Management of Fever in Children: Summary of the Italian Pediatric Society Guidelines

Elena Chiappini, PhD1; Nicola Principi, MD2; Riccardo Longhi, MD3; Pier-Angelo Tovo, MD4; Paolo Becherucci, MD5; Francesca Bonsignori, MD1; Susanna Esposito, MD2; Filippo Festini, RN1; Luisa Galli, MD1; Bice Lucchesi, RPh6; Alessandro Mugelli, MD7; and Maurizio de Martino, MD1; for the Writing Committee of the Italian Pediatric Society Panel for the Management of Fever in Children*

1Department of Pediatrics, University of Florence, Florence, Italy; 2Department of Maternal and Pediatric Sciences, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, University of Milan, Milan, Italy; 3Pediatric Unit, Sant’Anna Hospital, Como, Italy; 4Department of Pediatrics, University of Turin, Turin, Italy; 5Primary care practice, Florence, Italy; 6Health Authority 1, Massa, Italy; and 7Department of Preclinical and Clinical Pharmacology, University of Florence, Florence, Italy

ABSTRACT

Objective: This article summarizes the Italian Pediatric Society guideline on the management of the signs and symptoms of fever in children, prepared as part of the National Guideline Program (NGLP).

Methods: Relevant publications in English and Italian were identified through searches of MEDLINE and the Cochrane Database of Systematic Reviews from their inception through December 31, 2007. Based on the consensus of a multidisciplinary expert panel, the strength of the recommendations was categorized into 5 grades (A–E) according to NGLP methodology.

Summary: In the health care setting, axillary measurement of body temperature using a digital thermometer is recommended in children aged <4 weeks; for children aged ≥4 weeks, axillary measurement using a digital thermometer or tympanic measurement using an infrared thermometer is recommended. When body temperature is measured at home by parents or caregivers, axillary measurement using a digital thermometer is recommended for all children. Children who are afebrile when seen by the clinician but are reported to have had fever by their caregivers should be considered febrile. In special circumstances, high fever may be a predictive factor for severe bacterial infection. Use of physical methods of reducing fever is discouraged, except in the case of hyperthermia. Use of antipyretics—paracetamol (acetaminophen) or ibuprofen—is recommended only when fever is associated with discomfort. Combined or alternating use of antipyretics is discouraged. The dose of antipyretic should be based on the child’s weight rather than age. Whenever possible, oral administration of paracetamol is preferable to rectal administration. Use of ibuprofen is not recommended in febrile children with chickenpox or dehydration. Use of ibuprofen or paracetamol is not contraindicated in febrile children with asthma. There is insufficient evidence to form any recommendations concerning fever in children with other chronic conditions, but caution is advised in cases of severe hepatic/renal failure or severe malnutrition. Newborns with fever should always be hospitalized because of the elevated risk of severe disease; paracetamol may be used, with the dose adjusted to gestational age. Use of paracetamol or ibuprofen is not effective in preventing febrile convulsion or the adverse effects of vaccines. (Clin Ther. 2009;31:1826–1843) © 2009 Excerpta Medica Inc.

Key words: guidelines, children, fever, antipyretics.

INTRODUCTION

“Fever phobia” among parents and caregivers of children is widespread in Europe, and prescribing practices do not always conform to the scientific evidence.1–6 Overdoses of antipyretic agents have been reported...

*Other members are listed in the Acknowledgments.

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with increasing frequency.\textsuperscript{7–9} Considering concerns voiced in the literature,\textsuperscript{8,10,11} the Italian Pediatric Society recently developed and issued a national guideline for the management of children with fever for health care providers (including primary care physicians, hospital pediatricians, nurses, and pharmacists) and parents/caregivers.\textsuperscript{12}

**METHODS**

The guideline was developed according to methods accepted by the National Guideline Program (NGLP), a joint effort of the Italian Health Ministry and the National Health Institute that is aimed at promoting a high quality of care in the National Health Service.\textsuperscript{13} The full text of the guideline and related documents are available at the Web site of the Italian Pediatric Society.\textsuperscript{12}

**The Expert Panel**

The guideline was developed by a multidisciplinary panel of clinicians and experts in evidence-based medicine and the methodology of guideline development who were identified with the help of the participating scientific societies. Specifically, the panel included a referee from the NGLP National Board; experts in the fields of general pediatrics, emergency medicine, neonatology, epidemiology, infectious diseases, nursing practice, pharmacology, toxicology, research methodology; and a member of the parents’ association Noi per Voi. No panel member declared any conflict of interest.

The panel met in June 2007 and October 2008, and many of the consultations involved in the guideline development and draft processes took place interactively by e-mail or telephone contact. The panel members first defined the objectives of the guideline, the essential clinical questions, and the appropriate inclusion and exclusion criteria for the studies from which evidence would be derived. They also identified the information sources and biomedical databases that would be consulted, and the search terms that would be used in constructing the search strategy.

**Literature Search**

Once the specific clinical questions were developed, literature searches were performed for each question. Pertinent publications in English and Italian were identified through searches of the Cochrane Database of Systematic Reviews and MEDLINE from their inception through December 31, 2007. The results of these searches were then evaluated and selected based on both methodology and relevance. An updated literature search was performed before preparation of the final draft; this search identified no additional relevant publications. The search strategy is summarized in the appendix.

