2016 Update of the Italian Pediatric Society Guidelines for Management of Fever in Children

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Objective To review new scientific evidence to update the Italian guidelines for managing fever in children as drafted by the panel of the Italian Pediatric Society.

Study design Relevant publications in English and Italian were identified through search of MEDLINE and the Cochrane Database of Systematic Reviews from May 2012 to November 2015.

Results Previous recommendations are substantially reaffirmed. Antipyretics should be administered with the purpose to control the child's discomfort. Antipyretics should be administered orally; rectal administration is discouraged except in the setting of vomiting. Combined use of paracetamol and ibuprofen is discouraged, considering risk and benefit. Antipyretics are not recommended preemptively to reduce the incidence of fever and local reactions in children undergoing vaccination, or in attempt to prevent febrile convulsions in children. Ibuprofen and paracetamol are not contraindicated in children who are febrile with asthma, with the exception of known cases of paracetamol- or non-steroidal anti-inflammatory drug-induced asthma.

Conclusions Recent medical literature leads to reaffirmation of previous recommendations for use of antipyretics in children who are febrile. *(J Pediatr 2016;■■:■■-■■).*

In 2009, national guidelines for healthcare providers and parents/caregivers on management of fever in children were drafted by an expert panel on behalf of the Italian Pediatric Society.[1] A cross-sectional survey was conducted before their publication and 3 years later to investigate their impact on knowledge and behaviors of pediatricians. A reduction of some incorrect attitudes of Italian pediatricians was observed during the study interval, in particular the alternating use of antipyretics and anti-inflammatory drugs (27-11% of pediatricians, $P < .001$) and the rectal administration of antipyretics in absence of vomiting (44-25%, $P < .001$). Moreover, the rate of pediatricians discouraging physical methods for fever reduction increased (19-36%, $P < .001$).[2] A first update of the guidelines of the Italian Pediatric Society was published in 2012.[3] We aimed to review guidelines in light of new scientific evidence.

Methods

We identified relevant publications in English and Italian through search of MEDLINE and the Cochrane Database of Systematic Reviews from May 2012 to November 2015, as previously described.[1,3] Updated recommendations were considered using the previously described methodology.[1,3]

Results

Methods of Temperature Measurement

Methods and devices for body temperature measurement are controversial. There is no consensus on the best method that is relatively easy, safe, and noninvasive, to accurately predict core temperature.[4] Rectal temperature better reflects the central core temperature but is a physically and psychologically invasive method.[5] For this reason, the Italian guidelines recommend that axillary temperature measurement with a digital thermometer be used in school and home settings. In hospital or ambulatory care settings, an infrared thermometer should be used in children >1 year of age only by trained healthcare personnel because the use of these devices is prone to errors when used by untrained persons.[3] In infants <1 year of age, in every setting, for measurements of axillary temperature only the digital thermometer is recommended because evidence regarding other devices in this age group is poor.[5] After the release of the Italian Guidelines, several studies have been published regarding the use and the performance of infrared thermometers in different settings and age groups[5-16] (**Table**). Infrared thermometers can be noncontact or contact

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Table. Comparison of temporal artery scan thermometer and other classic methods used to measure body temperature

