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

Elena Chiappini, PhD[1]; Nicola Principi, MD[2]; Riccardo Longhi, MD[3]; Pier-Angelo Tovo, MD[4]; Paolo Becherucci, MD[5]; Francesca Bonsignori, MD[1]; Susanna Esposito, MD[2]; Filippo Festini, RN[1]; Luisa Galli, MD[1]; Bice Lucchesi, RPh[6]; Alessandro Mugelli, MD[7]; and Maurizio de Martino, MD[1]; for the Writing Committee of the Italian Pediatric Society Panel for the Management of Fever in Children*

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

Accepted for publication April 20, 2009.
doi:10.1016/j.clinthera.2009.08.006
0149-2918/$ - see front matter

with increasing frequency.[7–9] Considering concerns voiced in the literature,[3,10,11] 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.[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.[13] The full text of the guideline and related documents are available at the Web site of the Italian Pediatric Society.[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.[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**).[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,[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.[16] However, when the core temperature increases or decreases abruptly, rectal temperature changes more slowly and can be substantially different from

Table I. Evidence levels and strength of recommendations.[13]

Evidence levels

I. Evidence obtained from >1 randomized controlled clinical trial and/or systematic review of randomized trials

II. Evidence obtained from only 1 well-designed randomized clinical trial

III. Evidence obtained from nonrandomized cohort studies with a control group (either concurrent or historical) or a meta-analysis of such studies

IV. Evidence obtained from retrospective studies, such as case–control studies, or a meta-analysis of such studies

V. Evidence obtained from case series without a control group

VI. 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

Strength of recommendations

A. 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

B. It is doubtful that the particular procedure or intervention should always be recommended, but it should always be carefully taken into consideration

C. It is uncertain whether the procedure or intervention should or should not be recommended

D. The procedure or intervention is not recommended

E. The procedure or intervention is strongly discouraged

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 confounding 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 noninvasive 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?

Evidence

Measurements of body temperature taken by parents/caregivers may not be reliable.[2] Low socioeconomic class, poor education, and older parental age are predictive factors for inaccurate measurement of a child's body temperature.[34,35] Pediatricians should always reassess the body temperature reported by parents.[36] On the other hand, 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.[1,3]

Recommendation

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-Ita[37] 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.

Type of Thermometer	Site/Mode of Measurement	Cost to Public, Range, €	Advantages	Disadvantages	Comments
Mercury	Axillary, oral, rectal	2–5	Easy to read, low cost	Fragile, cannot be recalibrated, long measurement time (5–8 min) with classic nonprismatic type, potential for mercury toxicity	Will be withdrawn from the market by 2010 due to risk of mercury toxicity
Digital	Axillary, oral, rectal	4–8	High accuracy, low cost, short measurement time (1–2 min), has acoustic alarm to indicate end of measurement	Need to replace battery, calibration may be difficult to check, some models depend on change in temperature/time slope and can stop prematurely	Flexible models are preferred for safety reasons, "dummy" (pacifier) type has insufficient accuracy
Liquid crystal	Plastic strip placed on forehead	1–2	Easy to use, unbreakable, nontoxic	Insufficient accuracy and precision	"Mother's touch" type is more precise than other models
Infrared	Auricular Skin contact Noncontact	30–50 25–60 40–90	Very short measurement time (a few seconds)	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	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)

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

others have not.[43–46] Taken alone, a high body temperature (>39°C) has very low sensitivity and specificity for severe bacterial infection.[43] A high fever appears to represent a risk factor only when it is associated with other variables, such as a high white blood cell count or high levels of C-reactive protein.[47,48] In addition, a response to antipyretic drugs is not a predictive factor for the cause of fever.[49]

Recommendations

Recommendation 10: In itself, the degree of fever should not be taken as an indicator of the risk for severe bacterial infection (evidence level III; strength of recommendation E).

Recommendation 11: In special circumstances, such as age <3 months, concomitant leukocytosis, or an increase in C-reactive protein, high fever may be a predictive factor for severe bacterial infection (evidence level III; strength of recommendation C).

