complex medical condition.

Lastly, physical measures are, among other things, a way of devoting caring attention to the child, and this aspect alone certainly helps relieve the symptoms to some extent. External cooling with ice-water baths or cold compresses around the legs is not a reasonable form of treatment when performed alone (i.e., without antipyretic agents), as it promotes vasoconstriction and signals to the thermoregulatory center that more heat should be produced. This would lead, in turn, to even greater energy consumption than before (4, 27, e23). On the other hand, if

the child is suffering not from fever, but from hyperthermia (defined as a temperature above 41°C, as in heatstroke), the hypothalamic set point has not been up-regulated and external cooling with ice water or cold compresses may, indeed, be an effective treatment.

Overview

The most important component of the diagnostic assessment is physical examination, usually on repeated occasions, by a physician with experience in the care of children and adolescents. Expensive and labor-intensive testing is very rarely needed. In primary care, the first and most important step is to counsel the parents of a febrile child that fever usually helps more than it harms, and that antipyretic drugs are, therefore, only indicated in special situations. Fever without identifiable cause and fever of unknown origin present special challenges to the diagnostician: specific diagnostic evaluation and timely initiation of treatment may be necessary, sometimes in an inpatient setting.

Acknowledgements

I would like to express my thanks to Andrea Groth for her excellent help in the production of the manuscript and to Prof. Dr. Michael Weiß (Klinik für Kinder- und Jugendmedizin, Kliniken der Stadt Köln gGmbH) for his critical reading of the manuscript.

Conflict of interest statement

Prof. Niehues has served as a paid consultant for Wyeth. He has also received reimbursement of scientific meeting participation fees and of travel and accommodation costs and lecture honoraria from Abbott, Baxter, Novartis, Pfizer, Bristol Myers Squibb, ZLB Behring, Octapharma, and Glaxo SmithKline. He has received financial support from Glaxo SmithKline for a research project that he initiated.

Manuscript submitted on 28 March 2013, revised version accepted on 10 September 2013.

Translated from the original German by Ethan Taub, M.D.

REFERENCES

1. Fink W, Haidinger G: Die Häufigkeit von Gesundheitsstörungen in 10 Jahren Allgemeinpraxis. *Z Allg Med* 2007; 102–8.
2. Enarson MC, Ali S, Vandermeer B, Wright RB, Klassen TP, Spiers JA: Beliefs and expectations of Canadian parents who bring febrile children for medical care. *Pediatrics* 2012; 130: e905–12.
3. Ward M: Pathophysiology and management of fever in infants and children. *www.uptodate.com*, 2013. Last accessed 8 September 2013.
4. Nakamura K: Central circuitries for body temperature regulation and fever. *Am J Physiol Regul Integr Comp Physiol* 2011; 301: 1207–28.
5. El-Radhi AS: Measurement of body temperature. *Clinical Manual of Fever in Children*. Heidelberg: Springer 2009; 63–79.
6. El-Radhi AS: Is fever beneficial? *Clinical manual of fever in children*. Heidelberg: Springer 2009; 211–22.

The evidential basis for combination therapy

There is no evidence that alternating or combined drug regimens are any better than either paracetamol or ibuprofen alone.

Cold compresses and ice-water baths

The efficacy of physical measures has not been documented. They are generally considered of little value.