**Study Selection, Levels of Evidence, and Strength of Recommendations**

The selection of studies, evaluation of study methodology, and data extraction process were performed by specially trained personnel. For each study, data evaluation and extraction were carried out using translated and adapted methodologic checklists developed by the Scottish Intercollegiate Guidelines Network.\textsuperscript{14} The data extracted from each study were summarized in tables specific to each question and type of study. These summary tables were in the format suggested by the National Institute for Health and Clinical Excellence (NICE) or in a format specifically created by the panel.

The NGLP method was used to grade the study data according to 6 levels of evidence (I–VI) and 5 grades of recommendation (A–E) (Table I).\textsuperscript{13} Levels of evidence were assigned based on the study designs and methodology, as evaluated by the panel. The panel’s opinions were formalized using the Delphi consensus method.

**GUIDELINE SUMMARY**

**Question 1. How should body temperature be measured in children?**

**Evidence**

The ideal method of measuring body temperature in children should accurately reflect the central temperature, or core body temperature; should be economical, simple, and fast; and should not cause discomfort to the child. Because measurement of central temperature requires the use of invasive methods,\textsuperscript{15} body temperature is commonly measured in such easily accessible sites as the armpit, oral cavity, rectum, or tympanic membrane.

The temperature obtained by rectal measurement is generally considered the closest to central temperature.\textsuperscript{16} However, when the core temperature increases or decreases abruptly, rectal temperature changes more slowly and can be substantially different from
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Table I. Evidence levels and strength of recommendations.13

<table>
<thead>
<tr>
<th>Evidence levels</th>
<th>Description</th>
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<tbody>
<tr>
<td>I.</td>
<td>Evidence obtained from &gt;1 randomized controlled clinical trial and/or systematic review of randomized trials</td>
</tr>
<tr>
<td>II.</td>
<td>Evidence obtained from only 1 well-designed randomized clinical trial</td>
</tr>
<tr>
<td>III.</td>
<td>Evidence obtained from nonrandomized cohort studies with a control group (either concurrent or historical) or a meta-analysis of such studies</td>
</tr>
<tr>
<td>IV.</td>
<td>Evidence obtained from retrospective studies, such as case–control studies, or a meta-analysis of such studies</td>
</tr>
<tr>
<td>V.</td>
<td>Evidence obtained from case series without a control group</td>
</tr>
<tr>
<td>VI.</td>
<td>Evidence based on the opinion of experts or committees of experts, as indicated in guidelines or consensus conferences, or based on the opinion of members of the guideline development working group</td>
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<table>
<thead>
<tr>
<th>Strength of recommendations</th>
<th>Description</th>
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<tbody>
<tr>
<td>A.</td>
<td>Strong recommendation in favor of a particular procedure or diagnostic test; recommendation is supported by good-quality scientific evidence, although not necessarily type I or II</td>
</tr>
<tr>
<td>B.</td>
<td>It is doubtful that the particular procedure or intervention should always be recommended, but it should always be carefully taken into consideration</td>
</tr>
<tr>
<td>C.</td>
<td>It is uncertain whether the procedure or intervention should or should not be recommended</td>
</tr>
<tr>
<td>D.</td>
<td>The procedure or intervention is not recommended</td>
</tr>
<tr>
<td>E.</td>
<td>The procedure or intervention is strongly discouraged</td>
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</tbody>
</table>

the core temperature.15,16 Rectal measurement is not recommended in oncologic patients, newborns, or in the presence of diarrhea, neutropenia, or immune disorders.15 The presence of feces or blood and the extent to which the thermometer is inserted can affect the accuracy of the measurement.17 In addition, the rectal method entails a risk of rectal lesions or perforation,15 and a risk of bacterial cross-contamination has been reported in the absence of proper cleansing procedures.15,18 In addition, the potential discomfort to the child should be considered.15

Axillary measurement is easy to perform and is generally well tolerated.15,19 However, this method has been reported to have variable sensitivity and to be influenced by the type of thermometer used and the duration of measurement.19,20 An axillary reading is generally 0.5°C lower than a rectal reading, although an exact conversion factor between the 2 modes of measurement has not been established.20,21 Axillary measurement appears to be extremely accurate in newborns.18,20

Oral measurement of body temperature has variable accuracy and may be influenced by such con-founding factors as mucositis, intake of hot or cold food, temperature of inhaled air, and respiratory frequency. Moreover, oral measurement requires the patient’s cooperation.18,22,23 Given the potential for metal toxicity, mercury thermometers should not be used for oral measurement and, in fact, will be withdrawn from the market by 2010.24

Digital thermometers can be used for rectal, oral, or axillary measurement. Models may differ substantially. Some depend on the change in temperature/time slope and can stop prematurely. In others, this program can be disabled to obtain a more accurate measurement.

Some authors consider tympanic measurement using an infrared thermometer the best method for non-invasive measurement of central temperature.25–27 One study reported a high degree of accuracy with this mode of measurement,28 although others had conflicting results, particularly when measurements were not performed by health care professionals.25,29,30 Differences between models of infrared thermometers may lead to variable results. In addition, curvature of the auditory canal may make it difficult to reach the tympanic membrane, particularly in newborns.31 The
presence of hyperemia or earwax can also interfere with measurement.16

Digital “dummy” (pacifier-style) thermometers and liquid crystal thermometers are not accurate.15 Data on the cutaneous measurement of body temperature using an infrared thermometer should be interpreted with caution, as they are based on limited numbers of patients.32 Similarly, there are insufficient data to form any recommendations on the use of alcohol and gallium thermometers.33

The types of commonly used thermometers, including their advantages and disadvantages, are described in Table II.

Recommendations

Recommendation 1: Rectal measurement should not be used routinely in children aged <5 years because it is invasive and causes discomfort (evidence level III; strength of recommendation D).

