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One of the most common manifestations of disease, fever in children remains controversial, misunderstood, and often is thought to be mysterious. Fever has been recognized since antiquity and remains one of the most frequent complaints in emergency departments (EDs), physician offices, and clinics. Treatment of fever also is a lucrative business; an estimated \$6 billion dollars is spent worldwide each year on antipyretic drugs.^{1,2}

The clinician always should realize that fever is not a disease itself, but a manifestation of a number of different disease processes. Because there are substantial differences in the cause and outcome of fever-generating ill-

nesses in children of different ages, the discussion must consider age. Not surprisingly, there is a diversity of approaches to fever.³⁻⁶

—The Editor

Pediatric Fever: Myths and Management

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What Is Fever?

Fever is a state of elevated core temperature. It is a neurochemical response common to many animals and often is part of the defensive response to the invasion of microorganisms or inanimate matter recognized as alien or pathogenic by the host,⁷ making a strong argument that fever has a net benefit to the species.

Fever is found in almost all infectious diseases, but also occurs in neoplastic disorders, autoimmune disease, acute meta-

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bolic and endocrine disorders, granulomatous disorders, drug reactions, vascular thrombosis or infarction, and trauma. Unfortunately, fever is not the clearly defined concept that many believe it to be.

Definition of Fever

A temperature of 98.6°F is considered normal by some, but this doesn't account for individual variations, environmental exposure, or the slightly faster metabolism of a child. Most definitions of fever are based on an 1868 study by Dr. Carl Reinhold August Wunderlich, which defined normal as 98.6 °F. However, this study and other such studies did not involve children and did not account for individual variations, environmental exposure, or the slightly faster metabolism of a child. Body temperature also varies during the course of the day, with the highest temperature during the late afternoon.⁸ Conversely, children often have their lowest temperature early in the morning. With teenagers, the menstrual cycle also causes a cyclic variation in the temperature. Finally, body temperature varies with the part of the body that is measured. "Core" organs such as the liver have a higher temperature than the extremities. In a cold environment or in response to

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a decrease in core temperature, the cutaneous blood flow normally decreases as a means of retaining heat within the body core.

Measurement of Fever

The rectal thermometer is perceived to be the gold standard for measurement of a temperature in children. The rectal temperature is obtained by placing a lubricated thermometer in the rectum. The usually accepted reference range is 36.1-38.0°C (97-100.3°F.) Rectal temperatures do not respond quickly to induced heating or cooling of the body. (See Table 1.)

Oral temperatures usually are preferred in adults and children older than 5 years. Typically, a thermometer is placed under the tongue for four minutes when using a mercury thermometer or suitable substitute. The sublingual site is easily accessible and reflects the temperature of the lingual arteries. The oral temperature easily is influenced by the recent ingestion of hot or cold food and drink and by mouth breathing. Proper technique of oral temperature measurement includes having the child keep a sealed mouth, with the tongue depressed for about 3-4 minutes. This is not always attainable in a small child, an unconscious patient, or an uncooperative patient.

The accuracy of oral temperatures is somewhere between axillary and rectal temperatures. Generally, the older the child, the more accurate the measurement is. This may be due to better compliance on the part of the patient or better technique.

Pacifier thermometers are available, but have not been well evaluated for accuracy.⁹ The available data on these devices is quite limited. Electronic oral thermometers can ascertain the temperature more quickly. The usual oral normal reference range is 35.6-37.4°C (96.0-99.3°F)

Tympanic thermometers measure the thermal radiation emitted from the tympanic membrane (TM) and the ear canal. There are two techniques: measurement of the temperature by putting a thermocouple directly on the tympanic membrane or measurement of the reflected infrared radiation from the tympanic membrane. The former is potentially painful and invasive. It is not often used.

Tympanic thermometers that measure the infrared radiation from the eardrum also are called infrared radiation emission detectors (IRED). Because the amount of thermal radiation emitted is in proportion to the membrane's temperature, IRED accurately estimates TM temperature.¹⁰ In contrast with other sites of temperature measurement, the TM's blood supply is very similar in temperature and location to the blood bathing the hypothalamus, the site of the body's thermoregulatory center. It is, therefore, an ideal location for core temperature estimation. Crying, otitis media, or earwax have not been shown to change tympanic readings significantly.^{11,12}

Most models of tympanic probes use an offset or an internal calculation that transforms the measured ear temperature into a rectal equivalent or an oral equivalent. These offsets may represent a source of error. The formula often is based on adult data and subsequently is applied to all age groups. This formula may not apply to the child younger than 3 years. In one published study, this offset was adjusted, and the TM temperatures more

Table 1. Recommended Temperature Measurement Techniques

AGE	RECOMMENDED TECHNIQUE
Birth to 2 years	<ol style="list-style-type: none"> 1. Rectal 2. Tympanic—May have some inaccuracy in the very young, depending on the manufacturer and technique used. 3. Axillary—screening in neonates
Older than 2 years up to 5 years	<ol style="list-style-type: none"> 1. Rectal 2. Tympanic 3. Axillary
Older than 5 years	<ol style="list-style-type: none"> 1. Oral 2. Tympanic 3. Axillary

closely matched the rectal temperature.¹³ The actual ear reading was found to indicate temperature reliably in premature and full-term neonates.¹⁴

The size of the temperature probe in children younger than 3 years may not be small enough to be placed correctly in the ear canal. For the sensor to detect heat from the drum, it must be placed so that the sensor records infrared reflection from the drum, not from the canal walls. This requires that the ear canal is straightened as when using an otoscope—the pinna pulled down and back from children younger than 3 years.

At present, there appears to be no consensus about how accurate the tympanic IRED can be in assessing temperatures in children younger than 3 years of age. Even one manufacturer-sponsored study felt that the devices often were inaccurate in children younger than 3 years.¹⁵ Tympanic methods correlate fairly well after the age of three months, but if there is any doubt, obtain a rectal temperature.

Axillary temperatures have a sensitivity of only 50-70% for detecting elevated temperature documented by rectal thermometers. Despite its demonstrated low sensitivity and specificity in detecting fever, axillary temperature is recommended by the American Academy of Pediatrics as a screening tool for the evaluation of fever in neonates because of a perceived risk of rectal perforation with a rectal thermometer.¹⁶ Axillary temperatures are useful only as a screening tool for hypothermia when dealing with multiple casualties.¹⁷ The reference range for axillary temperatures is 37-37.4°C.

Temporal artery temperatures can be taken by a noninvasive IRED that measures the temperature of the area around the temporal artery.¹⁸ As the blood flow to the temporal artery is similar to the blood flow around the hypothalamus, this technique has attractions. The temporal artery has limited sensitivity for detecting fever in infants, but it may be more accurate than a tympanic thermometer.¹⁹ It is better tolerated than rectal temperatures. Further evaluation of this technique is needed.

Forehead temperature measurement devices are less accurate than axillary thermometers and should be discouraged.

Parents may report a fever in their child by subjective information (touching the forehead or the torso). This parental reporting of fever has been shown to be a moderately reliable indicator of an actual fever.²⁰ These patients may be afebrile when they present to the ED.

Although accurate temperatures may be important in helping make clinical decisions about required diagnostic procedures and subsequent treatments, the patient's temperature is only one risk factor in assessing an ill child. EPs must exercise clinical judgment in providing optimal care to the child with fever, irrespective of the instrument used to obtain this measurement.

Mechanism of Fever

Fever is a regulated rise in the body temperature after an alteration in the body's metabolic set point (at the hypothalamus) that is mediated by numerous endogenous and exogenous chemicals, including leukocytosis and phagocytosis. These chemicals induce the cyclooxygenase COX-2 activation of the arachidonic acid inflammatory cascade and enhanced biosynthesis of prostaglandin E2 by the hypothalamic vascular endothelial cells.²¹

Fever is tightly regulated by the immune response.²² Although infections are the most common cause of fever in children, there are multiple other triggers for the acute phase response and subsequent fever. These include transfusion reactions, juvenile rheumatoid arthritis, malignancy (especially lymphoma and leukemia), pulmonary embolism, connective tissue diseases, inflammatory reactions of trauma, burns, medications (including antihistamines, some antibiotics, and an overdose of NSAIDs—particularly aspirin), immunizations, and dehydration.

