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Fever and Antipyretic Use in Children

the Section on Clinical Pharmacology and Therapeutics and Committee on Drugs

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Guidance for the Clinician in Rendering Pediatric Care

Clinical Report—Fever and Antipyretic Use in Children

abstract

Fever in a child is one of the most common clinical symptoms managed by pediatricians and other health care providers and a frequent cause of parental concern. Many parents administer antipyretics even when there is minimal or no fever, because they are concerned that the child must maintain a "normal" temperature. Fever, however, is not the primary illness but is a physiologic mechanism that has beneficial effects in fighting infection. There is no evidence that fever itself worsens the course of an illness or that it causes long-term neurologic complications. Thus, the primary goal of treating the febrile child should be to improve the child's overall comfort rather than focus on the normalization of body temperature. When counseling the parents or caregivers of a febrile child, the general well-being of the child, the importance of monitoring activity, observing for signs of serious illness, encouraging appropriate fluid intake, and the safe storage of antipyretics should be emphasized. Current evidence suggests that there is no substantial difference in the safety and effectiveness of acetaminophen and ibuprofen in the care of a generally healthy child with fever. There is evidence that combining these 2 products is more effective than the use of a single agent alone; however, there are concerns that combined treatment may be more complicated and contribute to the unsafe use of these drugs. Pediatricians should also promote patient safety by advocating for simplified formulations, dosing instructions, and dosing devices. *Pediatrics* 2011;127:580–587

INTRODUCTION

Fever is one of the most common clinical symptoms managed by pediatricians and other health care providers and accounts, by some estimates, for one-third of all presenting conditions in children.[1] Fever in a child commonly leads to unscheduled physician visits, telephone calls by parents to their child's physician for advice on fever control, and the wide use of over-the-counter antipyretics.

Parents are frequently concerned with the need to maintain a "normal" temperature in their ill child. Many parents administer antipyretics even though there is either minimal or no fever.[2] Approximately one-half of parents consider a temperature of less than 38°C (100.4°F) to be a fever, and 25% of caregivers would give antipyretics for temperatures of less than 37.8°C (100°F).[1,3] Furthermore, 85% of parents (n = 340) reported awakening their child from sleep to give antipyretics.[1] Unfortunately, as many as one-half of parents administer incorrect doses of antipyretics; approximately 15% of parents give supratherapeutic doses of acetaminophen or ibuprofen.[4] Caregivers who under-

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KEY WORDS
fever, antipyretics, children

ABBREVIATIONS
NSAID—nonsteroidal anti-inflammatory drug

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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stand that dosing should be based on weight rather than age or height of fever are much less likely to give an incorrect dose.[4]

Physicians and nurses are the primary source of information on fever management for parents and caregivers, although there are some disparities between the views of parents and physicians regarding antipyretic treatment.[1] The most common indications for initiating antipyretic therapy by pediatricians are a temperature higher than 38.3°C (101°F) and improving the child's overall comfort.[5] Although only 13% of pediatricians specifically cite discomfort as the primary indication for antipyretic use,[6] this intent is generally implied in their recommendations. Most pediatricians (80%) believe that a sleeping ill child should not be awakened solely to be given antipyretics.[5]

Antipyretic therapy will remain a common practice by parents and is generally encouraged and supported by pediatricians. Thus, pediatricians and health care providers are responsible for the appropriate counseling of parents and other caregivers about fever and the use of antipyretics.[7]

PHYSIOLOGY OF FEVER

It should be emphasized that fever is not an illness but is, in fact, a physiologic mechanism that has beneficial effects in fighting infection.[8–10] Fever retards the growth and reproduction of bacteria and viruses, enhances neutrophil production and T-lymphocyte proliferation, and aids in the body's acute-phase reaction.[11–14] The degree of fever does not always correlate with the severity of illness. Most fevers are of short duration, are benign, and may actually protect the host.[15] Data show beneficial effects on certain components of the immune system in fever, and limited data have revealed that fever actually helps the body recover more quickly from viral infections, although the fever may result in discomfort in children.[11,16–18] Evidence is inconclusive as to whether treating with antipyretics, particularly ibuprofen alone or in combination with acetaminophen, increases the risks of complications with certain types of infections.[19,20] Potential benefits of fever reduction include relief of patient discomfort and reduction of insensible water loss, which may decrease the occurrence of dehydration. Risks of lowering fever include delayed identification of the underlying diagnosis and initiation of appropriate treatment and drug toxicity.