Recommendation 2: Oral measurement of body temperature should be avoided in children (evidence level III; strength of recommendation D).

Recommendation 3: Use of a mercury thermometer is not recommended because of the risk of breakage and metal toxicity (evidence level III; strength of recommendation E).

Recommendation 4: Axillary measurement using a digital thermometer is recommended in children aged <4 weeks (evidence level III; strength of recommendation B).

Recommendation 5: In the hospital or ambulatory care setting, axillary measurement using a digital thermometer or tympanic measurement using an infrared thermometer is recommended in children aged ≥4 weeks (evidence level II; strength of recommendation B).

Recommendation 6: For measurements taken at home by parents/caregivers, axillary measurement using a digital thermometer is recommended in all children (evidence level II; strength of recommendation B). Use of a tympanic infrared thermometer is not recommended, as this mode of measurement is prone to operator-related error.

Question 2. How should clinicians regard measurements of a child’s temperature taken by parents/caregivers?

Recommendation 7: Exact measurement of a child’s body temperature is best done by a health care professional. However, children who are apyretic at the time of examination but have a positive anamnesis of fever as reported by parents/caregivers, should be considered febrile (evidence level VI; strength of recommendation B).

Question 3. Is it appropriate to use physical methods to reduce a child’s body temperature?

Evidence

Physical methods of reducing fever include bathing, sponge baths, exposure to cold air, application of cooling blankets or ice bags, and rubbing the body with alcohol.37–42 Use of these methods may be associated with adverse events, including a paradoxical increase in fever as a consequence of vasoconstriction induced by body temperature reduction; shaking and prolonged shivering, with increased energy depletion beyond that caused by the fever itself; and severe hypoglycemia, coma, or even death in association with sponge baths with ethyl or isopropyl alcohol.37,39,40 Lukewarm sponge baths with water have not been linked to severe adverse effects, although they may be associated with discomfort.37,39

A meta-analysis by Meremikwu and Oyo-Ita37 included 7 studies comparing physical methods of reducing fever with the use of antipyretics or placebo. All 7 studies had potential methodologic limitations, and the authors indicated that the data should be interpreted with caution. Moreover, because not all physical methods have been studied and reported, it was not possible to draw any conclusions about the value of one method compared with another. With regard to lukewarm sponge baths, studies differed with respect to the kind of liquid employed and its temperature.42

Use of physical methods is not beneficial in children with fever, as their effect is limited and transient, and does not interfere with the central mechanisms of body temperature control. However, use of physical methods is recommended in cases of hyperthermia, in which body temperature increases independently of the action of the heat control center (ie, heat stroke and sunstroke).33
**Table II. Descriptions of common types of thermometers, based on telephone interviews with a random sample of community pharmacists in Italy in 2008.**

<table>
<thead>
<tr>
<th>Type of Thermometer</th>
<th>Site/Mode of Measurement</th>
<th>Cost to Public, Range, €</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury</td>
<td>Axillary, oral, rectal</td>
<td>2–5</td>
<td>Easy to read, low cost</td>
<td>Fragile, cannot be recalibrated, long measurement time (5–8 min) with classic nonprismatic type, potential for mercury toxicity</td>
<td>Will be withdrawn from the market by 2010 due to risk of mercury toxicity</td>
</tr>
<tr>
<td>Digital</td>
<td>Axillary, oral, rectal</td>
<td>4–8</td>
<td>High accuracy, low cost, short measurement time (1–2 min), has acoustic alarm to indicate end of measurement</td>
<td>Need to replace battery, calibration may be difficult to check, some models depend on change in temperature/time slope and can stop prematurely</td>
<td>Flexible models are preferred for safety reasons, “dummy” (pacifier) type has insufficient accuracy</td>
</tr>
<tr>
<td>Liquid crystal</td>
<td>Plastic strip placed on forehead</td>
<td>1–2</td>
<td>Easy to use, unbreakable, nontoxic</td>
<td>Insufficient accuracy and precision</td>
<td>“Mother’s touch” type is more precise than other models</td>
</tr>
<tr>
<td>Infrared</td>
<td>Auricular</td>
<td>30–50</td>
<td>Very short measurement time (a few seconds)</td>
<td>No standardization among models, possibility of incorrect calibration, some models (auricular) may be difficult to insert, skin-contact type requires routine disinfection or should be assigned to only 1 patient, measurement distance is critical for noncontact types</td>
<td>Auricular measurement may produce an accurate result when performed by trained health care providers, but is less accurate when performed by untrained subjects (eg, parents)</td>
</tr>
</tbody>
</table>

**Recommendations**

Recommendation 8: Use of physical methods to reduce fever is not recommended (evidence level I; strength of recommendation E).

Recommendation 9: Use of physical methods is recommended in cases of hyperthermia (evidence level I; strength of recommendation A).

**Question 4. Is there a correlation between the degree of fever and the severity of the underlying pathology?**

**Evidence**

Some studies in children have found a correlation between a body temperature ≥41.1°C and the risk of bacteremia and invasive bacterial infection, whereas...
with fever, although they may be used in children who show signs of general discomfort, including prolonged crying, irritability, reduced activity, reduced appetite, and disturbed sleep. In contrast, World Health Organization (WHO) guidelines recommend the use of paracetamol whenever body temperature is >39°C. A more recent WHO document, however, discouraged the routine use of antipyretics in children, particularly in situations in which the family must bear the entire cost of medications, and because the role of antipyretic drugs in children with malaria, sepsis, or chronic malnutrition has not yet been established.