7. Mackowiak PA, Wasserman SS, Levine MM: A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. *JAMA* 1992; 268: 1578–80.
8. Kliegman RM, Behrman RE, Jenson HB, Stanton BF: *Nelson Textbook of Pediatrics* 19th edition. Oxford: Saunders 2011.
9. Roos R, Bartmann P, Franz A, Knuf M, Handrick W: *Neonatale bakterielle Infektionen* (5th completely revised edition). DGPI Handbuch Infektionen bei Kindern und Jugendlichen. Stuttgart: Thieme 2009; 684–94.
10. El-Radhi AS, Carroll J, Klein N: *Clinical manual of fever in children*, 1st edition: Berlin, Heidelberg: Springer 2009.
11. Kallinich T: Fieber unklarer Genese. AWMF-Leitlinie der Gesellschaft für Kinder- und Jugendrheumatologie und der Deutschen Gesellschaft für Kinder- und Jugendmedizin. www.awmf.org/uploads/tx_szleitlinien/027-053l_S1_Fieber_unklarer_Ursache_2013-01.pdf 2013. Last accessed 8 September 2013
12. Dodd SR, Lancaster GA, Craig JV, Smyth RL, Williamson PR: In a systematic review, infrared ear thermometry for fever diagnosis in children finds poor sensitivity. *Journal of Clinical Epidemiology* 2006; 59: 354–7.
13. Richardson M, Lakhanpaul M, Guideline Development Group, the Technical Team: Assessment and initial management of feverish illness in children younger than 5 years: summary of NICE guidance. *BMJ* 2007; 334: 1163–4.
14. Chiappini E, Venturini E, Principi N, et al.: Update of the 2009 Italian Pediatric Society Guidelines about management of fever in children. *Clin Ther* 2012; 34: 1648–53.e3.
15. van den Bruel A, Haj-Hassan T, Thompson M, Buntinx F, Mount D: European Research Network on Recognising Serious Infection i: Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review. *Lancet* 2010; 375: 834–45.
16. Huppertz HI: Fieber ohne Fokus [Fever without focus]. *Monatsschr Kinderheilkd* 2013; 161: 204–10.
17. Volante E, Moretti S, Pisani F, Bevilacqua G: Early diagnosis of bacterial infection in the neonate. *J Matern Fetal Neonatal Med* 2004; 16: 13–6.
18. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P: Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis* 2013; 13: 426–35.
19. Pammi M, Flores A, Loefflang M, Versalovic J: Molecular assays in the diagnosis of neonatal sepsis: a systematic review and meta-analysis. *Pediatrics* 2011; 128: e973–85.
20. Weston EJ, Pondo T, Lewis MM, et al.: The burden of invasive early-onset neonatal sepsis in the United States, 2005–2008. *The Pediatric Infectious Disease Journal* 2011; 30: 937–41.
21. Stoll BJ, Hansen NI, Sanchez PJ, et al.: Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. *Pediatrics* 2011; 127: 817–26.
22. Shaikh N, Morone NE, Bost JE, Farrell MH: Prevalence of urinary tract infection in childhood: a meta-analysis. *The Pediatric Infectious Disease Journal* 2008; 27: 302–8.
23. Smitherman HF, Marias CG: Evaluation and management of fever in the neonate and young infant (less than three months of age). www.uptodate.com 2013. Last accessed 8 September 2013
24. Chow A, Robinson JL: Fever of unknown origin in children: a systematic review. *World J Pediatr* 2011; 7: 5–10.
25. Sullivan JE, Farrar HC: Fever and antipyretic use in children. *Pediatrics* 2011; 127: 580–7.
26. Lava SA, Simonetti GD, Ramelli GP, Tschumi S, Bianchetti MG: Symptomatic management of fever by Swiss board-certified pediatricians: results from a cross-sectional, web-based survey. *Clin Ther* 2012; 34: 250–6.
27. Kowalzik FZ, Zepp F: Das fiebernde Kind. Grundlagen der Behandlung. *Monatsschr Kinderheilkd* 2013; 161: 196–203.
28. El-Radhi AS: Management of fever. *Clinical manual of fever in children*. Heidelberg: Springer 2009; 223–50.
29. Lavonas EJ, Reynolds KM, Dart RC: Therapeutic acetaminophen is not associated with liver injury in children: a systematic review. *Pediatrics* 2010; 126: e1430–44.
30. Etminan M, Sadatsafavi M, Jafari S, Doyle-Waters M, Aminzadeh K, Fitzgerald JM: Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. *Chest* 2009; 136: 1316–23.
31. Pierce CA, Voss B: Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. *Ann Pharmacother* 2010; 44: 489–506.
32. Berezin SH, Bostwick HE, Halata MS, Feerick J, Newman LJ, Meadow MS: Gastrointestinal bleeding in children following ingestion of low-dose ibuprofen. *Journal of Pediatric Gastroenterology and Nutrition* 2007; 44: 506–8.
33. Misurac JM, Knoderer CA, Leiser JD, Nailescu C, Wilson AC, Andreoli SP: Nonsteroidal anti-inflammatory drugs are an important cause of acute kidney injury in children. *J Pediatr* 2013; 162: 1153–9.
34. van den Bruel A, Thompson MJ, Haj-Hassan T, et al.: Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. *BMJ* 2011; 342: d3082.
35. Thompson M, van den Bruel A, Verbakel J, et al.: Systematic review and validation of prediction rules for identifying children with serious infections in emergency departments and urgent-access primary care. *Health Technology Assessment* 2012; 16: 1–100.