There is no evidence that children with fever, as opposed to hyperthermia, are at increased risk of adverse outcomes such as brain damage.[7,9,21–23] Fever is a common and normal physiologic response that results in an increase in the hypothalamic "set point" in response to endogenous and exogenous pyrogens.[9,23] In contrast, hyperthermia is a rare and pathophysiologic response with failure of normal homeostasis (no change in the hypothalamic set point) that results in heat production that exceeds the capability to dissipate heat.[9,23] Characteristics of hyperthermia include hot, dry skin and central nervous system dysfunction that results in delirium, convulsions, or coma.[23] Hyperthermia should be addressed promptly, because at temperatures above 41°C to 42°C, adverse physiologic effects begin to occur.[7,9,24] Studies of health care workers, including physicians, have revealed that most believe that the risk of heat-related adverse outcomes is increased with temperatures above 40°C (104°F), although this belief is not justified.[5,23,25–27] A child with a temperature of 40°C (104°F) attributable to a simple febrile illness is quite different from a child with a temperature of 40°C (104°F) attributable to heat stroke. Thus, extrapolating similar outcomes from these different illnesses is problematic.

TREATMENT GOALS

A discussion of the use of antipyretics in febrile children must begin with consideration of the therapeutic end points. When counseling families, physicians should emphasize the child's comfort and signs of serious illness rather than emphasizing normothermia. A primary goal of treating the febrile child should be to improve the child's overall comfort. Most pediatricians observe, with some supporting data from research, that febrile children have altered activity, sleep, and behavior in addition to decreased oral intake.[28] Unfortunately, there is a paucity of clinical research addressing the extent to which antipyretics improve discomfort associated with fever or illness. It is not clear whether comfort improves with a normalized temperature, because external cooling measures, such as tepid sponge baths, can lower the body temperature without improving comfort.[7,29] The use of alcohol baths is not an appropriate cooling method, because there have been reported adverse events associated with systemic absorption of alcohol.[30] Furthermore, antipyretics have other clinical outcomes, including analgesia, which may enhance their overall clinical effect. Regardless of the exact mechanism of action, many physicians continue to encourage the use of antipyretics with the belief that most of the benefits are the result of improved comfort and the accompanying improvements in activity and feeding, less irritability, and a more reliable sense of the child's overall clinical condition. Because these are the most important benefits of antipyretic therapy, it is of paramount importance that parental counseling focus on monitoring of activity, observing for signs of seri-

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ous illness, and appropriate fluid intake to maintain hydration.

The desire to improve the overall comfort of the febrile child must be balanced against the desire to simply lower the body temperature. It is well documented that there are significant concerns on the part of parents, nurses, and physicians about potential adverse effects of fever that have led to a description in the literature of "fever phobia."[31] The most consistently identified serious concern of caregivers and health care providers is that high fevers, if left untreated, are associated with seizures, brain damage, and death.[1,25,32,33] It is argued that by creating undue concern over these presumed risks of fever, for which there is no clearly established relationship, physicians are promoting an exaggerated desire in parents to achieve normothermia by aggressively treating fever in their children.

There is no evidence that reducing fever reduces morbidity or mortality from a febrile illness. Possible exceptions to this could be children with underlying chronic diseases that may result in limited metabolic reserves or children who are critically ill, because these children may not tolerate the increased metabolic demands of fever.[34] Finally, there is no evidence that antipyretic therapy decreases the recurrence of febrile seizures.[22,35,36]

Despite insufficient evidence, many pediatricians recommend the routine practice of pretreatment with acetaminophen or ibuprofen before a patient receives immunizations to decrease the discomfort associated with the injections and subsequently at the injection sites and to minimize the febrile response.[9,17,37–39] In addition, results of 1 recent study suggested the possibility of decreased immune response to vaccines in patients treated early with antipyretics.[40]

Although the available literature is limited on the actual risks of fever and the benefits of antipyretic therapy, it is recognized that improvement in patient comfort is a reasonable therapeutic objective. Furthermore, at this time, there is no evidence that temperature reduction, in and of itself, should be the primary goal of antipyretic therapy.

Acetaminophen

After sufficient evidence emerged of an association between salicylates and Reye syndrome, acetaminophen essentially replaced aspirin as the primary treatment of fever. Acetaminophen doses of 10 to 15 mg/kg per dose given every 4 to 6 hours orally are generally regarded as safe and effective. Typically, the onset of an antipyretic effect is within 30 to 60 minutes; approximately 80% of children will experience a decreased temperature within that time (Table 1).

Although alternative dosing regimens have been suggested,[41–43] no consistent evidence has indicated that the use of an initial loading dose by either the oral (30 mg/kg per dose) or rectal (40 mg/kg per dose) route improves antipyretic efficacy. The higher rectal dose is often used in intraoperative conditions but cannot be recommended for use in routine clinical care.[44,45] The use of higher loading doses in clinical practice would add potential risks for dosing confusion leading to hepatotoxicity; therefore, such doses are not recommended.