**Recommendation**

Recommendation 12: Use of antipyretics in children is recommended only when the fever is associated with evident discomfort (e.g., prolonged crying, irritability, reduced activity, reduced appetite, disturbed sleep) (evidence level I; strength of recommendation B).

**Question 6. Which antipyretics and modes of administration should be used?**

**Evidence**

A meta-analysis of 8 trials comparing the antipyretic efficacy of paracetamol and ibuprofen found a greater decrease in body temperature in children treated with ibuprofen compared with paracetamol at both 4 hours (difference: 0.63°C; \( P < 0.001 \)) and 6 hours after administration (difference: 0.58°C; \( P = 0.005 \)). However, the authors did not provide details of their search strategy; furthermore, they included studies using different drug doses and excluded those that measured body temperature at times other than 4 and 6 hours.

A meta-analysis of 17 trials compared the antipyretic effect of ibuprofen and paracetamol, using as an outcome measure the effect size (ES) of reduction in fever after an initial single dose of either antipyretic. The use of acetylsalicylic acid is strongly discouraged in children aged <15 years because of the risk of Reye's syndrome. Steroids should not be used for fever in children because of their poor benefit–risk ratio. Among NSAIDs, ibuprofen has the lowest risk of severe upper gastrointestinal tract adverse effects. A meta-analysis of 12 studies yielded inconclusive evidence that paracetamol had greater antipyretic efficacy than placebo, although this finding may have been affected by the small numbers of patients in the included studies.

According to NICE guidelines, antipyretics should not be used routinely in the management of children with fever, although they may be used in children who show signs of general discomfort, including prolonged crying, irritability, reduced activity, reduced appetite, and disturbed sleep. In contrast, World Health Organization (WHO) guidelines recommend the use of paracetamol whenever body temperature is >39°C. A more recent WHO document, however, discouraged the routine use of antipyretics in children, particularly in situations in which the family must bear the entire cost of medications, and because the role of antipyretic drugs in children with malaria, sepsis, or chronic malnutrition has not yet been established.

**Recommendation**

Recommendation 12: Use of antipyretics in children is recommended only when the fever is associated with evident discomfort (e.g., prolonged crying, irritability, reduced activity, reduced appetite, disturbed sleep) (evidence level I; strength of recommendation B).
A loading dose of paracetamol or ibuprofen may be followed by lower doses. In a randomized, double-blind, controlled trial in 121 febrile children, an initial loading dose of paracetamol 30 mg/kg was more effective in reducing fever than a maintenance dose of 15 mg/kg. The mean (SD) maximum temperature decrease was significantly higher in the group that received paracetamol 30 mg/kg compared with the group that received paracetamol 15 mg/kg (2.3°C [0.7°C] vs 1.7°C [0.6°C], respectively; \( P < 0.05 \)), and the amount of time with a rectal temperature <38.5°C was significantly longer (250 [92] vs 185 [121] minutes; \( P < 0.05 \)). However, these differences were not considered clinically relevant. Moreover, this type of regimen may be confusing for caregivers, increasing the risk of overdose.

### Recommendations

**Recommendation 13:** Paracetamol and ibuprofen are the only antipyretic drugs recommended for use in children (evidence level I; strength of recommendation A).

**Recommendation 14:** Use of acetylsalicylic acid in children is not recommended because of the risk of Reye’s syndrome (evidence level III; strength of recommendation E).

**Recommendation 15:** Because of their poor benefit–risk ratio, steroids should not be used as antipyretics in children (evidence level III; strength of recommendation E).

**Recommendation 16:** Combined or alternating use of ibuprofen and paracetamol is not recommended (evidence level VI; strength of recommendation D).

### Question 7. Should paracetamol be administered rectally or orally?

#### Evidence

Oral and rectal preparations of paracetamol are commonly used interchangeably on the assumption that they have equal antipyretic effects. However, pharmacokinetic data for a single rectal dose of paracetamol suggest that drug absorption may be erratic and prolonged, varying with the suppository’s size, the composition of its base, the rate of dissolution, positioning in the rectum, and the rectal contents. It is difficult to interpret data on the antipyretic response to paracetamol, as hysteresis between pharmacokinetic and pharmacodynamic data has been reported. The response is not directly related to drug concentrations in the blood, but rather to a combination of factors including gastric emptying and absorption through the rectal mucosa.
would exceed the appropriate weight-based dose, another route of administration should be used (evidence level I; strength of recommendation A).

Question 8. Are antipyretics well tolerated in children?

Evidence

Both ibuprofen and paracetamol are well tolerated in children. Two randomized studies reported low risks of hospitalization for gastrointestinal bleeding, renal failure, or anaphylaxis with both paracetamol and ibuprofen.75,76 Among 27,065 febrile children aged 6 months to 2 years who were randomized to receive paracetamol or ibuprofen, the risk of hospitalization for any reason was 1.4% (95% CI, 1.3%–1.6%) and did not vary by the antipyretic received.75 No children were hospitalized for acute renal failure or anaphylaxis. Three children in the ibuprofen group were hospitalized for gastrointestinal bleeding, which yielded a risk for hospitalization of 17/100,000 (95% CI, 3.5–49), which did not differ significantly from the risk in the paracetamol group. In a study in 84,192 febrile children aged 6 months to 12 years who were randomized to receive ibuprofen or paracetamol, the risk of hospitalization for any cause was 1%.76 The risk of hospitalization for gastrointestinal bleeding in the ibuprofen group was 7.2/100,000 (95% CI, 2–18), which did not differ significantly from the risk in the paracetamol group. Again, no children were hospitalized for acute renal failure or anaphylaxis.