Non-infectious causes of fever include:

- Environmental factors such as high external temperatures;
- Over-bundling of children during the winter months;
- Malignancy;
- Rheumatoid diseases;
- Certain drugs;
- Salicylates, in particular, can cause fever when they are ingested in overdose. Other less common ingestions that can cause fever include phenothiazines, antidepressants, atropine, amphetamines, cocaine, and anticholinergic medications;
 - Recent immunizations;
 - Diphtheria/tetanus/pertussis (DPT) immunization may cause fever within a few hours after the injection that may last as long as 48 hours;
 - Measles/mumps/rubella (MMR) immunization can have delayed temperature elevations (up to 7-10 days after the injection);
 - Teething. Fever associated with teething is usually low-grade.^{23,24} A fever higher than 102 should be investigated and may well be due to some other illness.²⁵ Diarrhea, respiratory symptoms, pulling at the ears, high fever, or convulsions should not be attributed to teething and require medical attention;²⁶
 - Trauma and burns; and
 - Tissue infarction.

Patterns of Fever

Febrile patients with localizing signs present few difficulties

in diagnosis. Fever patterns are most helpful in diagnosing febrile illnesses that do not have localizing signs and may provide a clue for these difficult-to-diagnose patients. Use of antipyretics, steroids, and anti-inflammatory drugs with antipyretic properties all influence these patterns of fever.

Continuous Sustained Fever with Minimal Remissions (less than 2.0°F). This fever pattern is classic for the patient with lobar or gram-negative pneumonia, rickettsial diseases, typhoid fever, tularemia, and falciparum malaria.⁸

Intermittent Fever with Wide Fluctuations (Picket-fence fever, septic, quotidian). Intermittent fevers often are normal or low in the morning and peak between 4 and 8 PM. This group of fevers often includes localized pyogenic infections and bacterial endocarditis. Malaria often has a daily spike (quotidian), a spike every third day (tertian), or a spike every fourth day (quartan), depending on the species of malaria infecting the patient.⁸

Intermittent Hectic (Charcot's) Fever. This pattern consists of sporadic episodes of fever followed by periods of normal temperature and then recurrence of fever. This is a frequent and reliable pattern in cholangitis.⁸ It often is associated with cholelithiasis, jaundice, and toxic appearance, but may occur in patients without jaundice.

Pel-Ebstein Fever. The Pel-Ebstein pattern of fever is fever of a week or longer followed by an equally long afebrile period and then repetition of the cycle.⁸ It can occur in Hodgkin's disease, brucellosis, and relapsing fever. Occasionally, it can be found in tuberculosis.

Jarisch-Herxheimer Reaction. This is a fever associated with the treatment of primary or secondary syphilis, leptospirosis, and tick-borne relapsing fever. It occurs several hours after the beginning of antibiotics (penicillin) for these diseases. It is sometimes seen following tetracycline or chloramphenicol therapy for brucellosis.

Typhus Inversus Fever Pattern. The typhus inversus fever pattern is a reversal of the diurnal pattern of fever with the highest temperature occurring in the early morning hours rather than later in the afternoon or early evening. This pattern is found in military tuberculosis, salmonella, hepatic abscesses, and occasionally in bacterial endocarditis.

Saddle-back (Biphasic) Fever. This fever pattern is several days of fever, a distinct reduction in the fever for about a day, and then several additional days of high fever. This pattern is typical of dengue, yellow fever, Colorado tick fever, relapsing fever, Rift Valley fever, influenza, and other viral infections such as polio and lymphocytic choriomeningitis.^{8,27}

What Is Not Fever

Fever is not the same as hyperthermia. Hyperthermia occurs when heat production exceeds the heat losses or when heat loss mechanisms are defective.²⁸ Mechanisms for hyperthermia include neuroleptic malignant syndrome, malignant hyperthermia, and heatstroke.²⁹ These diseases are medical emergencies that require rapid external cooling. They do not reset the thermostat, and the patient's temperature will continue to rise until effective treatment is given. Only set point alteration fevers

respond to antipyretics.

A common example of hyperthermia is heatstroke associated with exercise or exposure to extreme heat, but hyperthermia can occur with perspiration-inhibiting drugs and modest temperature elevations. The elevated temperature associated with heat illnesses (heat production/gain greater than heat losses) will not respond to ibuprofen, aspirin, or acetaminophen.^{29,30}

As the core temperature rises, if the oxygen supply does not keep pace with the intracellular needs, the cells will become hypoxic and begin to die. In a conditioned athlete, the external heat load is dissipated well, and the heart and cardiovascular system can provide for the cardiovascular load of the heat dissipation, supply necessary oxygen and metabolic substrates, and meet the circulation needs of the exercise. In poorly conditioned, chronically ill, dehydrated, or very young patients, the cardiovascular system is not able to provide for the needs of both circulation and cooling.

As the temperature rises, the cardiovascular system becomes unable to both provide adequate circulation and continue cooling efforts at some point. The result is multi-system breakdown with diffuse cellular death. The cellular breakdown appears to be responsible for some of the delayed morbidity in those patients who survive the emergent phase of heat stroke. Survival from heat stroke depends on adequate response of the cardiovascular system, as more than normal cardiac output is needed to meet the elevated circulatory demands.³¹

Malignant hyperthermia is also not a fever. Malignant hyperthermia typically is due to a mutation in the calcium channel of the muscle sarcoplasmic reticulum. It most commonly occurs during the induction of general anesthesia with concurrent use of a depolarizing paralytic agent. The hyperthermia that ensues must be treated rapidly both with cooling and a calcium channel blocker with dantrolene to prevent further tissue damage.

Neuroleptic malignant syndrome is thought to be due to a tendency of some antipsychotic drugs to induce muscular rigidity and direct effects on hypothalamic heat-conserving mechanisms. Both of these effects are the result of blockade of dopamine receptors. Neuroleptically induced hyperthermia will respond to dantrolene and external cooling. (The antipsychotic agents also are implicated as a contributing factor for heatstroke.)²⁹

How Hot Is Too Hot?

Modern clinicians generally subscribe to the notion that the febrile range has an upper limit, but there is great controversy about the precise temperature defining this limit. Animal studies suggest that a body temperature of greater than 107.6°F in humans may trigger enough adverse effects on a cellular level to cause death. These studies were done by injecting pyrogens or by artificially heating the animals. This is not the same as a naturally occurring fever, but is the closest available laboratory model.

Not all of this animal-derived data are supported by human clinical research. Healthy volunteers can withstand core temperatures of 42°C (107.6°F) for as long as 4 hours without any ill effects.³² Indeed, marathon runners and other skilled athletes engaged in strenuous exercise often will have higher tempera-

Table 2. Thoughts to Share with Patients about Fever

- Fever is a normal response to many disease processes and is a useful defense against many illnesses.
- Fever is a symptom, not a disease.
- Fever will persist until the disease process resolves.
- Fever tops out at about 106°F. It won't keep rising.
- Fever determination does not need to be exact. (There really isn't any clinical difference between 101.4 and 101.6°F.)
- Temperatures should be taken about every 2-4 hours at most—certainly not more frequently. (With the physiology involved, it takes about 1-2 hours for the body to change a temperature, so you can't expect the fever to resolve in less time.)
- Fever does not always need to be treated (particularly low-grade fever).
- Antipyretic medications are medications with potentially serious problems in overdose.
- Overdoses are much more common when medications are mixed.
- Antipyretic medications should be used as therapy for patient comfort rather than control of the fever. If the patient is comfortable, you don't need to control the fever—the body will do that just fine.
- If you are worried about treating the fever for the comfort of the patient, don't use baths or sponging—these are among the most uncomfortable therapies for the patient.
- Treating a fever won't prevent febrile seizures. Some folks think that the febrile seizure is related to the rate of rise of the temperature, so treating a fever inappropriately would give *more* chances for febrile seizures, not less. (We can prevent them, but it takes anti-seizure medicine, not anti-fever medicine.)
- Clinical appearance may be more important than the height of the fever. (A fever greater than 104°F may have a higher incidence of bacterial disease, but this means the physician should consider more evaluation of the cause, not necessarily more worry about the fever.)

tures with no evidence of any damage.^{31,33} The ability to tolerate a high temperature is multifactorial and depends in part on conditioning, general health, oxygen supplies, hydration, and innate physiological differences.