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

Evidence

Fever is a part of the natural physiologic defense against infective agents. Immunologic mechanisms are enhanced in the presence of fever, and the ability of viruses and bacteria to replicate is decreased.[50] A randomized controlled trial in children with chickenpox found that administration of paracetamol (acetaminophen) did not alleviate the symptoms of fever and may have prolonged the illness.[51]

Nonetheless, it is common clinical practice to reduce the child's discomfort by treating the signs and symptoms of fever, mainly with antipyretic drugs.[52] The antipyretic drugs that are approved for use in children are paracetamol and ibuprofen.[37] The use of acetylsalicylic acid is strongly discouraged in children aged <15 years because of the risk of Reye's syndrome.[53–57] Steroids should not be used for fever in children because of their poor benefit–risk ratio.[37,58] Among NSAIDs, ibuprofen has the lowest risk of severe upper gastrointestinal tract adverse effects.[37,56] A meta-analysis of 12 studies yielded inconclusive evidence that paracetamol had greater antipyretic efficacy than placebo,[37] 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,[57] including prolonged crying, irritability, reduced activity, reduced appetite, and disturbed sleep.[59] In contrast, World Health Organization (WHO) guidelines recommend the use of paracetamol whenever body temperature is >39°C.[60] 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.[61]

Recommendation

Recommendation 12: Use of antipyretics in children is recommended only when the fever is associated with evident discomfort (eg, 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; $P = 0.005$).[62] 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.[63] At 4 to 6 hours after administration, 15% more children had a decrease in temperature in the ibuprofen group compared with the paracetamol group (ES after 2 hours: 0.19 [95% CI, 0.05–0.33]; ES after 4 hours: 0.31 [95% CI, 0.19–0.44]; ES after 6 hours: 0.33 [95% CI, 0.19–0.47]). A narrative review including 22 trials found that a single dose of ibuprofen was more effective in reducing fever in children than a single dose of paracetamol; that ibuprofen was more effective than paracetamol after 6 hours, but not be-

yond (temperature was evaluated up to 8 hours); and that there was no significant difference in antipyretic effect with one drug or the other in studies that involved multiple doses.[64]

The risk of adverse effects has been reported to be similar with paracetamol and ibuprofen and to be independent of the agent used.[65] In a recent trial, the antipyretic effect of ibuprofen appeared to be more rapid and longer lasting than that of paracetamol.[59] However, direct comparison of ibuprofen and paracetamol was not the primary end point of the study, and the differences did not appear to be clinically relevant.

A randomized controlled trial reported differences in body temperature in children receiving the combination of paracetamol and ibuprofen compared with those receiving either agent alone.[66] However, the differences compared with paracetamol and ibuprofen monotherapy were only 0.35°C (95% CI, 0.10–0.60; $P = 0.028$) and 0.25°C (95% CI, 0.01–0.50; P = NS), respectively. One study reported numerically lower temperatures at 0.5 and 2 hours after administration with combined use of the 2 antipyretic drugs compared with monotherapy,[67] a difference that was not considered clinically significant. Both of these trials included limited numbers of patients.

In a pilot study of alternating ibuprofen and paracetamol therapy every 4 hours (N = 70), a significantly higher percentage of children were afebrile at various time points in the alternating-therapy group compared with the monotherapy control group (83.3% vs 57.6%, respectively; $P = 0.018$).[68] Another study found that alternating paracetamol and ibuprofen every 4 hours for 3 days after administration of a loading dose was associated with a significantly lower mean body temperature compared with use of either agent alone ($P < 0.001$), without being associated with an increased incidence of adverse effects.[69] A recent randomized controlled trial reported greater antipyretic efficacy with combined treatment with paracetamol and ibuprofen compared with either agent alone: over 24 hours, the combination-therapy group was fever free a mean of 4.4 hours more than the paracetamol-alone group (95% CI, 2.4–6.3) and 2.5 hours more than the ibuprofen-alone group (95% CI, 0.6–4.4).[59] However, parents reported having difficulty following the combination-therapy regimen, suggesting a potential for confusion and increased toxicity risk.