The results of a meta-analysis supported the similar tolerability profiles of paracetamol and ibuprofen.63 With a risk ratio >1 indicating less potential harm for paracetamol relative to ibuprofen and a value <1 indicating less potential harm for ibuprofen relative to paracetamol, the point estimates of the risk ratios for minor and major harm were 0.96 (95% CI, 0.68–1.36) and 1.00 (95% CI, 0.55–1.82), respectively. A subsequent randomized, blinded trial in 304 children aged 3 months to 12 years found that both medications were equally well tolerated.65

Ibuprofen should be used with caution in the presence of dehydration due to the increased risk of renal failure.46 Use of ibuprofen is not recommended in children with chickenpox due to the potentially increased risk of skin and soft tissue superinfection and invasive streptococcal infection.46 There are case reports suggesting an increased risk of thoracic em-
Use of antipyretics without a prescription and/or without medical supervision increases the risk of overdose. It has been reported that half of parents taking children aged ≤10 years to the emergency department within 24 hours after administering a known dose of paracetamol or ibuprofen as an antipyretic had administered an incorrect dose. Children aged <1 year are at greater risk of receiving incorrect doses. In a study of dosing errors involving liquid medications, the most frequent mistakes involved misinterpretation of the information leaflet and use of teaspoons or tablespoons rather than measuring spoons or graduated oral syringes. A greater risk of overdose has been reported with rectal rather than oral administration of paracetamol, particularly in young children. A frequent cause of overdose was administration of an over-the-counter product containing paracetamol in addition to the paracetamol prescribed by the clinician. The advice about antipyretic dosing that should be given to parents/caregivers at each visit is summarized in Table III.

The child with suspected paracetamol poisoning should be referred immediately to a pediatric emergency department. Although some nonspecific signs (ie, anorexia, nausea, vomiting, discomfort, and diaphoresis) may be present in the early phase of paracetamol poisoning, there are often no early signs. Even a serious overdose can be asymptomatic.

N-acetylcysteine treatment for acute paracetamol poisoning is most effective when started early. Risk factors for death or the need for liver transplantation are delay in referral to the emergency department and/or delay in treatment and the presence of grade 3 or 4 hepatic encephalopathy. The patient should be assessed for the presence of concomitant risk factors for hepatic toxicity (ie, chronic liver disease, obesity, malnutrition, diabetes, and administration of carbamazepine, phenobarbital, phenytoin, or rifampicin). A Cochrane review of the management of patients with paracetamol overdose (n = 59 studies, none of which were randomized trials) found that the clinical benefit of using activated charcoal, gastric lavage, or ipecacuanha to reduce absorption of paracetamol is unclear, although there was some evidence that activated charcoal may be the best of these options. N-acetylcysteine appeared to be preferable to placebo (supportive treatment), dimercaprol, and cysteamine, although there was no evidence for its efficacy relative to methionine. N-acetylcysteine may reduce mortality.

Recommendations

Recommendation 21: Paracetamol and ibuprofen are generally well tolerated and effective antipyretics when used at the recommended dosage. For oral paracetamol, the standard dosage is 10 to 15 mg/kg per dose (maximum, 1 g per dose) given 4 to 6 times daily (ie, q4–6h). The maximum therapeutic doses are 60 mg/kg per day in children aged <3 months and 80 mg/kg per day in children aged ≥3 months (maximum, 3 g/d), and the toxic dose is >150 mg/kg in a single administration. For oral ibuprofen, the standard dosage is 10 mg/kg per dose (maximum, 800 mg per dose) given 3 or 4 times daily (ie, q6–8h). The maximum therapeutic dose is 30 mg/kg per day (maximum, 1.2 g/d), and the toxic dose is >100 mg/kg per day (evidence level I; strength of recommendation A).

Recommendation 22: Use of ibuprofen is not recommended in children with chickenpox or dehydration (evidence level V; strength of recommendation D).

Recommendation 23: Until further data are available, use of ibuprofen is not recommended in children with Kawasaki disease receiving acetylsalicylic acid therapy because of the risk of reduced anti-aggregating efficacy of acetylsalicylic acid (evidence level V; strength of recommendation D).

Question 9. What precautions should be taken to prevent antipyretic toxicity in children?

Evidence

Paracetamol toxicity can occur after intake of a single high dose or multiple excessive doses, even after >1 day, and may be associated with the potentially fatal adverse effect of acute liver necrosis. Although a single dose of paracetamol 150 mg/kg is usually reported as the threshold for liver toxicity in the pediatric age group, severe toxicity has been reported at lower doses. In particular, children with diabetes, those with a family history of liver toxicity reactions, obese children, those with chronic malnutrition, and those undergoing prolonged fasting are at increased risk for paracetamol toxicity. It must be stressed that the evidence for serious liver toxicity at therapeutic paracetamol doses is poor, relying mainly on parental reports of dosing and often ignoring plasma concentration data.
in patients with fulminant hepatic failure (odds ratio = 0.26; 95% CI, 0.09–0.94), although it is not clear which protocol has the most efficacy. Liver transplantation should be considered in selected cases.82

Approximately 20 pediatric cases of acute ibuprofen poisoning, some of them fatal, are reported in the literature.83,84 Doses of ibuprofen <100 mg/kg seldom have toxic effects in children, whereas doses >400 mg/kg are associated with severe toxicity. The clinical picture of ibuprofen poisoning includes nausea, vomiting, headache, epigastric pain, visual disturbance, and tachycardia; less frequent events include cardiocirculatory collapse, acidosis, hypocalcemia, hypomagnesemia, hypothermia, lung and gastrointestinal bleeding, renal failure, and multiorgan failure. Vertigo, apnea crisis, convulsions, and altered consciousness (including coma) have been reported.85 Comorbidities due to chronic liver disease increase the risk of ibuprofen toxicity.