Authors	Year	Study design	Objective	Population (n, age)	Sensitivity (%)	Specificity (%)	Other results	Recommend (R) and not recommend (not-R)
Allegaert et al[5]	2014	Observational	To assess the accuracy of tympanic, infrared skin, and temporal artery scan thermometers to rectal measurement	294, 0.02-17 y	RT >37.8°C: • TT: 18 • ISS: 18 • TAT: 34 RT > 38°C: • TT: 22 • ISS: 27 • TAT: 41	37,8°C cut-off RT: • TT: 99.6 • ISS: 99.5 • TAT: 94 38°C cut-off RT: • TT: 100 • ISS: 100 • TAT: 98	Mean temperature difference: • TT vs RT: 0.49°C (95% CI 1.69, –0.71) ($P < .0001$), • ISS vs RT: 0.34°C (95% CI 1.60, –0.92) ($P < .0001$), • TAT vs RT: 0°C,(95% CI 1.33, –1.32) ($P = .9288$).	R
Batra et al[4]	2013	Observational	To compare axillary, temporal artery, and tympanic membrane measurement to rectal measurement in the emergency department	100, 2-12 y	RT >38°C : • AT: 80 • TT: 98 • TAT: 80	RT >38°C : • AT: 100 • TT: 98 • TAT: 98	Correlation coefficient: • TAT vs RT: febrile 0.99 ($P < .0001$) afebrile 0.91 ($P < .0001$) • AT vs RT: febrile 0.95 ($P < .0001$) afebrile 0.94 ($P < .0001$)	R
Hamilton et al[7]	2013	Observational	To compare 2 infrared thermometers (ThermoScan PRO 4000 [Braun GmbH, Kronberg, Germany] prewarmed tip ear thermometer and the Temporal ScannerTM TAT-5000 TAT [Exergen Corp, Watertown, Massachusetts]) to CT	205, 0-18 y	CT ≥38°C : • TT: 91.6 • TAT: 72.6	CT ≥38°C : • TT: 94.5 • TAT: 96.4	Mean temperature difference: • TT vs TAT: 0.17 ± 0.48°C (CI –0.77, 1.11) • TT vs CT: –0.01 ± 0.39°C (CI –0.77, 0.77) • TAT vs CT: –0.17 ± 0.58°C. (CI –1.32, 0.98)	Not-R
Hoffman et al[8]	2013	Observational	To compare temporal artery temperature to RT in febrile children in an emergency department.	147, 0-36 mo	RT ≥38°C, TAT : 53 RT ≥39°C, TAT: 27	RT ≥38°C, TAT : 97 RT ≥39°, TAT: 79	Mean temperature difference • TAT and RT: 1.99°F (1.11°C) (95% CI 1.75°F-2.23°F).	Not-R
Isler et al[9]	2014	Observational	To compare temporal artery or temporal artery scan thermometers to mercury and digital axillary thermometer measurements.	218, 0-18 y	NA	NA	Mean temperature difference: • TAT vs Glass-mercury AT: 0.6°C, SE 0.08, $P = .000$ • TAT vs digital AT: 0.9°C SE 0.08, $P = .001$ • Mercury AT vs digital AT: 0.6°C, SE 0.08 $P = .000$	R
Moore et al[10]	2014	Observational	To compared temporal artery scan thermometers to detect high RT in children in emergency department.	239, 91 d-4 y	All subjects: TAT >38°C : • RT ≥38°C: 56 (95% CI 54, 58) • RT ≥39°C: 75 (95% CI 73,77) Injured subject: TAT > 38°C: • RT ≥38°C: 67 (95% CI 65,69) • RT ≥39°C: 100 (95% CI 98, 102)	All subject: 38°C TA cut-off: • RT ≥38°C: 93 (95% CI 92, 96) • RT ≥39°C: 85 (95% CI 83,87) Injured subject: 38°C TA cut-off: • RT ≥38°C:10 (95% CI 98, 102) • RT ≥39°C: 10 (95% CI 98, 102)	Mean RT (38.05 ± .99°C) vs mean TAT (37.55 ± .8°C) $P < .0001$.	Not-R

(*continued*)