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.[70] 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.[70]

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.[71–73] Moreover, it is difficult to interpret data on the antipyretic response to paracetamol, as hysteresis between pharmacokinetic and pharmacodynamic data has been reported.[71] The response is not directly related to drug concentrations in the blood, but rather to a com-

partment effect, and the maximum temperature reduction may occur 1 to 2 hours after attainment of C_{max}. The delay is dependent on body size, being shorter at lower weights. Thus, measurement of plasma concentrations at a single point provides limited information on the concentration–effect relationship.[71]

Two randomized controlled studies reported no significant difference in antipyretic efficacy when paracetamol was administered orally and rectally.[71,72] However, rectal administration of paracetamol has been associated with variable peaks in plasma drug concentrations. In fact, the plasma concentrations of paracetamol required to achieve an antipyretic effect (10–20 μg/mL) are not attained consistently. In addition, plasma T_{max} is longer with rectal administration. Other studies have reported that doubling the standard dose of rectally administered paracetamol did not achieve greater antipyretic effect compared with the standard dose given orally and increased the risk of toxicity.[72,73] Because the majority of studies have been carried out in carefully selected populations using strict exclusion criteria, the incidence of adverse effects with rectally administered paracetamol may have been underestimated. A greater risk of overdose has been reported in association with rectal administration of paracetamol, and it has been suggested that it is safer to base rectal dosing on the child's body weight rather than age.[74] The practice of dividing suppositories should be avoided because of the difficulty of achieving a precise dose.

Recommendations

Recommendation 17: Oral administration of paracetamol is preferable to rectal administration in children, because absorption is more constant and it is possible to achieve a more precise dosage based on body weight (evidence level I; strength of recommendation A).

Recommendation 18: Rectal administration should be considered only in the presence of vomiting or other conditions that prevent oral administration (evidence level I; strength of recommendation A).

Recommendation 19: Use of rectal doses of paracetamol that exceed the standard dose should be avoided in children due to the increased risk of toxicity (evidence level I; strength of recommendation E).

Recommendation 20: The rectal dose should be based on the child's weight rather than age. If the dose provided by commercially available suppositories 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-

pyema in association with ibuprofen use.[77] Ibuprofen use should be avoided in patients with Kawasaki disease treated with acetylsalicylic acid, as it inhibits the latter's platelet anti-aggregating effect.[78]

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.[79] 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.[79]

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.[80] 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.[81] A greater risk of overdose has been reported with rectal rather than oral administration of paracetamol, particularly in young children.[74] 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.[79] 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.[82] 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.[82] *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

Table III. Advice and information clinicians should give to parents/caregivers at all pediatric visits (including follow-up visits) to reduce the risk of antipyretic toxicity.

Provide detailed information about the drug formulation, correct dosage, maximum daily dose, intervals between doses, and duration of therapy.
Explain how to calculate the dosage based on the child's weight in kilograms.
Demonstrate the correct use of the dosing device, asking the parent to repeat the instructions and noting that it may be helpful to make a mark on the dosing device to indicate the correct dose.
Discourage use of the adult formulation in children (ie, dividing adult tablets).
Discourage use of rectal formulations without medical advice due to the difficulty of achieving the correct dosage per kilogram.
Explain the difference in concentration between paracetamol drops and syrup.
Dispel the misconception that the more drug the child takes, the more rapidly the fever will be controlled.
Stress that drugs should be administered by an adult.
Provide information about the risk of antipyretic overdose.
Describe the signs and symptoms of antipyretic toxicity (anorexia, nausea, vomiting, oliguria, abdominal pain, hyporesponsiveness, hypothermia) and emphasize the importance of taking the child to a pediatric emergency department immediately should any of these symptoms occur.

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.[56,85] 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

conditions), paracetamol is the only agent recommended by NICE for use as an antipyretic in the newborn.[57] Some studies in preterm and full-term newborns have evaluated the use of paracetamol and its prodrug proparacetamol, but for analgesic rather than antipyretic purposes.[100,101] Paracetamol clearance is reduced in the preterm infant (0.7 L/h × 70 kg^{-1}) and is 5 L/h × 70 kg^{-1} in the full-term newborn, corresponding to ~40% of paracetamol clearance in adults. Relative to older children and adults, the newborn also has a lower risk for drug hepatotoxicity, probably because of the reduced activity of oxidative enzymes (eg, CYP2E1) and increased turnover of glutathione.[100] On the other hand, reduced drug clearance and reduced time to gastric emptying may justify the use of reduced doses, depending on gestational age.

According to 2005 guidelines from the Italian Society of Neonatology,[102] the recommended dosage of paracetamol is 10 mg/kg 3 times daily in newborns with a gestational age of 28 to 32 weeks (maximum dose, 30 mg/kg/d); 10 to 15 mg/kg 3 to 4 times daily in newborns with a gestational age of 32 to 36 weeks (maximum dose, 60 mg/kg/d); and 10 to 15 mg/kg 4 to 6 times daily in newborns with a gestational age >36 weeks (maximum dose, 60 mg/kg/d).