In cases of ingestion of ibuprofen doses >100 mg/kg or in the symptomatic child, activated charcoal should be administered.82 Children aged <5 years seem to have a greater predisposition to development of apnea, coma, and convulsions at toxic ibuprofen doses.82 Ibuprofen toxicity increases in association with chickenpox and concomitant treatment with angiotensin-converting enzyme (ACE) inhibitors, cyclosporine, diuretics, methotrexate, lithium, baclofen, and quinolones. Coadministration of ibuprofen increases the anticoagulant effect of dicumarol derivatives.86,85 It should also be noted that there have been several case reports of renal complications in children receiving ibuprofen in the presence of intravascular volume depletion and/or preexisting renal problems.86

Recommendations

Recommendation 24: Doses should be administered using the measuring device provided with the drug package (evidence level V; strength of recommendation A).

Recommendation 25: It is crucial that the clinician consider the presence of factors that could increase the risk of toxicity with ibuprofen (eg, chickenpox, dehydration, concomitant treatment with ACE inhibitors, cyclosporine, methotrexate, lithium, baclofen, diuretics, quinolones, and dicumarol derivatives) or paracetamol (diabetes, obesity, malnutrition, family history of hepatotoxic reaction, prolonged fasting, concomitant treatment with carbamazepine, isoniazid, phenobarbital and other barbiturates, primidone, and rifampicin) (evidence level V; strength of recommendation A).
Recommendation 26: When antipyretic toxicity is suspected, the child should be referred immediately to a poison treatment center or emergency department, as prompt intervention is associated with a better prognosis (evidence level I; strength of recommendation A).

**Question 10. Can antipyretics be used in children with chronic conditions?**

**Evidence**

Randomized controlled trials that have reported tolerability data on paracetamol and ibuprofen in the pediatric age group have often excluded children with chronic conditions.75,76 Although no randomized controlled trials were identified in children with chronic malnutrition, a systematic review found an increased risk of hepatotoxicity in malnourished subjects.61 Indeed, malnutrition is associated with glutathione depletion, which affects the body’s drug detoxification mechanisms.87 Prolonged fasting may alter the glucuronidation and sulfatation mechanisms involved in paracetamol metabolism and reduce the formation of glucuronic acid, thus inducing reduced drug elimination and increased metabolism through the microsomal oxidative system, mediated by the cytochrome P450 (CYP) 2E1 isozyme, with formation of the potentially hepatotoxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). Fasting reduces CYP activity, and a reduction in this activity is associated with reduced production of toxic metabolites on the one hand and accumulation of those that are produced on the other.87

When investigated in a meta-analysis of 3 randomized controlled trials in febrile children, no significant association was found between the use of paracetamol or ibuprofen and asthma episodes.88 It has also been suggested that paracetamol may be associated with a modest increase in the risk of wheezing.75,88,89 A recent multicenter questionnaire survey of the parents of >200,000 children aged between 6 and 7 years found that the use of paracetamol during the first year of life was an independent risk factor for subsequent development of asthma.90 However, the study design was cross-sectional, and data were obtained based on parents’ recollection. It is possible that the parents of children with asthma may be more inclined than other parents to report the use of drugs during the first year of life. Other confounding factors that were not included in the multivariate analysis, such as the presence of underlying respiratory pathology, may also have influenced the results. Use of paracetamol and ibuprofen is contraindicated in febrile children with documented paracetamol- or NSAID-induced asthma.91,92

No randomized controlled studies were identified on the use of antipyretics in children with chronic hepatic disease. A potential increase in the hepatotoxicity of paracetamol has been posited in patients with chronic hepatopathy, possibly caused by depletion of hepatic glutathione deposition leading to accumulation of the hepatotoxic intermediate metabolite NAPQI.93 However, the available studies have involved small numbers of patients.93,94 Ibuprofen is considered to be less hepatotoxic than other NSAIDs, with an incidence of acute hepatic damage at therapeutic doses of 1.6 per 100,000 subjects of any age.95 Nevertheless, possible effects on platelet function and the risk of gastrointestinal bleeding should be considered in febrile patients with chronic hepatopathy.96,97

In children with chronic cardiopathy, paracetamol and ibuprofen should be used with caution to avoid the cardiovascular overload that may occur during fever.98 Possible interactions of ibuprofen with antihypertensive drugs and diuretics should be considered. There is a need for specific studies in this subset of children with fever.

**Recommendations**

Recommendation 27: Use of ibuprofen and paracetamol is not contraindicated in febrile children with asthma. Paracetamol and ibuprofen are contraindicated in known cases of paracetamol- or NSAID-induced asthma (evidence level I; strength of recommendation A).

Recommendation 28: There is insufficient evidence to evaluate the use of paracetamol and ibuprofen in febrile children with other chronic pathologies (ie, malnutrition, chronic cardiopathy, and chronic hepatopathy). Caution is warranted in cases of severe hepatic or renal failure/dysfunction or in children with severe malnutrition (evidence level III; strength of recommendation C).