Corresponding author

Prof. Dr. med. Tim Niehues
HELIOS Klinikum Krefeld
Zentrum für Kinder- und Jugendmedizin
Lutherplatz 40, 47805 Krefeld, Germany
tim.niehues@helios-klinden.de

For eReferences please refer to:
www.aerzteblatt-international.de/ref4513

FURTHER INFORMATION ON CME

This article has been certified by the North Rhine Academy for Postgraduate and Continuing Medical Education. Deutsches Ärzteblatt provides certified continuing medical education (CME) in accordance with the requirements of the Medical Associations of the German federal states (*Länder*). CME points of the Medical Associations can be acquired only through the Internet, not by mail or fax, by the use of the German version of the CME questionnaire. See the following website: cme.aerzteblatt.de.

Participants in the CME program can manage their CME points with their 15-digit “uniform CME number” (einheitliche Fortbildungsnummer, EFN). The EFN must be entered in the appropriate field in the cme.aerzteblatt.de website under “meine Daten” (“my data”), or upon registration. The EFN appears on each participant’s CME certificate.

The present CME unit can be accessed until 9 February 2014.

The CME unit “Common Causes of Poisoning” (Issue 41/2013) can be accessed until 12 January 2014.

The CME unit “Degenerative Lumbar Spinal Stenosis in Older People” (Issue 37/2013) can be accessed until 8 December 2013.

The CME unit “Shortness of Breath and Cough in Patients in Palliative Care” can be accessed until 17 November 2013.

For Issue 49/2013, we plan to offer the topic “The Diagnosis and Treatment of Celiac Disease.”

Please answer the following Questions to participate in our certified Continuing Medical Education program. Only one answer is possible per Question. Please select the answer that is most appropriate.

Question 1

Which cytokine plays the key role in the generation of fever?

- a) TGF β
- b) TNF β
- c) IL-1 β
- d) IL-10
- e) IL-17

Question 2

Endogenous pyrogens cause a shift in the hypothalamic set point of body temperature from a normal value of (say) 37°C to 40°C. What group of moderators produced by the hypothalamic epithelial cells plays the most important role in elevating the set point?

- a) histamines
- b) serotoninins
- c) melatoninins
- d) prostaglandins
- e) kallikreins

Question 3

A 3-year-old boy who has had fever for two days appears abnormal on physical examination and has one of the findings listed below. Which of these findings is associated with an elevated risk of severe bacterial infection?

- a) truncal exanthem
- b) conjunctivitis
- c) aphthous ulcers of the mouth
- d) cyanosis
- e) molluscum contagiosum

Question 4

What is the correct way to measure the body temperature of an acutely ill 5-year-old child with cancer?

- a) rectal digital thermometer
- b) oral digital thermometer
- c) ear infrared thermometer
- d) oral infrared thermometer
- e) axillary digital thermometer

Question 5

Which of the following is among the most common causes of fever of unknown origin in children?