Why Be Concerned?

As noted earlier, fever is a common pediatric presentation to the ED. Nearly 30% of pediatric office and ED visits for children after three months of age are for fever.³⁴ In most clinical situations, fever causes only minor discomfort, does no major harm, and actually may benefit the host defense mechanisms. Although fever usually is associated with a non-serious, self-limited disease, it also is a cardinal sign of a serious bacterial infection. Therein lies the crux of the problem.

Both health professionals and parents may believe in a lower standard for fever and react completely out of proportion to the severity of the illness. In a Johns Hopkins interview paper, 90%

of parents felt that fevers were always a source of concern, 21% felt that a fever alone would kill a child, and 85% felt that a child should be wakened to administer an antipyretic.³⁵ Fifty-two percent of these caregivers would check their child's temperature at least every hour if the child had a fever. Interestingly, when compared with similar surveys in the 1980s, the parents today are in command of less correct information than those raising children in the '80s.³⁵

Fever must be considered in the context of the patient's overall condition, age, and prior history. A 3-year-old child with a temperature of 104.5°F, industriously at play in the ED waiting room, has an exceptionally low likelihood of having serious illness. The limp and lethargic 4-month-old child with a temperature of 99.9 is critically ill.

Unfortunately, parents often are quite concerned about the fever and want ED clinicians to do something, a feeling, in part, driven by advertising. The manufacturers of acetaminophen and ibuprofen alike run ads encouraging parents to treat fever rapidly with implications that not to do so is inappropriate parental behavior.

Studies have shown that many caregivers believe fever may cause seizures, brain damage, death, dehydration, coma, delirium, or blindness.^{35,36} Many caregivers feel that fever will continue to rise to potentially lethal levels if left untreated. These caregivers are unaware that the febrile response is homeostatic and the body does not allow fever to rise out of control to potentially lethal levels. Surprisingly, these beliefs are shared by some pediatric health care providers. A survey of 172 pediatricians found that 65% felt that fever alone could produce "serious complications" if not treated ... and were unable to cite these serious complications.³⁷ Pediatric emergency nurses were no more reliable, with almost one-third of polled pediatric ED nurses feeling that a fever of under 104°F was dangerous.³⁸ Parents also may believe that every fever requires antibiotic therapy for their child. The emergency physician needs to invest time educating parents about the dangers of indiscriminant use of antibiotics.

Obsession with a number can detract from the overall care of the patient. Fortunately, more discriminating and evidence-based practice patterns will decrease this pervasive fever phobia. The aware physician realizes how important it is to educate the parent and the health care provider alike that fever is a sign and a symptom, not a disease. Caregivers need to be educated that fever is a physiologic response to an insult that stimulates the body's inflammatory defenses. (See Table 2.)

There is no question that during hyperthermic disorders such as heat stroke and malignant hyperthermia, the core temperature can rise to levels that are lethal. Fortunately, fever and hyperthermia are two different disease processes.

The Risk/Benefit Analysis: Should Fever Be Treated?

Should fever be treated? The answer to this question is not easy and depends upon the goals of treatment. Although the complex biochemistry of antipyretics is becoming better under-

stood, the indications for use clearly are not.

Two critical assumptions are made when prescribing an antipyretic. One is that the fever is, at least in part, noxious. The other is that suppression of the fever will reduce the fever's noxious effects without harm to the patient. Neither of these assumptions has been validated adequately. In fact, consideration of the mechanisms of fever indicates that in the absence of brain injury, fever is a normal and adaptive physiologic response.^{39,40} As noted earlier, there is considerable evidence that fever is an important part of the body's resistance to infection.

Beneficial Effects of Fever

Multiple studies have reported a benefit of fever on the overall outcome of infections.^{41,42} Fever can retard the growth and reproduction of bacterial and viral microorganisms, enhance neutrophil production and T-cell proliferation, and aid the body's acute phase reaction. Fever was used to treat syphilis, and artificially induced hyperthermia has been used to treat gonococcal endocarditis. (Indeed, the Nobel prize was awarded for the treatment of neurosyphilis by induction of fever.)⁴³

Numerous animal studies of infection show that antipyretic therapy increases the morbidity and mortality of the host.⁴⁴ A high temperature has been associated with lower mortality in spontaneous bacterial peritonitis. Patients who have gram-negative bacteremia and an elevated temperature on the day of bacteremia have better survival.

The elevation of body temperature by a few degrees may improve the efficiency of macrophages in killing invading bacteria, while it impairs the reproduction of many microorganisms, giving the immune system an adaptive advantage.^{39,40}

Conversely, increased mortality is found in patients with sepsis, bacteremia, or meningitis who are unable to mount a febrile response. Gathering evidence points to IL1 and TNF-alpha (endogenous mediators of the febrile response) as contributing factors in the pathophysiology of bacterial sepsis, and possibly to the disability associated with other infectious diseases.

Unfortunately, critical controlled studies are lacking that demonstrate that a low-grade fever can improve the outcome of infectious illness in humans.

Detrimental Effects of Fever

There are a few truly detrimental effects of the febrile response that often are not appreciated. The most persuasive evidence of the adverse effects of the febrile response appear in studies about gram-negative bacterial sepsis.⁴² In these studies, tumor necrosis factor and interleukin-1 induce fever, hypoglycemia, shock, and death. As noted above, both of these substances are cytokines that are elaborated by the febrile response. When animals develop induced tolerance to tumor necrosis factor, they are protected against the hypotension, hypothermia, and lethality of gram-negative bacterial sepsis.⁴⁵ Similar data suggest that pyrogenic cytokines also may mediate some of the systemic and local manifestations of sepsis caused by gram-positive bacteria and some other infections in laboratory animals.⁴⁵

Whether the febrile response may be beneficial or detrimental

to the individual may be determined by the peak systemic concentrations of cytokines achieved during the infection. If the concentrations of the cytokines are low, the effects seem to be beneficial. If the concentrations are above a yet-to-be-determined critical level, the same cytokines may contribute to the damage caused by sepsis. It is, of course, difficult to separate the effects of the febrile part of the febrile response from the inflammatory cascade that is both cause and effect within the febrile response.

Fortunately for the clinician, these effects are relatively rare. The clinical implications of this data in human practice have not yet been determined. Indeed, there is no proof that these theoretical effects of fever actually contribute to an adverse clinical outcome of infections. At least one author proposes the hypothesis that the physiological response to sepsis accelerates the inevitable demise of a hopelessly infected and potentially contagious individual to limit the spread of infection within the species.⁴⁵

The septic patient, therefore, may benefit in some cases from measures directed specifically against pyrogenic cytokines. Further research in this complex manifestation of the febrile response surely will be forthcoming.

Please note, however, that these detrimental effects of fever are *not* the effects seen in the vast majority of patients in the ED practice. They also are not the effects of fever feared by parents and practitioners alike and popularized by the manufacturers.

Detrimental Effects of Treating Fever

Giving an antipyretic can disrupt fever patterns. This important diagnostic sign is characteristic of only a few diseases and often based on geographically dependent epidemiology as previously discussed. Because only a few diseases have characteristic fever curves, the utility of this sign often is not appreciated by those who have not been involved in the diagnosis and treatment of these diseases.

Finally, fever is an important indicator of disease progression. Suppression of this fever may delay needed diagnostic studies or changes in antimicrobial therapy.

The Rationale for Treatment of Fever

Theoretically valid reasons for treatment of fever include (*see Table 3*):

- Increased metabolic stress and increased oxygen demand caused by an elevated temperature, particularly in patients with poor cardiac reserves or poor pulmonary reserves.

In fact, the metabolic and cardiovascular costs of fever are substantial, especially during the "chill" phase of the response with its shivering-induced increase in metabolic rate, peripheral vasoconstriction, and increased arterial blood pressure.²² Van't Hoff's rule states, in part, that the cellular metabolism increases about 13% for each centigrade degree rise in temperature. At 40.5°C (105° F), the cellular metabolism is 50% above normal. Although antipyretic therapy has theoretical merit in this regard, this theory has not been confirmed experimentally, even in patients with underlying cardiac and pulmonary diseases.²¹

- Patient comfort.