**Question 11. How should fever be managed in children aged <28 days?**

**Evidence**

Hospitalization is always recommended in the febrile newborn because of the high risk of severe complications.3,99 Although ibuprofen may be used in newborns for other indications (eg, for the treatment of cardiac
ministered before or at the time of vaccination and every 4 to 8 hours for at least 12 hours thereafter were significantly more effective than placebo in reducing fever, pain, and local reactions ($P < 0.01$). Therefore, use of antipyretics may be indicated to reduce the incidence of adverse reactions to DTP vaccination. However, since this vaccine was replaced by the acellular type (DTPa), no beneficial effect of the preventive use of antipyretics has been reported, primarily because the newer vaccine is associated with far fewer adverse effects compared with the older one.103,105

**Recommendation**

Recommendation 31: Use of paracetamol or ibuprofen is not recommended to reduce the incidence of fever and local reactions in children undergoing vaccination (evidence level II; strength of recommendation E).

**Question 12. Should antipyretics be used to prevent adverse events associated with childhood vaccinations?**

**Evidence**

A systematic review of 5 studies suggested no benefit associated with the use of ibuprofen or paracetamol for the prevention of adverse reactions (including fever) to vaccines. A study in >300 children vaccinated against diphtheria, tetanus, and cellular pertussis (DTP) found no protective effect of paracetamol or ibuprofen on the incidence of fever, erythema, pain, edema, or hives. In 3 randomized studies of administration of the DTP vaccine, both paracetamol and ibuprofen administered before or at the time of vaccination and every 4 to 8 hours for at least 12 hours thereafter were significantly more effective than placebo in reducing fever, pain, and local reactions ($P < 0.01$). Therefore, use of antipyretics may be indicated to reduce the incidence of adverse reactions to DTP vaccination. However, since this vaccine was replaced by the acellular type (DTPa), no beneficial effect of the preventive use of antipyretics has been reported, primarily because the newer vaccine is associated with far fewer adverse effects compared with the older one.

**Recommendation**

Recommendation 32: Preventive use of paracetamol or ibuprofen is not recommended for the prevention of febrile convulsions in febrile children (evidence level II; strength of recommendation E).

**Question 13. Should antipyretics be used to prevent febrile convulsions in children?**

**Evidence**

Two reviews of clinical trials on the use of antipyretics for the prevention of febrile convulsions concluded that given the methodologic limitations of the available studies, there was no positive evidence for such use. A double-blind, controlled study compared paracetamol plus placebo, paracetamol plus diazepam, diazepam plus placebo, and placebo alone in 180 febrile children with previous febrile convulsions and found no significant differences in the incidence of febrile convulsive episodes in the 4 groups. In a comparison of paracetamol given every 4 hours or as needed in 104 febrile children (age range, 6 months–5 years) with a history of febrile convolution, there was no significant difference in the frequency of convulsions at 72 hours between groups.

**Recommendation**

Recommendation 32: Preventive use of paracetamol or ibuprofen is not recommended for the prevention of febrile convulsions in febrile children (evidence level II; strength of recommendation E).

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Scientific societies represented on the panel were the Italian Pediatric Society, the Italian Society of Pediatric Infectious Diseases, the Clinical Section of the Italian Society of Pharmacology, the Italian Society of Neonatology, the Italian Society of Pediatric Emergency and Urgent Medicine, the Italian Federation of Pediatricians, the Italian Society of Nursing Sciences, and the parents’ association Noi per Voi.

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Address correspondence to: Prof. Maurizio de Martino, Department of Pediatrics, University of Florence, Viale Pieraccini, 24, I-50139 Florence, Italy. E-mail: maurizio.demartino@unifi.it
Appendix. Literature search strategy.

For all questions, PubMed/MEDLINE and the Cochrane Database of Systematic Reviews were searched from their inception through December 31, 2007, for relevant studies published in English or Italian.

Question 1. How should body temperature be measured in children?

**Search strategy.** Key words: (fever OR body temperature) AND (thermometry OR thermometer) AND (accuracy OR sensitivity OR specificity); limits: children aged 0–18 years.

**Evidence synthesis.** Identified: 136 studies, of which 36 were excluded due to lack of relevance. Considered: 100 studies, of which 81 were excluded because they were included in meta-analyses. Selected: 19 studies (13 clinical trials, 5 systematic reviews, 1 practice guideline).

Question 2. How should clinicians regard measurements of a child’s temperature taken by parents/caregivers?

**Search strategy.** Key words: fever AND (parents OR mother OR management OR attitudes); field: meta-analysis/randomized controlled trial; limits: human, meta-analysis, practice guideline, randomized controlled trial, review, English, children aged 0–18 years.

**Evidence synthesis.** Identified: 37 studies, of which 27 were excluded due to lack of relevance, poor methodology, or duplicate references. Selected: 10 studies (9 observational studies, 1 narrative review).

Question 3. Is it appropriate to use physical methods to reduce a child’s body temperature?

**Search strategy.** Key words: fever AND (treatment OR physical methods OR external cooling); field: meta-analysis/randomized controlled trial; limits: human, meta-analysis, practice guideline, randomized controlled trial, review, English, children aged 0–18 years.

**Evidence synthesis.** Identified: 39 studies, of which 31 were excluded due to lack of relevance, poor methodology, or duplicate references. Selected: 8 studies (5 randomized controlled trials, 2 narrative reviews, 1 meta-analysis).

Question 4. Is there a correlation between the degree of fever and the severity of the underlying pathology?