- a) urinary tract infection
- b) septic granulomatosis
- c) tuberculous brain abscess
- d) cat-scratch disease
- e) viral myositis

Question 6

Which of the following is a valid argument *in favor of* giving an antipyretic drug to a febrile child?

- a) inhibition of inflammation, which shortens the course of the underlying disease
- b) analgesia, potentially leading to improved fluid intake
- c) rapid lowering of temperature, which protects the child from febrile seizures
- d) reassurance of parents, leading to more rapid defervescence
- e) inhibition of inflammation, which protects the child from CNS damage

Question 7

Which of the following is a valid argument *against* giving an antipyretic drug to a febrile child?

- a) frequent side effects
- b) inadequate efficacy for temperatures above 39.5°C
- c) risk of underappreciating other manifestations of underlying illness
- d) excessively long latency of effect in severe cases
- e) highly effective only when drugs with different mechanisms of action are combined

Question 8

A nurse on the maternity ward notices that a newborn infant is drinking poorly. Its mother had premature rupture of the membranes and fever shortly before delivery. She wants to take the baby home now. What should be done?

- a) hospitalize, await test results
- b) hospitalize, give IV antibiotics
- c) hospitalize, give oral antibiotics
- d) send home, re-evaluate soon in outpatient setting, give IV antibiotics
- e) send home, re-evaluate soon in outpatient setting, give oral antibiotics

Question 9

A 3-year-old child has had fever to 40°C over the last two days without any identifiable focus and appears lethargic. The treating physician hospitalizes the child and decides to draw a first blood sample for testing. Which of the following tests should be ordered?

- a) multiplex PCR
- b) procalcitonin
- c) IL-6
- d) IL-1
- e) CRP

Question 10

A 3-month-old child has had fever to 40°C over the last two days without any identifiable focus, appears lethargic, and is dehydrated because of significant fluid loss. The treating physician decides to give an antipyretic drug. Which of the following actions is correct in this situation?

- a) Dosing of the antipyretic drug according to the child's age, not body weight
- b) Administration of a well-tolerated steroid
- c) Alternatively, administration of a drug that inhibits interleukin-1
- d) Initiation of combination therapy with both paracetamol and ibuprofen, which is superior to treatment with either one of these drugs alone
- e) Administration of either ibuprofen or paracetamol as the single drug of choice