Antipyretic therapy often is advocated to make the child com-

fortable. Carefully controlled studies of efficacy have not been able to give any indication of how much comfort is provided by fever control.⁴⁶ The general experience seems to support this rationale, however.

Febrile patients feel ill not simply because they have an elevated temperature. In fact, an elevated body temperature may not be particularly troublesome—as evidenced by the wide popularity of hot tubs and saunas. Anecdotally, multiple running, playing children with temperatures as high as 104°F in many EDs attest to the fact that fever alone may not be a comfort crisis.

Much of the discomfort surrounding illness comes from symptoms other than the fever. Generalized symptoms such as anorexia, headache, nausea, malaise, myalgias, and back pain often accompany the fever as constitutional symptoms. Since all of the antipyretic agents also are analgesic agents, many of these symptoms will be relieved by the use of antipyretic agents.

- Reduction of morbidity and mortality.
- Fever may increase survival in sepsis.

This point has been addressed previously in the discussion about mechanism of fever. Only one randomized study in humans has looked at survival of septic patients treated with antipyretics. This study found that antipyretic therapy with ibuprofen did not improve survival in patients with sepsis. Recent data demonstrating fever-induced expression of several heat-shock proteins that are protective against sepsis raise the concern that antipyretic therapy actually may potentiate the adverse effects of sepsis in some patients.⁴⁷

- Fever may shorten viral illnesses.

This point also has been addressed previously in the discussion about mechanism of fever. The use of antipyretic treatment may have an adverse effect on the human immune system. Adults infected with rhinovirus treated with either aspirin or acetaminophen had increased and more prolonged viral shedding than the placebo control group. Children with varicella who are treated with acetaminophen have been shown to have a longer duration of lesions than a placebo group.⁴⁸ Recent reports also have shown enhancement of resistance to viral and bacterial infections by pyrogenic cytokines.^{49,50}

Additional reasons for use of antipyretic medications in adults

- Reduction of cognitive impairment.

Antipyretic therapy might be beneficial in reducing the confusion, dementia, and mental dysfunction that sometimes is associated with fever. In one study, fever-associated cognitive impairment was reduced with aspirin.⁵¹ In another study, increased anxiety and depression together with worsened memory were noted in patients with laboratory-induced fever relative to control patients.⁵² Unfortunately, this study did not look at the use of antipyretic therapy to decrease such symptoms.

Possibly inappropriate reasons often cited to treat fever:

- Parent comfort;
- Provider comfort; and
- The urge to do something.

Despite the pervasive application of antipyretics by physicians, nurses, pharmacists, and parents, it remains unclear whether reducing the core temperature actually will benefit the

Table 3. Reasons Cited for Use of Antipyretic Medications in Children

- Patient comfort
- Possibly useful
- Reduction of morbidity and mortality
- Unsubstantiated
- Fever may increase survival in sepsis
- Prevention of febrile seizures
- Unsubstantiated
- Antipyretics shown NOT protective

Additional Reasons for Use of Antipyretic Medications in Adults

- Reduction of cognitive impairment
- Substantiated by some experiments
- Improving outcome in patients with stroke or brain injury
- Unproven—theoretically valid
- Increased metabolic stress and increased oxygen demand caused by an elevated temperature, particularly in patients with...
 - Poor cardiac reserves
 - Poor pulmonary reserves
 - Unproven—theoretically valid

Probably Inappropriate Reasons often Cited to Treat Fever:

- Parent comfort
- Provider comfort
- The urge to do something

febrile patient.⁵³ This feeling of the importance of treatment of the fever is pervasive.

Indeed, in several studies, the speed at which the fever fell was considered an important variable.⁵⁴⁻⁵⁶ In one study, the caregivers would awaken their child to take a temperature every hour or less and give antipyretics during a febrile illness. This is certainly not looking out for the patient's comfort.³⁵

The patient's real disease will not disappear just because the fever has been treated, no matter how reassuring this is to provider, nursing staff, and parent alike. Indeed, a small older pediatric study showed that appropriate changes in antibiotic regimens were delayed for children who received antipyretics compared to those who had none.⁵⁷

The wise emergency provider always realizes that they are never treating just a child, but also treating the parents. Indeed, that provider also may be treating him/herself and/or the nursing staff when faced with a febrile child. The physician may realize that fever is not the disease, but remain under significant pressure from multiple sources to make the child better by treating the fever.⁵⁸ (A similar battle is being waged about the inappropriate use of antibiotics for minor upper respiratory illnesses.)

- The possibility of febrile seizures.

Children between 3 months and 5 years have an incidence of seizures during episodes of fever at a frequency of between 2 and 5% in the United States and Western Europe.⁵⁹ The majority of children with febrile seizures have temperatures above 39.0°C at the time of their seizure. A common myth is that treating a fever can prevent a febrile seizure. This myth is often cited by parents

of children who have had a febrile seizure and may be echoed by nursing staff.

Unfortunately, there is no evidence to show that antipyretic therapy is effective in prevention of these seizures.⁶⁰ More recent studies have shown that it doesn't matter whether acetaminophen is given in moderate doses or in high doses. It still fails to reduce the rate of recurrence of febrile seizures.⁶¹⁻⁶³ Ibuprofen also fails to prevent recurrent febrile seizures.⁶⁴ There is simply no evidence that bringing the fever down by any means will stop or prevent a febrile seizure. The practice of giving acetaminophen or ibuprofen around the clock is not supported in the literature and may contribute to parental fever phobia.

- The child will have (brain or other organ) damage from the fever.

(This point has been previously discussed and there is little clinical validity to this argument. The emergency physician should carefully separate the consequences of fever from those of hyperthermia.)

- The height of the fever is a marker for serious illness. (This may or may not be true in the post-haemophilus influenza immunization era.)

Numerous early investigators of the consequences of fever have noted that there is a significant correlation between the height of fever and the incidence of serious bacterial infections in children.⁶⁵⁻⁶⁹ In these studies, the likelihood of such bacterial infections increases sharply in children with a temperature greater than 40°C. These studies may or may not continue to be valid in the face of newer epidemiology caused by the immunizations currently recommended and offered to children. The emergency physician should have a heightened suspicion for bacterial illness in these patients, but also should remember that these studies were conducted prior to institution of haemophilus influenza immunization. The emergency physician also should be aware that many viral illnesses can provoke high fevers. While the height of the fever has some positive correlation, the cogent emergency physician must realize that it is an inefficient discriminator as some children with serious bacterial illness will not have an elevated temperature.

Many investigators have suggested that the response of a fever to the administration of an antipyretic may be an important diagnostic maneuver. "When the fever falls and the child looks better, then that illness is not serious." There are two parts to this myth:

- Resolution of the fever with antipyretics will *not* indicate that the illness is less serious.

Unfortunately, resolution of fever does not appear to be an appropriate diagnostic maneuver when the response of children with bacteremic and non-bacteremic infections are compared. Of six such investigations in recent history, only one found that there was a difference in the response of children with bacteremic or non-bacteremic fever.⁷⁰⁻⁷⁵ Unlike the five prospective investigations that showed no difference, this single study was retrospective. In short, fevers due to serious infections are just as responsive to antipyretic therapy as innocuous infections.

Resolution of the fever with antipyretics is thought by some to be an important discriminator in the treatment decision of the

child. Unfortunately, the efficacy of antipyretics as a risk stratification factor for the presence of serious bacterial illness in the febrile child has never been proven. In fact, in at least one very well done study, the reaction of the child to an antipyretic was unable to distinguish between children with non-bacterial infections, meningitis, and bacteremia.⁷⁶ Failure of antipyretics to control the fever has not been proven to correspond with the severity of the illness.⁷⁴

- Improved appearance of the child (independent of the child's temperature) after administration of antipyretics *does not* mean that the illness is less serious.

As noted above, all of the antipyretic medications have additional actions, including pain relief, that can make the child look better after their effects. There aren't any data showing that improvement of the child is an accurate discriminator of the seriousness of the illness.^{71,73,77,78} (Indeed, the data cited above about the treatment of the temperature argue eloquently that the serious disease process can respond, for a time, to the effects of antipyretic medications.)⁷¹

Indeed, evaluation of the child *prior* to the reduction of the fever correlated better with the presence of a serious bacterial illness than after treatment with an antipyretic.⁷³ Treatment of the fever, with or without improvement of the child, has not done anything to treat or diagnose the process that is causing the fever. Fever is a symptom, not a disease.