**Search strategy.** Key words: fever AND (prediction rule OR prediction tool OR risk factors OR bacteremia OR severity of disease); field: meta-analysis/randomized controlled trial; limits: human, meta-analysis, practice guideline, randomized controlled trial, review, English, children aged 0–18 years.

**Evidence synthesis.** Identified: 24 studies, of which 19 were excluded due to lack of relevance, poor methodology, or duplicate references. Selected: 5 studies (all observational).

Question 5. Is the use of antipyretic drugs advisable in children with fever?

**Search strategy.** Key words: fever AND (paracetamol OR ibuprofen OR acetaminophen OR antipyretic); field: meta-analysis/randomized controlled trial; limits: human, meta-analysis, practice guideline, randomized controlled trial, review, English, children aged 0–18 years.

**Evidence synthesis.** Identified: 88 studies, of which 83 were excluded due to lack of relevance, poor methodology, or duplicate references, and 1 was excluded because it involved adults. Selected: 4 studies (2 meta-analyses, 2 practice guidelines).

Question 6. Which antipyretics and modes of administration should be used?

**Search strategy.** Key words: fever AND (paracetamol OR ibuprofen OR acetaminophen OR antipyretics); field: meta-analysis/randomized controlled trial; limits: human, meta-analysis, practice guideline, randomized controlled trial, review, English, children aged 0–18 years.

**Evidence synthesis.** Identified: 88 studies, of which 76 were excluded due to lack of relevance, poor methodology, or duplicate references, and 1 was excluded because it involved adults. Selected: 11 studies (8 randomized controlled trials, 2 meta-analyses, 1 systematic review).

(continued)
Question 7. Should paracetamol be administered rectally or orally?

**Search strategy.** Key words: fever AND (acetaminophen OR paracetamol) AND oral AND rectal; field: title/abstract; limits: meta-analysis, randomized controlled trial, review, human, children aged 0–18 years.

**Evidence synthesis.** Identified: 11 studies, of which 6 were excluded due to lack of relevance. Considered: 5 studies, of which 2 were excluded for poor methodology. Selected: 3 studies (3 randomized controlled trials).

Question 8. Are antipyretics well tolerated in children?

**Search strategy.** Key words: (fever AND (antipyretics OR paracetamol OR ibuprofen)) AND (side effects OR toxicity OR tolerability OR interactions); field: title/abstract; limits: meta-analysis, randomized controlled trial, review, human, children aged 0–18 years.

**Evidence synthesis.** Identified: 31 studies, of which 13 were excluded because of lack of relevance or inclusion of adults. One narrative review published in French was included. Considered: 18 studies, of which 4 were excluded for poor methodology and 6 because they were included in meta-analyses. Selected: 8 studies (4 randomized controlled trials, 3 reviews, 1 meta-analysis).

Question 9. What precautions should be taken to prevent antipyretic toxicity in children?

**Search strategy.** Key words: (acetaminophen OR paracetamol OR ibuprofen); field: title/abstract; limits: human, meta-analysis, practice guideline, randomized controlled trial, review, English, children aged 0–18 years.

**Evidence synthesis.** Identified: 47 studies, of which 40 were excluded due to lack of relevance or duplicate references. Considered: 7 studies, of which 1 was excluded because it was included in a meta-analysis. Selected: 6 studies (2 systematic reviews, 2 observational studies, 1 meta-analysis, 1 practice guideline).

Question 10. Can antipyretics be used in children with chronic conditions?

**Search strategy.** Key words: (acetaminophen OR paracetamol OR ibuprofen OR antipyretic) AND (cystic fibrosis OR diabetes OR chronic liver disease OR malnutrition OR asthma OR chronic disease); field: title/abstract; limits: human, meta-analysis, practice guideline, randomized controlled trial, review, English, children aged 0–18 years.

**Evidence synthesis.** Identified studies: 36, of which 31 were excluded because of lack of relevance. Selected studies: 5 (3 randomized controlled trials, 2 meta-analyses).

Question 11. How should fever be managed in children aged <28 days?

**Search strategy.** Key words: (acetaminophen OR paracetamol) AND newborn; field: title/abstract; limits: human, meta-analysis, English, children aged 0–18 years.

**Evidence synthesis.** Identified: 19 studies, of which 9 were excluded due to lack of relevance. Considered: 10 studies, of which 7 were excluded because they were included in meta-analyses or reviews. Selected: 3 studies (2 practice guidelines, 1 review).

Question 12. Should antipyretics be used to prevent adverse events associated with childhood vaccinations?

**Search strategy.** Key words: (acetaminophen OR paracetamol OR ibuprofen OR antipyretic) AND (immunization OR vaccine); field: title/abstract; limits: human, meta-analysis, practice guideline, randomized controlled trial, review, English, children aged 0–18 years.

**Evidence synthesis.** Identified: 18 studies, of which 13 were excluded due to lack of relevance. Considered: 5 studies, of which 3 were excluded because they were included in meta-analyses or reviews. Selected: 2 studies (1 systematic review, 1 randomized controlled trial).

Question 13. Should antipyretics be used to prevent febrile convulsions in children?

**Search strategy.** Key words: (febrile seizures OR febrile convulsion) AND (acetaminophen OR paracetamol OR ibuprofen OR antipyretics); field: all fields; limits: meta-analysis, randomized controlled trial, review, practice guideline, English, children aged 0–18 years.

**Evidence synthesis.** Identified: 29 studies, of which 21 were excluded due to lack of relevance. Considered: 8 studies, of which 1 was excluded due to poor methodology. Selected: 7 studies (3 systematic reviews, 3 randomized controlled trials, 1 nonrandomized clinical trial).