CONTINUING MEDICAL EDUCATION

The Febrile Child: Diagnosis and Treatment

Tim Niehues

eREFERENCES

- e1. Poirier MP, Collins EP, McGuire E: Fever phobia: a survey of caregivers of children seen in a pediatric emergency department. *Clinical Pediatrics* 2010; 49: 530–4.
- e2. Reckert T: Beratung zum Umgang mit Fieber und Abbau der Fieberangst. *Zeitschrift Kinder- und Jugendarzt* 2011/2012; 12/11 + 1/12: 695–7.
- e3. Craig JV, Lancaster GA, Taylor S, Williamson PR, Smyth RL: Infrared ear thermometry compared with rectal thermometry in children: a systematic review. *Lancet* 2002; 360: 603–9.
- e4. Craig JV, Lancaster GA, Williamson PR, Smyth RL: Temperature measured at the axilla compared with rectum in children and young people: systematic review. *BMJ* 2000; 320: 1174–8.
- e5. Duce SJ: A systematic review of the literature to determine optimal methods of temperature measurement in neonates, infants and children. *DARE Review* 1994; 4: 1–124.
- e6. Chiappini E, Principi N, Longhi R, et al.: Management of fever in children: summary of the Italian Pediatric Society guidelines. *Clinical therapeutics* 2009; 31: 1826–43.
- e7. Trautner BW, Caviness AC, Gerlach GR, Demmler G, Macias CG: Prospective evaluation of the risk of serious bacterial infection in children who present to the emergency department with hyperpyrexia (temperature of 106 degrees F or higher). *Pediatrics* 2006; 118: 34–40.
- e8. Gomez B, Bressan S, Mintegi S, et al.: Diagnostic value of procalcitonin in well-appearing young febrile infants. *Pediatrics* 2012; 130: 815–22.
- e9. Krishna NK, Cunnion KM: Role of molecular diagnostics in the management of infectious disease emergencies. *The Medical Clinics of North America* 2012; 96: 1067–78.
- e10. Manzano S, Bailey B, Girodias JB, Galetto-Lacour A, Cousineau J, Delvin E: Impact of procalcitonin on the management of children aged 1 to 36 months presenting with fever without source: a randomized controlled trial. *The American Journal of Emergency Medicine* 2010; 28: 647–53.
- e11. Lehmann LE, Herpichboehm B, Kost GJ, Kollef MH, Stuber F: Cost and mortality prediction using polymerase chain reaction pathogen detection in sepsis: evidence from three observational trials. *Critical Care* 2010; 14: R186.
- e12. Baker MD, Bell LM: Unpredictability of serious bacterial illness in febrile infants from birth to 1 month of age. *Archives of Pediatrics & Adolescent Medicine* 1999; 153: 508–11.
- e13. Kadish HA, Loveridge B, Tobey J, Bolte RG, Corneli HM: Applying outpatient protocols in febrile infants 1–28 days of age: can the threshold be lowered? *Clinical Pediatrics* 2000; 39: 81–8.
- e14. Bachur RG, Harper MB: Predictive model for serious bacterial infections among infants younger than 3 months of age. *Pediatrics* 2001; 108: 311–6.
- e15. Bressan S, Berlese P, Mion T, Masiero S, Cavallaro A, Da Dalt L: Bacteremia in feverish children presenting to the emergency department: a retrospective study and literature review. *Acta Paediatrica* 2012; 101: 271–7.
- e16. Kalies H, Verstraeten T, Grote V, et al.: Four and one-half-year follow-up of the effectiveness of diphtheria-tetanus toxoids-acellular pertussis/Haemophilus influenzae type b and diphtheria-tetanus toxoids-acellular pertussis-inactivated poliovirus/H. influenzae type b combination vaccines in Germany. *The Pediatric Infectious Disease Journal* 2004; 23: 944–50.
- e17. van der Linden M, Weiss S, Falkenhofst G, Siedler A, Imohl M, von Kries R: Four years of universal pneumococcal conjugate infant vaccination in Germany: impact on incidence of invasive pneumococcal disease and serotype distribution in children. *Vaccine* 2012; 30: 5880–5.
- e18. Pasic S, Minic A, Djuric P, et al.: Fever of unknown origin in 185 paediatric patients: a single-centre experience. *Acta Paediatrica* 2006; 95: 463–6.
- e19. Goldman RD, Ko K, Linett LJ, Scolnik D: Antipyretic efficacy and safety of ibuprofen and acetaminophen in children. *The Annals of Pharmacotherapy* 2004; 38: 146–50.
- e20. Perrott DA, Piira T, Goodenough B, Champion GD: Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: a meta-analysis. *Archives of Pediatrics & Adolescent Medicine* 2004; 158: 521–6.
- e21. Autret-Leca E, Gibb IA, Goulder MA: Ibuprofen versus paracetamol in pediatric fever: objective and subjective findings from a randomized, blinded study. *Current Medical Research and Opinion* 2007; 23: 2205–11.
- e22. Southey ER, Soares-Weiser K, Kleijnen J: Systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric pain and fever. *Current Medical Research and Opinion* 2009; 25: 2207–22.
- e23. Meremikwu M, Oyo-Ita A: Physical methods for treating fever in children. *The Cochrane Database of Systematic Reviews* 2003: CD004264.
- e24. Meremikwu M, Oyo-Ita A: Paracetamol for treating fever in children. *The Cochrane Database of Systematic reviews* 2002: CD003676.