Approaches and Mechanisms to Treat the Fever

As this article has previously pointed out, treatment of the fever should be considered in a completely different light than treatment of the disease that is causing the fever.

Various treatments have been used to treat fever for well over two millennia. The marketplace is now replete with drugs capable of suppressing fever. The following treatments have been currently recommended and are discussed in detail:

- Antipyretics to reset the set point;
- Acetaminophen;
- Ibuprofen;
- Aspirin;
- A combination of antipyretics;
- Alternative medications;
- Environmental manipulation;
- Sponging; and
- Undressing the patient.

Antipyretics. The drugs most commonly used today to suppress fever are acetaminophen, ibuprofen, and other non-steroidal anti-inflammatory drugs (NSAIDs), and the salicylates (sodium salicylate and acetylsalicylic acid -ASA).³⁰ Acetaminophen, aspirin, and the NSAIDs all seem to block the conversion of arachidonic acid to prostaglandin E₂ by inhibition of cyclooxygenase (COX) 2. Production of PGE₂ at sites within the hypothalamus is widely thought to be a critical step in the process responsible for raising core temperature after the febrile response is activated.²¹

COX-1 has three folding subunits: a growth-factor-like domain, a membrane binding section, and an enzymatic domain.

COX-1 sites are probably the cause of gastrointestinal side effects such as damage to the stomach lining.

The structure of COX-2 closely resembles that of COX-1. The active site of COX-2 is a little larger and can accommodate larger structures than that of COX-1. COX-2 is induced by inflammatory stimuli and by cytokines. COX-2 sites are probably the source of the anti-inflammatory actions of acetaminophen and the NSAIDs.

Antipyretics block or reverse fever's cytokine-mediated rise in core temperature but do not affect the body temperature in the afebrile state. The reader needs to be aware that antipyretic therapy is not indicated for the treatment of exogenous hyperthermia (such as heat stroke), and is potentially dangerous.

The duration of action of an antipyretic drug depends upon both its concentration at the site of action and whether it is a reversible or an irreversible COX inhibitor. Because aspirin is an irreversible COX inhibitor, its antipyretic activity will persist until new enzyme is generated at the site of action. Other NSAIDs are reversible inhibitors of COX and have activities that vary with the concentration at the site of action.

There is a delay between the time that an antipyretic agent is administered, absorbed, reaches its site of action, and the time that the core temperature begins to fall. This antipyretic latency period also might be influenced by the capacity of arachidonic acid metabolites (such as PGE₂) to decrease the production of pyrogenic cytokines. This delay explains why the maximal effect of the antipyretic agents occurs some three to four hours after oral administration.

Studies of the relative effects, potencies, and timing of administration of the various types of antipyretics have involved multiple clinical settings, numerous dosage patterns and formulations of the antipyretic agents, and differing measures of clinical efficacy. As a result, comparison of these agents in a comprehensive meta-analysis is not possible.

Even though these studies cannot be combined into a meta-analysis, there are several studies that compare ibuprofen with acetaminophen in children that are useful to examine.^{55,79-86} These studies suggest that ibuprofen is possibly more potent than acetaminophen when both are administered by the oral route. The difference in the effects of the two drugs is small, and they have a similar time course.

There is little evidence to support one antipyretic over another when considering effectiveness of the medication in treatment of fever.^{55,84,87,88} No evidence exists that delivery by either rectal or oral is more effective than the other. In the United States, there is no injectable antipyretic. (Ketorolac [Toradol] does have significant antipyretic properties, but is not approved for this indication—see comment about ketorolac below.)

Aspirin. Ancient Assyrian, Egyptian, and Greek physicians all exploited the antipyretic properties of extracts of the bark of the willow tree (*Salix alba*).⁸⁸ Applying Peruvian cinchona bark as an antipyretic dates to the early 1600s.⁹⁰ In 1763, Reverend Edward Stone, suffering from a shortage of cinchona, described the clinical benefits of willow bark to the Royal Society of London.^{91,92} Although his finding appeared novel, it simply confirmed the ancient physician's observations.

Eighty years later, as related in an article on the history of antipyretic agents, salicylic acid first was prepared from a glycoside component of willow bark by Dr Piria.⁹³ Synthesis of salicylic acid often is credited to Kolbe and Lautemann in 1874, but probably belongs to Gerland who synthesized it in 1852.⁹⁴ Felix Hoffman developed acetylsalicylic acid during efforts to find a better tasting form of salicylate. Bayer introduced the new drug as Aspirin in 1899 and sales have been brisk ever since.

Aspirin was implicated by epidemiologic studies in the 1980s to as a cause of Reye's syndrome in children.⁹⁵⁻⁹⁷ It is no longer recommended as an antipyretic in children in the United States. (It still is used as a children's antipyretic in several European and South American countries.)

Acetaminophen (Tylenol). Acetaminophen is a para-aminophenol derivative that inhibits cyclooxygenase and the formation and release of prostaglandin. It is absorbed in the gastrointestinal tract and reaches peak concentration within 30-60 minutes. Adverse reactions include allergic reactions and hepatotoxicity following overdose. Acetaminophen is an excellent antipyretic available in multiple concentrations, flavors, and dosage forms.

The use of acetaminophen for fever is relatively recent. Although precursors of acetaminophen such as acetanilid and phenacetin were developed in the early part of the 19th century, acetaminophen was not used as an antipyretic or analgesic until the 1950s.^{93,98} Phenacetin, a once-popular antipyretic and analgesic, fell out of favor because of a variety of reported side effects, including hepatic toxicity and nephrotoxicity.⁹⁹ Because of the fewer side effects and less severe manifestations of these side effects, acetaminophen replaced phenacetin as an analgesic and antipyretic. Popular use of acetaminophen as an antipyretic and analgesic has blossomed since the 1950s.

Explanation of the antipyretic and analgesic activity of acetaminophen is thought to be based on tissue specific COX inhibition that is not found with the NSAIDs. Acetaminophen easily penetrates the blood-brain barrier and achieves cerebrospinal fluid levels that are comparable to those in the serum.¹⁰⁰ Acetaminophen reduces the production of prostaglandins in brain preparations more potently than it does in other tissues.¹⁰¹ Indeed, central nervous system levels of PGE₂ rise during fever and fall to normal levels when acetaminophen is given.¹⁰²

Acetaminophen has a relatively weak activity against peripheral COX, and thus acts primarily in the central nervous system to reduce fever. This weak peripheral activity accounts for some of the poor anti-inflammatory action of acetaminophen. (Acetaminophen is only 5% as effective as aspirin in inhibition of peripheral COX.)^{103,104}

Despite multiple literature recommendations, popular and professional acceptance, and wide media coverage of the use of acetaminophen to treat fever, at least one literature review and meta-analysis notes that there is a paucity of hard data that actually support the clinical utility of acetaminophen to treat fever.⁴⁶ The authors noted that although acetaminophen is significantly better than placebo at resolving fever within 2 hours, the overall time to resolution of symptoms did not significantly differ

between the two groups. Evaluation of defervescence at 2 hours comparing acetaminophen vs. cooling yielded inconsistent results. Meta-analysis showed no significant difference in adverse events between the comparison groups.

The average maximum decrease of the fever is about 1.6 to 2.0 °C when using the usual dose of 10-20 mg/kg every 4-6 hours. The peak effect occurs at 2 hours with 10 mg/kg dose and 2-4 hours with 20 mg/kg doses. There are multiple brand names, concentrations, and flavors of acetaminophen.

Ibuprofen (Advil, Motrin). Ibuprofen is a non-steroidal anti-inflammatory propionic acid derivative that also inhibits the biosynthesis of prostaglandin. It is absorbed in the gastrointestinal tract and reaches its peak plasma concentration in 2 hours. As with acetaminophen, metabolism takes place in the liver.

Adverse reactions include allergic reactions, exacerbation of asthma, renal toxicity, and gastrointestinal irritation.