Table. Continued

Authors	Year	Study design	Objective	Population (n, age)	Sensitivity (%)	Specificity (%)	Other results	Recommend (R) and not recommend (not-R)
Odinaka et al[11]	2014	Observational	To compare temporal artery measurement to rectal measurement.	156, <5 y	RT >38.0°C, TAT >38.0°C: 64.6 RT >38°C, TAT >37.7°C: 83.5	RT > 38.0°C, TAT > 38.0°C: 94.8 RT > 38°C, TAT > 37.7°C: 88.3	Mean temperature difference: TAT vs RT: 0.26 ± 0.65°C ($P < .001$). Neonates mean temperature difference: TAT vs RT 0.02 ± 0.59°C ($P = .810$). Positive correlation between the RT and TAT r = 0.80 ($P < .01$).	Not-R
Reynolds et al[12]	2014	Observational	To compare the accuracy of temporal artery temperatures and axillary temperatures to RT in pediatric emergency department.	52, <4 y	NA	NA	TAT vs RT, percentage of temperature difference: • >±1.0°C: 15% • >±1.5°C: 6% AT vs RT, percentage of temperature differences: • >±1.0°C: 39% • >±1.5°C: 14%	R
Teran et al[15]	2012	Observational	To compare the infrared NCT (Thermofocus [Technimed, Varese, Italy]) to temporal artery scan thermometers and RT.	434, 1-48 mo	RT ≥38: • NCT: 97 (95% CI 92.7-98.8) • TAT: 91.0 (95% CI 85.3-94.7)	RT ≥38: • NCT: 97 (95% CI 93.9-98.6) • TAT: 99.6 (95% CI 97.6-99.9)	Mean temperature difference : • NCT vs RT: 0.029 ± 0.01°C ($P < .001$). • TAT vs RT: –0.20 ± 0.27°C ($P < .001$).	Not-R

AT, axillary thermometer; *CT*, contact thermometer (oral or rectal); *ISS*, infrared skin scan thermometer; *NCT*, noncontact thermometer; *RT*, rectal temperature; *TAT*, temporal artery thermometer; *TT*, tympanic thermometer.

devices. Noncontact thermometers measure the emitted infrared heat of various parts of the body, mainly from the forehead, without direct skin contact. A particular noncontact infrared thermometer, the tympanic scan, measures infrared heat produced by the tympanic membrane.[5] A study comparing tympanic vs traditional methods (rectal and axillary measurement) in 400 children under 5 years of age showed no significant difference between recorded rectal and tympanic temperatures (mean temperature: 38.8°C vs 38.7°C, respectively; $P = .14$). Moreover, the sensitivity in determining fever by tympanic thermometer was higher compared with axillary measurement (92% vs 54%).[6] This study was included in a recent meta-analysis of 25 studies on infrared tympanic temperature measurement, including 5749 children.[16] The calculated pooled sensitivity and specificity of this method was 70% (95% CI 68 and 72) and 86% (95% CI 85 and 88), respectively. The authors also concluded that tympanic measurement seems not to be influenced by surgical procedures, injuries of tympanic membrane, otitis media, baby-crying, effusion, and cerumen in the ear.[16] In another study including 434 children, a high sensitivity (97%; 95% CI 92.7 and 98.8) and specificity (97%; 95% CI 93.9 and 98.6) of noncontact skin infrared method to detect fever was found.[15] The main reported limitation of this device seems to be its lower accuracy in presence of irritability and sweating, which is common in children who are febrile. The performance of other noncontact infrared devices for detecting fever in influenza epidemics has been assessed recently with discordant results.[13]

Contact thermometers are divided into temporal artery and axillary sites. Temporal artery thermometer measures the naturally emitted infrared heat from the temporal artery on the forehead and the mastoid area adjusted for the skin temperature.[5,11,15] Temporal artery thermometer is a hygienic, quick, and noninvasive method. However, data on its accuracy in the diagnosis of fever are conflicting.[5] The use of temporal artery thermometer has been assessed in 9 studies totaling 1845 children (**Table**).[3,5,7-12,14,15] The results of these studies are controversial. Four studies support the use of temporal artery thermometer in children as an alternative noninvasive method in the emergency department setting.[4,5,9,12] Reynolds et al[12] found that the temporal artery measurement bias was −0.46°C with limits of agreement of ±0.5°C compared with rectal measurement. The bias and precision values of this method was within the acceptable range set by experts, making it suitable for body temperature detection in children younger than 4 years of age.[12] In a recent study, authors conclude that temporal artery thermometer tends to overestimate lower temperatures and underestimate higher temperatures.[5] Five other studies do not support the use of temporal artery thermometer for fever detection in children.[7,8,10,11,15] In a large study, including 205 children recruited in an emergency department in Argentina, overall false-negative rate was 3-fold higher using temporal artery thermometer compared with tympanic infrared thermometer.[7] In the study by Moore et al,[10] the overall sensitivity and specificity of temporal artery measurement in detecting high fever was low (75% and 85%, respectively). However, the authors encouraged the use of temporal artery thermometer in selected populations, such as injured children, in whom temporal artery thermometer was found to have a sensitivity and specificity of 100%. A major study limitation was the small number of injured children studied (n = 27). Two studies have been conducted in neonates showing conflicting results.[11,17] The available data do not permit a definitive conclusion on the use of temporal artery thermometer in the pediatric population.