Recommendations

Recommendation 29: Febrile newborns aged <28 days should always be hospitalized due to the elevated risk of severe disease (evidence level I; strength of recommendation A).

Recommendation 30: Paracetamol is the only antipyretic indicated for use in newborns. The dose and frequency of administration in newborns should be adjusted based on gestational age (evidence level III; strength of recommendation A).

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.[103] 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.[104] 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 ($P < 0.01$).[103] 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 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.[37,106] 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.[107] 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 convulsion, there was no significant difference in the frequency of convulsions at 72 hours between groups.[108]

Recommendation

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

ACKNOWLEDGMENTS

Publication of this paper was supported by Abbott SRL, Campoverde di Aprilia, Italy. Meetings of the expert panel were supported by Angelini ACRAF SpA, Rome, Italy, and Reckitt Benckiser Italia SpA, Milan, Italy.

Other participants in the Italian Pediatric Society Panel on the Management of Fever in Children were Andrea de Maria, Institute Giannina Gaslini, University of Genova, Genova; Giacomo Faldella, Neonatology Unit, University of Bologna, Bologna; Gian Luigi Marseglia, Department of Pediatric Sciences, Policlinico San Matteo, IRCCS Foundation, Pavia; Lorenzo Minoli, Department of Infectious Diseases, Policlinico San Matteo, IRCCS Foundation, Pavia; Paola Pecco, Department of Pediatrics, Children's Hospital Regina Margherita, Turin; Simona Squaglia, Department of Allied Health Professions, Health Authority C, Rome; Paolo Tambaro, primary care pediatrician, Caserta; Pasquale Tulimiero, president of the parents' association *Noi per Voi*, Florence; and Giorgio Zavarise, Center for Tropical Diseases, Hospital Sacro Cuore–Don Calabria, Verona.

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*.

REFERENCES

1. Walsh A, Edwards H, Fraser J. Influences on parents' fever management: Beliefs, experiences and information sources. *J Clin Nurs*. 2007;16:2331–2340.
2. Betz MG, Grunfeld AF. 'Fever phobia' in the emergency department: A survey of children's caregivers. *Eur J Emerg Med*. 2006;13:129–133.
3. Ishimine P. The evolving approach to the young child who has fever and no obvious source. *Emerg Med Clin North Am*. 2007;25:1087–1115.
4. Richardson M, Lakhanpaul M. Feverish illness in children under 5 years. *Arch Dis Child Educ Pract Ed*. 2008;93:26–29.
5. Seow VK, Lin AC, Lin IY, et al. Comparing different patterns for managing febrile children in the ED between emergency and pediatric physicians: Impact on patient outcome. *Am J Emerg Med*. 2007;25:1004–1008.
