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.

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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 reticuloendothelial 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...
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).

### 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.
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 \[\geq 3\] sec, cyanosis, somnolence, dyspnea, edema, dehydration, oliguria, meningeval irritation, impaired mobility [e.g., the child does not walk anymore], 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 life.

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 neurocutaneous-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

Deutsches Ärzteblatt International | Dtsch Arztebl Int 2013; 110(45): 764–74
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, and

### 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
    - 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, elevated IL-6/IL-8 values

- **According to meta-analysis** (15, 34, 35)
  - strong red flags
    - degree of parental concern
    - physician’s clinical instinct
  - red flags
    - cyanosis
    - tachypnea
    - poor peripheral perfusion
    - petechiae
    - temperature above 40°C
  - to exclude severe bacterial infection:
    - CRP <0.8 mg/dL
    - procalcitonin <2 ng/L

* Beware: erythroblasts
* Physiologically elevated in neonates 24-36 hours after birth
* Meta-analysis of approximately 4000 studies, selection of appropriately designed studies in the outpatient setting with subjects aged 1 month to 18 years
* 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!
**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.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Frequency of fever</th>
<th>Pathogens in order of frequency</th>
<th>Frequency of SBI</th>
<th>Treatment/procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates ≤ 3 days</td>
<td>rare</td>
<td>GBS, <em>E. coli</em>, <em>Staphylococcus aureus</em>, klebsiellae, enterococci, streptococci <em>(A + C)</em>, <em>Listeria monocytogenes</em>, fungi, herpes simplex virus <em>(from maternal rectovaginal flora)</em></td>
<td>ca. 10%</td>
<td>always hospitalize! empirical treatment with IV antibiotics, e.g., ampicillin + cefotaxime +/– aminoglycoside <em>(such as tobra-gentamycin)</em></td>
</tr>
<tr>
<td>&gt;3 days</td>
<td></td>
<td>coagulase-negative staphylococci, <em>Pseudomonas</em>, <em>Enterobacter</em>, <em>Citrobacter</em>, serratiae, klebsiellae, <em>Salmonella</em>, <em>Haemophilus influenzae</em></td>
<td>ca. 5%</td>
<td>hospitalization if there are risk factors for SBI *(Box): IV antibiotics, e.g., cefotaxime <em>(empirical treatment)</em></td>
</tr>
<tr>
<td>Infants up to 3 months</td>
<td>common</td>
<td>RSV, influenza A, <em>(winter)</em>, <em>Enterobacter</em> <em>(summer)</em>, GBS, <em>Listeria monocytogenes</em>, <em>Salmonella enteritidis</em>, <em>E. coli</em>, <em>Neisseria meningitidis</em>, pneumococci, <em>Haemophilus influenzae</em> b, <em>Staphylococcus aureus</em></td>
<td>&lt;0.5% – 1%</td>
<td></td>
</tr>
<tr>
<td>Infants and toddlers from 3 months to 6 years</td>
<td>very common</td>
<td>viruses, pneumococci, <em>Haemophilus influenzae</em> b, <em>Neisseria meningitidis</em>, <em>Salmonella</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 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.

### The dosage of antipyretic drugs

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

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**TABLE 2**

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

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)
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.

REFERENCES
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) TGFβ
- b) TNFβ
- c) IL-1β
- 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) serotonin
- c) melatonin
- 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, appears lethargic, and is dehydrated because of significant fluid loss. 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

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eREFERENCES