Recommendation. Axillary temperature measurement using a digital thermometer is recommended in children younger than 4 weeks of age in all settings (evidence level III; strength of recommendation, B). In the hospital or ambulatory care setting, axillary temperature measurement using a digital thermometer or an infrared thermometer (tympanic or with or without skin contact) is recommended in children older than 4 weeks (evidence level II; strength of recommendation, B).

Use of Antipyretic Drugs

Paracetamol and ibuprofen are the only antipyretic drugs recommended for use in children. The existing debate regards their combined use.[18,19] A Cochrane review of 6 trials, including 915 children, reported that paracetamol and ibuprofen use in children who are led to a lower mean temperature at 1 and 4 hours compared with use of a single antipyretic (mean difference at 1 hour: −0.27°C; 95% CI −0.4 and −0.08; mean difference at 4 hours: −0.70°C; 95% CI −1.05 and 0.35).[20] Moreover, alternating paracetamol and ibuprofen when fever fails to resolve or recurs after a dose of a single agent, might result in a lower mean temperature at 1 hour after the second dose (mean difference −0.60°C, 95%CI −0.94 and −0.26). Although no serious adverse event was reported in this systematic review, the authors raise the concern for limited safety assessment of the combined and alternating regimens.[20]

In a randomized comparative trial conducted on 99 children who are febrile aged 6 months to 12 years, the mean tympanic temperature in the combined paracetamol and ibuprofen group was significantly lower compared with the paracetamol group 4 hours after drug administration (mean reduction in temperature 2.19 ± 0.83 vs 1.48 ± 0.94; $P < .05$).[21] The authors noted that, despite the statistically significant different temperature reduction between the 2 groups, the difference was not clinically relevant. Moreover, no significant differences were observed between ibuprofen alone and combination treatment ($P = .167$) and between paracetamol and ibuprofen monotherapy ($P = .102$).[21] Also, there are concerns about the increased risk of inaccurate dosages using combined or alternating regimens.

The National Institute for Health and Care Excellence update guidance of May 2013 does not recommend the combination of paracetamol and ibuprofen.[22] The alternating regimen could be considered in children who are febrile only in the case of persistent or recurrent distress.[22] In conclusion, based on previous studies and considering the lack of safety trials, the combined or alternating use of paracetamol and ibuprofen is not recommended in children. Moreover, alternating use of antipyretics may encourage fever phobia. Compared with ibuprofen, paracetamol can be used in infants under 3 months

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of age as well as in cases of dehydration.[18] Moreover, ibuprofen is not recommended in chickenpox or Kawasaki disease and can cause severe acute kidney injury, even when correctly dosed (reference). A systematic review of 13 unpublished and 40 published clinical trials,[23] enrolling 3037 children overall who received an oral dose of 10-15 mg/kg of paracetamol, concluded that dosage recommendation remains appropriate.[24] Moreover, compared with 10 mg/kg, the dosage of 15 mg/kg appears to maintain low temperature for longer time and to be more effective in decreasing the mean temperature from baseline (1.6°C vs 1.2°C).[24] A retrospective analysis of paracetamol-associated acute liver failure in 14 children showed hepatotoxicity was mainly related to medication error, specifically in relation to dosage, frequency, and length of treatment.[25] In general, it should be remembered that toxicity in children tends to occur after administration of single doses ranging from 120 to 150 mg/kg, corresponding to 10-15 times the recommended dosage.[1] Therefore, paracetamol should be used at the dosage of 40 mg/kg per day, divided in 4 doses. At this dosage, paracetamol appears to be as safe and effective as ibuprofen.