6. Dlugosz CK, Chater RW, Engle JP. Appropriate use of nonprescription analgesics in pediatric patients. *J Pediatr Health Care*. 2006;20:316–325.
7. Italian Drug Agency. Paracetamol overdose cases—February 16th, 2007. http://www.agenziafarmaco.it/ATTUALITA/section7b1e.html?target=&area_tematica=ATTUALITA%C2%A7ion_code=AIFA_ATTUALITA&entity_id=111.50419.1171624853975. Accessed July 17, 2009.
8. Isaacman DJ, Kaminer K, Veligeti H, et al. Comparative practice patterns of emergency medicine physicians and pediatric emergency medicine physicians managing fever in young children. *Pediatrics*. 2001;108:354–358.
9. Baraff LJ. Editorial: Clinical policy for children younger than three years presenting to the emergency department with fever. *Ann Emerg Med*. 2003;42:546–549.
10. Rampersad A, Mukundan D. Fever. *Curr Opin Pediatr*. 2009; 21:139–144.
11. Smaldone A. Paracetamol plus ibuprofen increased time without fever compared with paracetamol but did not differ from ibuprofen in children. *Evid Based Nurs*. 2009;12: 41.
12. Gestione del segno/sintomo febbre in pediatria. Linee Guida della Società Italiana di Pediatria. http://www.sip.it/lineeguida/home/IsComitati/1. Accessed June 2, 2009.
13. Il Programma nazionale per le linee guida (PNLG). Methodological handbook—how to produce, disseminate and update clinical practice recommendations. http://www.pnlg.it/en_method#. Accessed June 2, 2009.
14. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 50: A guideline developer's handbook. http://www.sign.ac.uk/guidelines/fulltext/50/index.html. Accessed July 22, 2009.
15. El-Radhi AS, Barry W. Thermometry in paediatric practice. *Arch Dis Child*. 2006;91:351–356.
16. Martin SA, Kline AM. Can there be a standard for temperature measurement in the pediatric intensive care unit? *AACN Clin Issues*. 2004;15:254–266.
17. Nimah MM, Bshesh K, Callahan JD, Jacobs BR. Infrared tympanic thermometry in comparison with other temperature measurement techniques in febrile children. *Pediatr Crit Care Med*. 2006;7:48–55.
18. Chaturvedi D, Vilhekar KY, Chaturvedi P, Bharamble MS. Comparison of axillary temperature with rectal or oral temperature and determination of optimum placement time in children. *Indian Pediatr*. 2004;41:600–603.
19. Craig JV, Lancaster GA, Williamson PR, Smyth RL. Temperature measured at the axilla compared with rectum in children and young people: Systematic review. *BMJ*. 2000;320:1174–1178.
20. Falzon A, Grech V, Caruana B, et al. How reliable is axillary temperature measurement? *Acta Pediatr*. 2003;92:309–313.
21. Dew PL. Is tympanic membrane thermometry the best method for recording temperature in children? *J Child Health Care*. 2006;10:96–110.
22. Ciuraru NB, Braunstein R, Sulkes A, Stemmer SM. The influence of mucositis on oral thermometry: When fever may not reflect infection. *Clin Infect Dis*. 2008;46:1859–1863.
23. Morley CJ. Measuring infants' temperature. *Midwives Chron*. 1992;105:26–29.
24. Committee on the Environment, Public Health and Food Safety. Report on the proposal for a regulation of the