Ibuprofen is an excellent antipyretic, available in multiple brands, concentrations, and flavors. This drug works slightly faster than acetaminophen and may be somewhat better at fever reduction. The difference in potency is very small, and the two agents have a similar time course with the maximum activity occurring 3-4 hours after administration.²¹

A 10 mg/kg dose usually is effective for 6-8 hours. There is scant data for use of this drug in children younger than 6 months of age. The parents/caregiver should be counseled against misuse, overuse, and frank overdoses of ibuprofen.

Other NSAIDs. Both pediatric and adult studies of the relative activity of other NSAIDs are sparse. Ketorolac is the only NSAID that can be given intramuscularly or intravenously. It is not indicated for fever, but has been studied, at least in adults, in the treatment of acute fever in the ED.^{106,107} This drug shows some promise in the treatment of fever in patients with intractable vomiting and diarrhea. An intravenous antipyretic possibly may be appropriate in these patients if treatment of the fever is deemed appropriate.

Overdose and Toxicity of Antipyretics. In addition to excessive fever monitoring, caregivers may be dangerously liberal with their antipyretic medications. Caregivers may give antipyretic medications for frankly normal temperatures and may give medicines at inappropriate doses or intervals. The parents/caregiver should be counseled against misuse, overuse, and frank overdoses of acetaminophen or ibuprofen. The risk for iatrogenic overdose with antipyretic agents is increased when:

- the caregivers are confused by the dosing information given. This is particularly true when multiple agents are recommended at multiple times as discussed above,¹⁰⁸
- formulation-specific differences in acetaminophen preparation are not considered;
- adult-strength formulations are used for children;
- sustained-release preparations are administered at dosing intervals less than indicated on the product label;
- caregivers feel that the initial attempts at antipyretic therapy are ineffective and increase the dose under the principle that "more is better." Remember that the maximum effect of antipyretics in common use is between 3-4 hours by the oral

route;

- knowledgeable healthcare providers react inappropriately by treating playful, nontoxic children with low grade temperatures with antipyretic agents in EDs. This gives parents the impression that the fever is the disease.

Toxicity of Aspirin. Aspirin can cause fever in overdose. Aspirin is a relatively non-selective COX inhibitor and can have significant gastrointestinal irritation, even in quite modest doses.

As previously noted, aspirin was implicated by epidemiologic studies in the 1980s as a cause of Reye's syndrome in children.⁹⁵⁻⁹⁷ For this reason alone, parents should be counseled to avoid aspirin as an antipyretic in children, since so many febrile episodes are due to viral illnesses.

Toxicity of Acetaminophen. Because acetaminophen has little peripheral COX inhibition, there are few reports of either gastric or renal toxicity.

While acetaminophen usually is metabolized by glucuronidation and sulfation, in excess, it is metabolized by the p450 2E1 pathway to N-acetyl-p-benzoquinoneimine (NAPQ1). Normally NAPQ1 is conjugated to glutathione. If NAPQ1 is produced in excess during the metabolism of acetaminophen, acute hepatotoxicity results. If glutathione stores are depleted, the risk of acetaminophen-induced hepatic toxicity is markedly increased.¹⁰⁹ Concomitant use of medications, such as rifampin and phenytoin that induce the cytochrome P-450 enzyme system may potentiate toxicity through enhanced metabolism of acetaminophen to NAPQ1.

While the risk of hepatic toxicity in the setting of a massive overdose is well known, only recently has the literature addressed the risk of hepatic injury in doses that are at or slightly above the recommended ranges (4 grams in 24 hours). The results of one study suggest that acetaminophen may be toxic in doses as low as 1.7 times the manufacturer's recommended dose and near those doses often prescribed for fever relief.¹¹⁰ In a recent series involving 71 cases of acetaminophen-induced liver damage, about one-third of the cases resulted from accidental overdoses in patients using the drug for pain relief.¹¹¹

Multiple reports of children with significant hepatotoxic effects, including death, after unintentional overdoses at the hands of parents and other caretakers underscore the potential problems associated with this agent.^{112,113} In most of these accidental overdoses, infants and children are febrile and acutely malnourished. Reduction in caloric or protein intake, combined with multiple doses of acetaminophen can have significant effects in children.

The number of cases reported in the literature is small when compared to the total number of doses of acetaminophen administered. These reports probably are far less than the total number of cases of hepatotoxicity due to this drug. Presumably, other less severely affected patients have not been reported or even diagnosed. Parents should be advised about the potential hepatotoxicity of acetaminophen when given to children that exceed the weight-based recommendations. This is particularly important in the management of the child who is not eating because of the illness.

Toxicity of Ibuprofen. A number of adverse effects has been

attributed to NSAIDs, including ibuprofen. The most important of these are renal dysfunction and gastrointestinal irritation/bleeding.^{87,114} These adverse effects are a direct byproduct of their ability to inhibit COX.

Renal impairment in NSAID users occurs primarily among patients with pre-existing disease or other conditions associated with low intravascular volume or low cardiac output.¹¹⁴ Acute renal failure after ibuprofen overdose and interstitial nephritis after ibuprofen used in clinical doses has been described in patients without pre-existing renal disease.

A number of reports have linked ibuprofen use to renal complications in children, and three have described renal failure in children younger than 15 years who were treated with ibuprofen in therapeutic doses.¹¹⁴ Unfortunately, case reports don't give any estimates of the rate at which renal failure occurs during treatment of children with short-term ibuprofen therapy for fever.

In a large survey examining antipyretic drug toxic effects, Lesko and Mitchell randomized more than 84,000 to one of two doses of oral ibuprofen or acetaminophen and later queried patients about adverse medical effects.¹¹⁵ The median duration of treatment for the fever was 3 days. Of 55,785 patients dosed with recommended doses of ibuprofen, four children developed gastrointestinal bleeding. There were no episodes of Reye's syndrome, anaphylaxis, or acute renal failure among these patients. Autret and his colleagues also found an increase in adverse effects with ibuprofen compared with acetaminophen.⁸² No children had renal failure in this study. Children with serious dehydration, pre-existing renal, endocrine, or neoplastic disease were excluded from the study due to concerns that these children would have a higher incidence of renal failure.

The number of cases reported in the literature is small when compared to the total number of doses of ibuprofen administered. These reports probably are far less than the total number of cases of transient nephrotoxicity or gastrointestinal bleeding/erosions due to this drug. Presumably, other less severely affected patients have not been reported or even diagnosed. Parents should be advised about the potential nephrotoxicity and potential for gastrointestinal irritation of ibuprofen when given to children that exceed the weight-based recommendations.

Alternative Medications. Herbs, vitamins, supplements, homeopathic remedies, and acupuncture all have been used by caregivers and alternative health care providers to treat fever. Western herbalists use tea preparations containing herbs such as bupleurum root or boneset to reduce fever.¹¹⁶ Mild herbs such as peppermint, elderflower, or yarrow are recommended to provide comfort to the child who has a mild fever. Other remedies include elder tea, cinnamon, coriander, feverfew, and ginger. There is no set of randomized, controlled studies that address these alternative medications.¹¹⁶

Corticosteroids also are effective antipyretic agents, but their adverse side effects and effects on the host immune system make them undesirable for antipyretic agents.

Is a Combination of Acetaminophen and Ibuprofen Better Therapy? Parents often are instructed by healthcare providers that although either ibuprofen or acetaminophen is quite effec-

tive, the combination of the two will be more effective than either drug given alone. These healthcare providers teach that alternating ibuprofen and acetaminophen will provide better fever reduction than one drug alone. These practitioners also feel that the additive antipyretic effects will lead to a faster defervescence than either drug alone can provide. (Interestingly, 70% of clinicians in practice for fewer than 5 years endorse this practice, but only 45% of those in practice for more than 5 years will use this practice.)¹¹⁷ The use of such a combination often results when the desired therapeutic response to the initial dose of antipyretic is not observed shortly after administration of the drug.