Although hepatotoxicity with acetaminophen at recommended doses has been reported rarely, hepatoxicity is most commonly seen in the setting of an acute overdose. In addition, there is significant concern over the possibility of acetaminophen-related hepatitis in the setting of a chronic overdose. The most commonly reported scenarios are those of children receiving multiple supratherapeutic doses (ie, >15 mg/kg per dose) or frequent administration of appropriate single doses at intervals of less than 4 hours, which has resulted in doses of more than 90 mg/kg per day for several days.[46,47] Giving an adult preparation of acetaminophen to a child may result in supratherapeutic dosing. In 1 case series,[46] half of the children with hepatotoxicity had received adult preparations of acetaminophen.

One safety concern is the effect of acetaminophen on asthma-related symptoms; although asthma has also been associated with acetaminophen use, causality has not been demonstrated.[48–51]

Ibuprofen

The use of ibuprofen to manage fever has been increasing, because it seems to have a longer clinical effect related to lowering of the body temperature

TABLE 1 Antipyretic Information

Variable	Acetaminophen	Ibuprofen
Decline in temperature, °C	1–2	1–2
Time to onset, h	<1	<1
Time to peak effect, h	3–4	3–4
Duration of effect, h	4–6	6–8
Dose, mg/kg	10–15 every 4 h	10 every 6 h
Maximum daily dose, mg/kg	90 mg/kg[a]	40 mg/kg
Maximum daily adult dose, g/d	4	2.4
Lower age limit, mo[b]	3	6

Data represent approximate averages from referenced sources.[42,43,52,54,71,82]

[a] Label is for 75 mg/kg; 90 mg/kg per day should be limited to less than 3 consecutive days.[83–85]

[b] Unless specifically recommended by a health care provider for the younger patient and, then, only after the infant has been examined by a health care provider.

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(Table 1). Studies in which the effectiveness of ibuprofen and acetaminophen were compared have yielded variable results; the consensus is that both drugs are more effective than placebo in reducing fever and that ibuprofen (10 mg/kg per dose) is at least as effective as, and perhaps more effective than, acetaminophen (15 mg/kg per dose) in lowering body temperature when either drug is given as a single or repetitive dose.[52–57] Data also show that the height of the fever and the age of the child (rather than the specific medication used) may be the primary determinants of the efficacy of antipyretic therapy; those who have a higher fever and are older than 6 years show decreased efficacy or response to antipyretic therapy.[54] Studies that compare the effect of ibuprofen versus acetaminophen on children's behavior and comfort are generally lacking.

There is no evidence to indicate that there is a significant difference in the safety of standard doses of ibuprofen versus acetaminophen in generally healthy children between 6 months and 12 years of age with febrile illnesses.[58] Similar to other nonsteroidal anti-inflammatory drugs (NSAIDs), ibuprofen can potentially cause gastritis,[59,60] although no data suggest that this is a common occurrence when used on an acute basis, such as during a febrile illness.[58] However, there have been case reports of bleeding, gastritis, and ulcers of the stomach, duodenum, and esophagus associated with many NSAIDs, including ibuprofen, even when used in typical antipyretic and analgesic doses.[59,60] Ibuprofen does not seem to worsen asthma symptoms.

Concern has been raised over the nephrotoxicity of ibuprofen. In numerous case reports, children with febrile illnesses developed renal insufficiency when treated with ibuprofen or other NSAIDs. Thus, caution is encouraged when using ibuprofen in children with dehydration or with complex medical illnesses.[61–63] In children with dehydration, prostaglandin synthesis becomes an increasingly important mechanism for maintaining appropriate renal blood flow. The use of ibuprofen or any NSAID interferes with the renal effects of prostaglandins, which reduces renal blood flow and potentially precipitates or worsens renal dysfunction.[61,63] However, it is not possible to determine the actual incidence of ibuprofen-related renal insufficiency after short-term use, because it has not been systematically investigated or reported.[64] Children who are at greatest risk of ibuprofen-related renal toxicity are those with dehydration, cardiovascular disease, preexisting renal disease, or the concomitant use of other nephrotoxic agents.[62] Another potential group at risk is infants younger than 6 months because of the possibility of differences in ibuprofen pharmacokinetics and developmental differences in renal function.[65] Data are inadequate to support a specific recommendation for the use of ibuprofen for fever or pain in infants younger than 6 months (there are dosing data for neonatal closure of patent ductus arteriosus[66,67]), although the package insert states to "ask a doctor" for guidance on its use in this population. Another potential risk associated with the use of ibuprofen is the possible association between ibuprofen and varicella-related invasive group A streptococcal infection.[68,69] However, at the time of this report, data were insufficient to support a causal relationship between ibuprofen and invasive group A streptococcal disease.