European Parliament and of the Council on the banning of exports and the safe storage of metallic mercury. June 11, 2007. http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+REPORT+A6-2007-0227+0+DOC+XML+V0//EN&language=EN. Accessed June 2, 2009.
25. Dodd SR, Lancaster GA, Craig JV, et al. In a systematic review, infrared ear thermometry for fever diagnosis in children finds poor sensitivity. *J Clin Epidemiol*. 2006;59:354–357.
26. Robinson JL, Seal RF, Spady DW, Joffres MR. Comparison of esophageal, rectal, axillary, bladder, tympanic, and pulmonary artery temperatures in children. *J Pediatr*. 1998; 133:553–556.
27. Wells N, King J, Hedstrom C, Youngkins J. Does tympanic temperature measure up? *MCN Am J Matern Child Nurs*. 1995;20:95–100.
28. El-Radhi AS, Patel S. An evaluation of tympanic thermometry in a paediatric emergency department. *Emerg Med J*. 2006;23:40–41.
29. Devrim I, Kara A, Ceyhan M, et al. Measurement accuracy of fever by tympanic and axillary thermometry. *Pediatr Emerg Care*. 2007;23:16–19.
30. Craig JV, Lancaster GA, Taylor S, et al. Infrared ear thermometry compared with rectal thermometry in children: A systematic review. *Lancet*. 2002;360:603–609.
31. Kenney RD, Fortenberry JD, Surrat SS, et al. Evaluation of an infrared tympanic membrane thermometer in pediatric patients. *Pediatrics*. 1990;85;854–858.
32. De Curtis M, Calzolari F, Marciano A, et al. Comparison between rectal and infrared skin temperature in the newborn. *Arch Dis Fetal Neonatal Ed*. 2008;93:F55–F57.
33. Sermet-Gaudelus I, Chadelat I, Lenoir G. Body temperature measurement in daily practice [in French]. *Arch Pediatr*. 2005;12:1292–1300.
34. Crocetti M, Moghbeli N, Serwint J. Fever phobia revisited: Have parental misconceptions about fever changed in 20 years? *Pediatrics*. 2001; 107:1241–1246.
35. Walsh A, Edwards H. Management of childhood fever by parents: Literature review. *J Adv Nurs*. 2006;54: 217–227.
36. Taveras EM, Durousseau S, Flores G. Parents' beliefs and practices regarding childhood fever: A study of a multiethnic and socioeconomically diverse sample of parents. *Pediatr Emerg Care*. 2004;20:579–587.
37. Meremikwu M, Oyo-Ita A. Physical methods for treating fever in children. *Cochrane Database Syst Rev*. 2003; (2):CD004264.
38. Kinmonth AL, Fulton Y, Campbell MJ. Management of feverish children at home. *BMJ*. 1992;305:1134–1136.
39. Mahar AF, Allen SJ, Milligan P, et al. Tepid sponging to reduce temperature in febrile children in a tropical climate. *Clin Pediatr (Phila)*. 1994;33: 227–231.
40. Sharber J. The efficacy of tepid sponge bathing to reduce fever in young children. *Am J Emerg Med*. 1997;15:188–192.
41. Friedman AD, Barton LL, for the Sponging Study Group. Efficacy of sponging vs acetaminophen for reduction of fever. *Pediatr Emerg Care*. 1990;6:6–7.
42. Purssell E. Physical treatment of fever. *Arch Dis Child*. 2000;82:238–239.
43. Alpert G, Hibbert E, Fleisher GR. Case-control study of hyperpyrexia in children. *Pediatr Infect Dis J*. 1990; 9:161–163.
44. Trautner BW, Caviness AC, Gerlacher GR, et al. Prospective evaluation of the risk of serious bacterial infection in children who present to the emergency department with hyperpyrexia (temperature of 106 degrees F or higher). *Pediatrics*. 2006; 118:34–40.
45. Stanley R, Pagon Z, Bachur R. Hyperpyrexia among infants younger than 3 months. *Pediatr Emerg Care*. 2005; 21:291–294.
46. Press S. Association of hyperpyrexia with serious disease in children. *Clin Pediatr (Phila)*. 1994;33:19–25.
47. Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. *Pediatrics*. 2001; 108:311–316.
48. Baraff LJ. Management of fever without source in infants and children. *Ann Emerg Med*. 2000;36:602–614.
49. Mackowiak PA. Diagnostic implications and clinical consequences of antipyretic therapy. *Clin Infect Dis*. 2000;31(Suppl 5):S230–S233.
50. Kramer MS, Naimark LE, Roberts-Bräuer R, et al. Risks and benefits of paracetamol antipyresis in young children with fever of presumed viral origin. *Lancet*. 1991;337:591–594.
51. Doran TF, De Angelis C, Baumgardner RA, Melliti ED. Acetaminophen: More harm than good for chickenpox? *J Pediatr*. 1989;114:1045–1048.
52. El-Radhi AS. Why is the evidence not affecting the practice of fever management? *Arch Dis Child*. 2008; 93:918–920.
53. Hall SM, Plaster PA, Glasgow JF, Hancock P. Preadmission antipyretics in Reye's syndrome. *Arch Dis Child*. 1998;63:857–866.
54. US Food and Drug Administration. Labeling for oral and rectal over-the-counter drug products containing aspirin and nonaspirin salicylates: Reye's Syndrome warning. Final rule. *Fed Regist*. 2003;68:18861–18869.
55. Porter JD, Robinson PH, Glasgow JF, et al. Trends in the incidence of Reye's syndrome and the use of aspirin. *Arch Dis Child*. 1990;65:826–829.
56. BNF for children. http://bnfc.org/bnfc/index.htm. Accessed June 2, 2009.
57. Richardson M, Lakhanpaul M, for the Guideline Development Group and the technical team. NICE guidelines: Assessment and initial management of feverish illness in children younger than 5 years: Summary