The American Academy of Pediatrics often is cited as the source for this dosing technique, although the AAP has never endorsed this practice. A computerized search of the medical literature for scientific data supporting the safety and efficacy of this practice was conducted without any success. A single article in *eMedicine* advocated this approach, but offered no evidence to support the practice.¹¹⁸ (None of the references cited in this electronic article offered scientific data that supported the practice.) Other writers have contacted the Food and Drug Administration, and they disapprove of the use of this combination.¹¹⁹ McNeil pharmaceutical company was contacted by Mofenson and colleagues, and the company disclaimed and disagreed with this combination practice.¹²⁰

Both acetaminophen and ibuprofen may have renal toxicity. Acetaminophen accumulates in the renal medulla, and its metabolites can cause cellular necrosis when glutathione is low or absent. Ibuprofen reduces renal blood flow by blocking production of renal prostaglandins and inhibits glutathione production.^{121,122} These effects may be synergistic.^{112,123}

Future Antipyretic Therapy. Cyclooxygenase (COX)-2-selective inhibitors are attracting the attention of pharmaceutical companies for their ability to suppress fever. These companies are working on second- and third-generation derivatives with more potent activity against COX-2, some of which can be administered parenterally.¹²⁴ Preliminary data indicate that these agents may well have substantial antipyretic activity as well as anti-inflammatory activity.

Efforts to reduce the toxicity of antipyretic agents have taken a number of different clinical approaches. This includes the use of enteric coating, parenteral and rectal administration, and concomitant administration of H₂-receptor antagonists.

Perhaps the most important task for the future is to develop more intelligent criteria for the use of antipyretic therapy. To do so requires research into the risk of fever, benefits of fever, and the actual benefits of the various modes of therapy that have been used to treat the fever.

Environmental Manipulation. Physical methods of lowering temperature are based on loss of body heat through evaporation, radiation, convection, or conduction. Other environmental methods include air conditioning, hypothermic (cooling) blankets, and fans. These physical methods may be life-saving for patients with heat stroke or with malignant hyperthermia. Antipyretic agents are the preferred method for fever reduction when such therapy is indicated. Physical methods of lowering temperature

are preferred for the treatment of hyperthermia, heat stroke, malignant hyperthermia, and neuroleptic malignant syndrome.

Two questions that remain to be answered about external cooling methods include: Is the discomfort of physical cooling in young children justified by any reduction in the complications of a high fever such as incidence of seizures? Is external cooling associated with lower morbidity than is treatment with antipyretic drugs alone? The latter question is provoked by the unwanted side effects of all of the physical methods of cooling including induction of shivering, hypermetabolic activity, and sympathetic activation.

External Cooling. External cooling has been used since antiquity to treat fever in both adults and children. Prior to his death in 323 BC, Alexander the Great suffered from a febrile illness that his physicians treated with cool baths.⁹³ It continues to be employed in intensive care units to treat both children and adults with fever. A wide variety of techniques are used for external cooling. These include sponging with multiple different fluids, application of cold packs or ice, and exposure to wind blown from fans (often in conjunction with sponging).

In contrast to antipyretic drugs, external cooling lowers the temperature of febrile patients by overwhelming the body's ability to produce heat. Unless antipyretic agents are given to lower the hypothalamic set point, or shivering is inhibited by other pharmacology, the patient will begin using every body defense (including shivering) to maintain body temperature.

When external cooling is used, evaporation and convection (a continuous spray of water combined with a relatively high velocity fan blowing warm air) will provide, perhaps, the most rapid cooling. This is the basis of the Body Cooling Unit proposed by Khogali.¹²⁵

Sponging/Baths. Multiple physicians, nurses, and caregivers have recommended sponge baths for children. These have ranged from ice water baths, alcohol-water baths, and tepid water baths. Although the use of a water bath or sponging to cool the child appears to be a rapid way to reduce the child's temperature, the result is quite counterintuitive.

Iced water baths are significantly less comfortable and are tolerated poorly by sick children, but are more effective at actually cooling the patient. While less effective in lowering febrile temperatures, sponging with tepid water has been reported to offer greater comfort than sponging with either ice water or alcohol in water.¹²⁶

Before the 1950s, sponging was performed with alcohol (isopropyl or ethyl) mixed with the water or used alone to more rapidly cool the patient. Alcohol has the potential to cause dehydration and hypoglycemia in children, particularly in young children, and should not be used.¹²⁷ Some children developed profound hypoglycemia, subsequent coma, and died.¹²⁸⁻¹³² Despite these recommendations, alcohol still is used in certain communities in the United States and morbidity continues.^{119,133}

Two large randomized trials compared the use of antipyretics and sponge baths for the treatment of young children with temperatures over 38.9°C.¹³⁴⁻¹³⁵ Both trials unequivocally demonstrated the superiority of antipyretic drugs for the reduction of

temperature. Differences in patient comfort were not assessed in these studies.

How about using sponge baths and an antipyretic? Unfortunately, multiple studies also have shown that there is no significant difference in temperature at one hour between children treated with antipyretics and children treated with sponging and antipyretics.^{124,136} The studies did show that there was a transient rapid lowering of the temperature in the first half-hour. Indeed, in one such study the children had a rebound increase in temperature after the bath was terminated.¹³⁷ Newman found that tepid water baths combined with acetaminophen were no more effective than acetaminophen alone.

The use of sponging and/or water baths might be justified if, in fact, it decreased the rate of febrile seizures in children. Since acetaminophen does not protect against seizures and antipyretics cool more efficiently, it is unlikely that the addition of sponging would provide any such decrease in the incidence of seizures. There is, however, no study that proves just this point.

Water baths and sponging are uncomfortable for children. There appears to be increasing discomfort with cooler bath water. If this discomfort actually achieved an objective, then the discomfort could be tolerated as a necessary evil in the care of the patient. (Paradoxically, a major cited reason for treatment of fever is patient comfort.) Despite abundant evidence that shows there isn't any significant difference between the use of water baths in the treatment of fever and the use of antipyretics alone in the treatment of fever, many physicians continue to recommend this treatment. There simply doesn't seem to be any justification for this outdated practice in the treatment of fever in children. This is not true for the treatment of environmental hyperthermia.

Hypothermia Blankets. Hypothermia blankets are not often used in children. In a prospective study of adults treated in an ICU, hypothermia blankets induced wider fluctuations and more episodes of hypothermia than antipyretics alone.¹³⁸ In comparison with usual antipyretic agents, they added no significant cooling effect to the antipyretic effects. They are not recommended for children for this reason. Use of hypothermia blankets was typically initiated by nursing staff, often without the knowledge of physicians. This made interpretation of antibiotic effectiveness and patient progress more difficult.

Evaporative Cooling. Evaporative methods of cooling have been thought to be some of the most effective means of promoting heat loss in the febrile patient. These methods often are thought to be the least likely method to induce shivering. There is no comparative trial that establishes this or any other methods of external cooling as superior.

Undressing the Patient. Perhaps the most physiologic treatment for fever is to simply undress the child. With the increased surface area to mass ratio of the child, radiation loss of heat will rapidly lower a temperature with few side effects or complications.

A common myth is that the patient should be carefully covered with blankets if chills are present. Unfortunately covering up only keeps in the heat. Chills are evidence of the hypothalamus causing the body to generate heat to reach the new set point.

Age-directed Approach to Evaluation of the Disease Causing the Fever

The physician needs to separate the assessment of the disease that is causing the fever from the fever itself. Because the cause of fever in children of different ages has different causes and consequences, the evaluation of possible diseases should be, in part, age-related. Multiple protocols for evaluation of the febrile child have been developed and are vigorously defended by each of their proponent groups and agencies. Each of these protocols is based on the statistical inference that since there is a percentage of children/infants (or even adults) that will have a serious bacterial illness that manifests itself with the first and only symptom of fever, all of the children/infants/adults should be subjected to a certain level of scrutiny (with radiographs/laboratory testing/cultures/in-hospital observation) and therapy (observation/hospitalization/antibiotics) to eliminate or reduce the missed percentage. Each of the proponent groups has its own level of comfort with their practitioners and the chance of missed serious illness and this comfort level drives the resulting protocol.

Summary

There is no question that fever remains a source of great concern to parent and physician alike. Parental fear of fever is certainly responsible for many ED visits and phone calls requesting advice and diagnosis. These concerns focus the parents on fever control and away from the more important issue—that fever is the symptom of a disease process. This inappropriate focus has been augmented by a multi-million dollar industry and its advertising intended to convince parents of the importance of reducing fever.