Alternating or Combination Therapy

A practice frequently used to control fever is the alternating or combined use of acetaminophen and ibuprofen. In a convenience sample survey of 256 parents or caregivers, 67% reported alternating acetaminophen and ibuprofen for fever control, 81% of whom stated that they had followed the advice of their health care provider or pediatrician.[70] Although 4 hours was the most frequent interval, parents reported alternating therapy every 2, 3, 4, and 6 hours, which suggests that there is no consensus on dosing instructions.

At the time of this report, 5 studies had been identified that compared alternating ibuprofen and acetaminophen versus either acetaminophen or ibuprofen as single agents.[71–75] Initially, changes in temperature were similar for all groups in these studies, regardless of therapy. However, 4 or more hours after the initiation of treatment, lower temperature was consistently observed in the combination-treatment groups. For example, 6 and 8 hours after the initiation of the study, a greater percentage of children were afebrile in the combination group (83% and 81%, respectively) compared with those in the group that received ibuprofen alone (58% and 35%, respectively).[71] Only 1 study[72] evaluated issues related to stress and comfort and found lower stress scores and less time missed from child care in the combination-treatment group. Another study[73] showed a trend toward a normalization of fever-related symptoms by 24 and 48 hours after institution of therapy, but these trends disappeared by day 5.

Although the aforementioned studies provide some evidence that combination therapy may be more effective at lowering temperature, questions remain regarding the safety of this practice as well as the effectiveness in improving discomfort, which is the primary treatment end point. The possibility that parents will either not receive or not understand dosing instructions, combined with the wide array of formulations that contain

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these drugs, increases the potential for inaccurate dosing or overdosing.[76,77] Finally, this practice may only promote the fever phobia that already exists.

Although there is some evidence that combination therapy may result in a lower body temperature for a greater period of time, there is no evidence that combination therapy results in overall improvement in other clinical outcomes. Also, these studies have not contained adequate numbers of subjects to fully evaluate the safety of this practice. Therefore, there is insufficient evidence to support or refute the routine use of combination treatment with both acetaminophen and ibuprofen. Practitioners who choose to follow this practice should counsel parents carefully regarding proper formulation, dosing, and dosing intervals and emphasize the child's comfort instead of reduction of fever.

INSTRUCTIONS FOR CAREGIVERS

It is critically important for pediatricians to clearly describe the appropriate use (ie, formulation, dose, and dosing interval) of acetaminophen and ibuprofen to caregivers (Table 1). Child safety will be further enhanced by clear labeling and the development of simplified dosing methods, standardized drug concentrations, and standardized delivery devices.[78–80] Cough-and-cold products that contain acetaminophen and ibuprofen should not be given to children because of the possibility that parents may unintentionally give their child simultaneous doses of an antipyretic and a cough-and-cold medication that contains the same antipyretic. In addition, there is a lack of proven efficacy for this class of combination products for children. For children who require liquid preparations, physicians should encourage families to only use 1 formulation. Acetaminophen is the most common single ingredient implicated in emergency department visits for medication overdoses among children, and more than 80% of these emergency visits are a result of unsupervised ingestions[81]; therefore, proper handling and storage of antipyretics should be encouraged.

SUMMARY

Appropriate counseling on the management of fever begins by helping parents understand that fever, in and of itself, is not known to endanger a generally healthy child. In contrast, fever may actually be of benefit; thus, the real goal of antipyretic therapy is not simply to normalize body temperature but to improve the overall comfort and well-being of the child. Acetaminophen and ibuprofen, when used in appropriate doses, are generally regarded as safe and effective agents in most clinical situations. However, as with all drugs, they should be used judiciously to minimize the risk of adverse drug effects and toxicity. Combination therapy with acetaminophen and ibuprofen may place infants and children at increased risk because of dosing errors and adverse outcomes, and these potential risks must be carefully considered. When counseling a family on the management of fever in a child, pediatricians and other health care providers should minimize fever phobia and emphasize that antipyretic use does not prevent febrile seizures. Pediatricians should focus instead on monitoring for signs/symptoms of serious illness, improving the child's comfort by maintaining hydration, and educating parents on the appropriate use, dosing, and safe storage of antipyretics. To promote child safety, pediatricians should advocate for a limited number of formulations of acetaminophen and ibuprofen and for clear labeling of dosing instructions and an included dosing device for antipyretic products.

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