of NICE guidance. *BMJ*. 2007;334: 1163–1164.
58. Aronoff DM, Neilson EG. Antipyretics: Mechanisms of action and clinical use in fever suppression. *Am J Med*. 2001;111:304–315.
59. Hay AD, Costelloe C, Redmond NM, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): Randomised controlled trial. *BMJ*. 2008;337: a1302. doi:10.1136/bmj.a1302.
60. World Health Organization. Handbook IMCI: Integrated management of childhood illness. http://whqlibdoc.who.int/hq/2000/WHO_FCH_CAH_00.12_pp1-82.pdf. Accessed July 22, 2009.
61. Russell FM, Shann F, Curtis N, Mulholland K. Evidence on the use of paracetamol in febrile children. *Bull World Health Organ*. 2003;81: 367–372.
62. Purssell E. Treating fever in children: Paracetamol or ibuprofen? *Br J Community Nurs*. 2002;7:316–320.
63. Perrot DA, Piira T, Goodenough B, Champion GD. Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: A meta-analysis. *Arch Pediatr Adolesc Med*. 2004;158:521–526.
64. Goldman RD, Ko K, Linett LJ, Scolnik D. Antipyretic efficacy and safety of ibuprofen and acetaminophen in children. *Ann Pharmacother*. 2004;38:146–150.
65. Autret-Leca E, Gibb IA, Goulder MA. Ibuprofen versus paracetamol in pediatric fever: Objective and subjective findings from a randomized, blinded study. *Curr Med Res Opin*. 2007;23:2205–2211.
66. Erlewyn-Lajeunesse MD, Coppens K, et al. Randomised controlled trial of combined paracetamol and ibuprofen for fever. *Arch Dis Child*. 2006; 91:414–416.
67. Lal A, Gomber S, Talukdar B. Antipyretic effects of nimesulide, paracetamol and ibuprofen-paracetamol. *Indian J Pediatr*. 2000;67:865–870.
68. Nabulsi MM, Tamim H, Mahfoud Z, et al. Alternating ibuprofen and acetaminophen in the treatment of febrile children: A pilot study [ISRCTN30487061]. *BMC Med*. 2006;4:4.
69. Sarrell EM, Wielunsky E, Cohen HA. Antipyretic treatment in young children with fever: Acetaminophen, ibuprofen, or both alternating in a randomized, double-blind study. *Arch Pediatr Adolesc Med*. 2006;160: 197–202.
70. Tréluyer JM, Tonnelier S, d'Athis P, et al. Antipyretic efficacy of an initial 30-mg/kg loading dose of acetaminophen versus a 15-mg/kg maintenance dose. *Pediatrics*. 2001; 108:E73.
71. Gibb IA, Anderson BJ. Paracetamol (acetaminophen) pharmacodynamics: Interpreting the plasma concentration. *Arch Dis Child*. 2008;93: 241–247.
72. Scolnik D, Kozer E, Jacobson S, et al. Comparison of oral versus normal and high-dose rectal acetaminophen in the treatment of febrile children. *Pediatrics*. 2002;110:553–556.
73. Nabulsi M, Tamim H, Sabra R, et al. Equal antipyretic effectiveness of oral and rectal acetaminophen: A randomized controlled trial [ISRCTN11886401]. *BMC Pediatr*. 2005;5:35.
74. Bilenko N, Tessler H, Okbe R, et al. Determinants of antipyretic misuse in children up to 5 years of age: A cross-sectional study. *Clin Ther*. 2006; 28:783–793.
75. Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics*. 1999;104:e39.
76. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *JAMA*. 1995;273: 929–933.
77. Byington CL, Spencer LY, Johnson TA, et al. An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: Risk factors and microbiological associations. *Clin Infect Dis*. 2002;34: 434–440.
78. Sohn S, Kwon K. Accelerated thrombotic occlusion of a medium-sized coronary aneurysm in Kawasaki disease by the inhibitory effect of ibuprofen on aspirin. *Pediatr Cardiol*. 2008;29:153–156.
79. American Academy of Pediatrics, Committee on Drugs. Acetaminophen toxicity in children. *Pediatrics*. 2001;108:1020–1024.
80. Li SF, Lacher B, Crain EF. Acetaminophen and ibuprofen dosing by parents. *Pediatr Emerg Care*. 2000;16:394–397.
81. Madlon-Kay DJ, Mosch FS. Liquid medication dosing errors. *J Fam Pract*. 2000;49:741–744.
82. Brok J, Buckley N, Gluud C. Interventions for paracetamol (acetaminophen) overdose. *Cochrane Database Syst Rev*. 2006;(2):CD003328.
83. Holubek W, Stolbach A, Nurok S, et al. A report of two deaths from massive ibuprofen ingestion. *J Med Toxicol*. 2007;3:52–55.
84. Volans G, Monaghan J, Colbridge M. Ibuprofen overdose. *Int J Clin Pract Suppl*. 2003;135:54–60.
85. Easley RB, Altemeier WA III. Central nervous system manifestations of an ibuprofen overdose reversed by naloxone. *Pediatr Emerg Care*. 2000; 16:39–41.
86. Moghal NE, Hulton SA, Milford DV. Care in the use of ibuprofen as an antipyretic in children. *Clin Nephrol*. 1998;49:293–295.
87. Kurtovic J, Riordan SM. Paracetamol-induced hepatotoxicity at recommended dosage. *J Intern Med*. 2003; 253:240–243.
88. Kanabar D, Dale S, Rawat M. A review of ibuprofen and acetaminophen use in febrile children and the occurrence of asthma-related symptoms. *Clin Ther*. 2007;29:2716–2723.
89. McIntyre J, Hull D. Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. *Arch Dis Child*. 1996;74:164–167.