Fever during systemic infections or inflammation is a normal adaptive response to circulating cytokines. The intrinsic mechanisms that produce the coordinated autonomic, endocrine, and behavioral response of fever appear to depend on systemic inflammatory mediators as neuro-modulators in the central nervous system to regulate the acute phase reaction of fever. The antipyretic medications all block the COX pathway of inflammatory response.

The physician should document a clear need for the use of antipyretic medication (just as with any other medication). Use of multiple medications is not supported by the manufacturers, let alone the data. All fevers should be evaluated as extensively as necessary to identify a site or source of infection.

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Physician CME Questions

121. The normal temperature for a child is 98.6°F (37°C).
 - A. True
 - B. False
122. Which of the following represents fever?
 - A. A temperature of 104.5°F after running a marathon in hot weather
 - B. A temperature of 101.2°F in a 4-year-old with the sniffles
 - C. A temperature of 102.3°F in a steel worker at work in a foundry
 - D. All of the above
123. Which of the following is *not* a recommended method of measuring temperature in a 4-year-old child?
 - A. Rectal thermometer
 - B. Ear thermometer (IRED)
 - C. Oral thermometer
 - D. Axillary thermometer

124. Which of the following statements accurately describe(s) a fever?
 - A. An alteration of the body's temperature set-point to a higher temperature as regulated by the hypothalamus
 - B. An overwhelming of the patient's thermal regulatory mechanism by a heat source
 - C. A temperature of 104.5°F in a 4-year-old
 - D. All of the above
125. The perceived gold standard for the measurement of temperature in children is:
 - A. Oral
 - B. Rectal
 - C. Tympanic
 - D. Axillary
126. Once a fever starts to rise, unless the physician treats it, it will continue to rise to dangerous levels.
 - A. True
 - B. False
127. Which of the following is/are valid reasons to treat fever?
 - A. A temperature of 102.5°F in a playful, smiling 3-year-old
 - B. As a diagnostic maneuver to ensure that the fever is not caused by something serious
 - C. For patient comfort
 - D. All of the above
128. Which of the following statements is true?
 - A. Fever will cause brain damage.
 - B. Vigorous use of antipyretics in young children will prevent febrile seizures.
 - C. Studies have reported a benefit of fever in the overall outcome of infections.
 - D. The therapeutic index of acetaminophen is safe in children at all times.
129. Which of the following mechanisms can cause an elevated temperature?
 - A. Immunizations
 - B. Malignancy
 - C. Teething
 - D. All of the above
130. Inappropriate reasons to treat a fever include all of the following *except*:
 - A. parent comfort.
 - B. provider comfort.
 - C. patient comfort.
 - D. the urge to do something.

CME Answer Key

121. B; 122. B; 123. C; 124. A; 125. B; 126. B; 127. C; 128. C; 129. D; 130. C

The Practical Journal for Emergency Physicians

Emergency Medicine Reports

Pediatric Fever

Recommended Temperature Measurement Techniques

AGE	RECOMMENDED TECHNIQUE
Birth to 2 years	<ol style="list-style-type: none"> 1. Rectal 2. Tympanic—May have some inaccuracy in the very young, depending on the manufacturer and technique used. 3. Axillary—screening in neonates
Older than 2 years up to 5 years	<ol style="list-style-type: none"> 1. Rectal 2. Tympanic 3. Axillary
Older than 5 years	<ol style="list-style-type: none"> 1. Oral 2. Tympanic 3. Axillary

Thoughts to Share with Patients about Fever

- Fever is a normal response to many disease processes and is a useful defense against many illnesses.
- Fever is a symptom, not a disease.
- Fever will persist until the disease process resolves.
- Fever tops out at about 106°F. It won't keep rising.
- Fever determination does not need to be exact. (There really isn't any clinical difference between 101.4 and 101.6°F.)
- Temperatures should be taken about every 2-4 hours at most—certainly not more frequently. (With the physiology involved, it takes about 1-2 hours for the body to change a temperature, so you can't expect the fever to resolve in less time.)
- Fever does not always need to be treated (particularly low-grade fever).
- Antipyretic medications are medications with potentially serious problems in overdose.
- Overdoses are much more common when medications are mixed.
- Antipyretic medications should be used as therapy for patient comfort rather than control of the fever. If the patient is comfortable, you don't need to control the fever—the body will do that just fine.
- If you are worried about treating the fever for the comfort of the patient, don't use baths or sponging—these are among the most uncomfortable therapies for the patient.
- Treating a fever won't prevent febrile seizures. Some folks think that the febrile seizure is related to the rate of rise of the temperature, so treating a fever inappropriately would give *more* chances for febrile seizures, not less. (We can prevent them, but it takes anti-seizure medicine, not anti-fever medicine.)
- Clinical appearance may be more important than the height of the fever. (A fever greater than 104°F may have a higher incidence of bacterial disease, but this means the physician should consider more evaluation of the cause, not necessarily more worry about the fever.)

Reasons Cited for Use of Antipyretic Medications in Children

- Patient comfort
- Possibly useful
- Reduction of morbidity and mortality
- Unsubstantiated
- Fever may increase survival in sepsis
- Prevention of febrile seizures
- Unsubstantiated
- Antipyretics shown NOT protective

Additional Reasons for Use of Antipyretic Medications in Adults

- Reduction of cognitive impairment
- Substantiated by some experiments
- Improving outcome in patients with stroke or brain injury
- Unproven—theoretically valid
- Increased metabolic stress and increased oxygen demand caused by an elevated temperature, particularly in patients with...
 - Poor cardiac reserves
 - Poor pulmonary reserves
 - Unproven—theoretically valid

Probably Inappropriate Reasons often Cited to Treat Fever:

- Parent comfort
- Provider comfort
- The urge to do something

Disposition

Real goals for real medicine include:

- Triage the critically ill child into appropriate care.
- Clinicians should document a therapeutic need to manage fever such that the benefits of treating the fever clearly outweigh the risks of treatment.

- Treat the child, not the number.

- Administer an age/weight appropriate dose and formulation of a single agent at an appropriately scheduled interval.

Acetaminophen 10-15 mg/kg per dose, not to exceed five doses in 24 hours, is the author's preferred pharmacologic agent.

- Identify the contributing diagnosis.

- Many fevers will have an identifiable cause. The older the child, the more likely that the cause will be identifiable from history and/or physical examination.

- Once the cause has been identified, then consider whether to treat the fever per se.

- Eighty to ninety percent of fevers are caused by an infection, either viral or bacterial.

- The younger the child, the higher the index of suspicion for serious bacterial infections as an etiology—despite the degree of temperature elevation.

- Several studies suggest that children with temperatures greater than 41°C (105.8°F) have a greater chance of having a bacterial illness. Give consideration to an extended workup (including blood cultures) in these patients.

- Children 3-24 months of age with a low-grade fever, no risk factors for serious bacterial illness, no localized signs of infection, non-toxic appearance, and without significant irritability require only close follow-up. These patients do not routinely need laboratory evaluation or chest x-ray. There is no indication for empiric antibiotics in these children.

- Criteria for discharge from the ED should not include reduction of the fever to a certain arbitrary level. There is no evidence that indicates that fever reduction is needed for discharge from the ED.

- Provide support for home care.

- If antipyretics are chosen for patient/parent/caregiver comfort, ensure that clear instructions using a *single* agent are given with a weight-appropriate dose.

- Ensure that the patient and parents are aware that there is little correlation between serious illness and the response to antipyretics.

- Ensure that the patient and parents are aware that antipyretics *do not treat* the disease.

- Don't ever recommend or use a formulation of acetaminophen that you aren't familiar with ... read the label and ensure that you are prescribing the appropriate dose per weight or have the patient ask to speak with a pharmacist.

- Ensure that there is a plan for follow-up care (in case your analysis is not correct).

Supplement to *Emergency Medicine Reports*, June 13, 2005: "Pediatric Fever: Myths and Management" Author: **Charles E. Stewart, MD, FACEP**, Emergency Physician, Colorado Springs, CO. **Peer Reviewers:** **Ronald M. Perkin, MA**, Professor and Chairman, Department of Pediatrics, Brody School of Medicine at East Carolina University, Greenville, NC; and **Christian Montagano, DO**, Emergency Physician, Assistant Director of the Emergency Department, Our Lady of Lourdes Hospital, Camden, NJ.

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