90. Beasley R, Clayton T, Crane J, et al, for the ISAAC Phase Three Study Group. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: Analysis from Phase Three of the ISAAC programme. *Lancet*. 2008;372:1039–1048.
91. Allmers H, Skudlik C, John SM. Acetaminophen use: A risk for asthma? *Curr Allergy Asthma Rep*. 2009;9: 164–167.
92. Ponvert C, Scheinmann P. Allergic and pseudoallergic reactions to analgesics, antipyretics and nonsteroidal anti-inflammatory drugs [in French]. *Arch Pediatr*. 2007;14: 507–512.
93. al-Obaidy SS, McKiernan PJ, Li Wan Po A, et al. Metabolism of paracetamol in children with chronic liver disease. *Eur J Clin Pharmacol*. 1996; 50:69–76.
94. Cormack CR, Sudan S, Addison R, et al. The pharmacokinetics of a single rectal dose of paracetamol (40 mg x kg(-1)) in children with liver disease [published correction appears in *Paediatr Anaesth*. 2006; 16:708]. *Paediatr Anaesth*. 2006;16: 417–423.
95. Leroy S, Mosca A, Landre-Peigne C, et al. Ibuprofen in childhood: Evidence-based review of efficacy and safety [in French]. *Arch Pediatr*. 2007;14:477–484.
96. Riley TR III, Smith JP. Ibuprofen-induced hepatotoxicity in patients with chronic hepatitis C: A case series. *Am J Gastroenterol*. 1998;93: 1563–1565.
97. Andrade RJ, Lucena MI, García-Cortés M, et al. Chronic hepatitis C, ibuprofen, and liver damage. *Am J Gastroenterol*. 2002;97:1854–1855.
98. Pavlicevi´c I, Kuzmani´c M, Rumboldt M, Rumboldt Z. Interaction between antihypertensives and NSAIDs in primary care: A controlled trial. *Can J Clin Pharmacol*. 2008;15:e372–e382.
99. Baraff LJ. Management of infants and young children with fever without source. *Pediatr Ann*. 2008;37: 673–679.
100. Anderson BJ, van Lingen RA, Hansen TG, et al. Acetaminophen developmental pharmacokinetics in premature neonates and infants: A pooled population analysis. *Anesthesiology*. 2002;96:1336–1345.
101. Palmer GM, Atkins M, Anderson BJ, et al. I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth*. 2008;101:523–530.
102. Lago P, Ancora G, Bellini CV, et al, for the Analgesia and Sedation Study Group, Italian Society of Neonatology. Recommendations for the prevention and the treatment of pain in the newborn. http://www.neonatologia.it/atom/Atom/allegato/102.pdf. Accessed June 2, 2009.
103. Manley J, Taddio A. Acetaminophen and ibuprofen for prevention of adverse reactions associated with childhood immunization. *Ann Pharmacother*. 2007;41:1227–1232.
104. Jackson LA, Dunstan M, Starkovich P, et al. Prophylaxis with acetaminophen or ibuprofen for prevention of local reactions to the fifth diphtheria-tetanus toxoids-acellular pertussis vaccination: A randomized, controlled trial. *Pediatrics*. 2006;117:620–625.
105. Taddio A, Manley J, Potash L. Routine immunization practices: Use of topical anesthetics and oral analgesics. *Pediatrics*. 2007; 120:e637–e643.
106. El-Radhi AS, Barry W. Do antipyretics prevent febrile convulsions? *Arch Dis Child*. 2003;88: 641–642.
107. Uhari M, Rantala H, Vainionpää L, Kurttila R. Effect of acetaminophen and of low intermittent doses of diazepam on prevention of recurrences of febrile seizures. *J Pediatr*. 1995;126:991–995.
108. Schnaiderman D, Lahat E, Sheefer T, Aladjem M. Antipyretic effectiveness of acetaminophen in febrile seizures: Ongoing prophylaxis versus sporadic usage. *Eur J Pediatr*. 1993;152:747–749.

(continued on next page)

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)

Appendix (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*) AND (*poisoning* OR *overdose*); 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).