Recommendations. Paracetamol and ibuprofen are the only antipyretic drugs recommended for use in children (evidence level I; strength of recommendation, A). Combined or alternating use of ibuprofen and paracetamol is not recommended (evidence level VI; strength of recommendation, D).

Antipyretics at Immunization Episodes

One study is available on the use of antipyretics to prevent febrile and other common vaccination reactions associated with childhood vaccinations.[26] In this trial, 301 healthy infants (<14 months of age) who received routine 7-valent pneumococcal conjugate vaccine co-administered with hexavalent vaccine were randomized to receive no paracetamol or 2 doses of paracetamol (at the vaccination and 6-8 hours after vaccination).[26] Paracetamol use was significantly associated with reduction of fever ≥38°C in children receiving the infant vaccine doses (2, 3, and 4 months), with a computed efficacy of 43% (95% CI 17.4 and 61.2), whereas use was not statistically significant for the toddler dose (11-14 months) (efficacy 15.9%; 95% CI −19.9 and 41.3). Authors concluded that use of paracetamol might not be justified considering that fever was rarely >39°C, and the other adverse events usually were mild and of no concern.[26]

This study was included in a systematic review of 13 randomized controlled trials of antipyretic use with immunization.[27] Overall, 5077 children were included. A significant reduction of temperature ≥38.0°C was seen in the first 24-48 hours in the prophylactic paracetamol group compared with placebo both after primary (OR 0.35; 95% CI 0.26 and 0.48) and booster (OR 0.60; 95% CI 0.39 and 0.93) vaccinations. In this systematic review, the antibody response to vaccinations was assessed in children receiving the paracetamol prophylactically. The geometric mean concentrations of antibody was lower in the prophylactic group after primary and booster vaccination for all the pneumococcal vaccine serotypes, tetanus, and diphtheria. However, antibody levels were still above correlates of protection.[27] The authors conclude that available data are inclusive to establish the real clinical and epidemiologic relevance of this finding.

Paracetamol has been studied when given prophylactically at the time of the multicomponent meningococcal serogroup B vaccination.[28] This vaccine was highly reactogenic with 70% of immunized infants having fever ≥38.5°C at least once in the first 3 days after the primary dose. Fever was less common (39%) in infants receiving paracetamol prophylactically just before or at the time of vaccination followed by 2 further administrations at 4- to 6-hour intervals.

Neither the American Academy of Pediatrics nor the US Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recommends antipyretics before or at the time of immunization.[29,30] Cited reasons are lack of evidence to support use, lack of demonstrable effect in prevention of febrile seizures in children who had a previous febrile seizure, and concern for potential detrimental effect on the immune response to the vaccine(s) being administered. Neither organization is opposed to use of antipyretic should fever or local discomfort occur following vaccination.

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

Antipyretics to Prevent Febrile Convulsions

A recent meta-analysis of 3 studies, including overall 540 children (6-72 months of age) with previous febrile seizures, assessed the use of antipyretics for prevention of febrile convulsions.[31] In this study, no statistically significant difference was found in the rate of febrile seizures between children who received prophylactic antipyretics or placebo (OR 0.9, 95% CI 0.57 and 1.43).[31]

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

Paracetamol and Risk of Asthma

Association between paracetamol administration and wheezing episode was studied in a double blind placebo-controlled trial, conducted on 42 children with asthma and 21 healthy age-matched controls.[32] This study showed no bronchoconstriction and no increase in airway inflammation 60 minutes after the administration of a single dose of paracetamol in children with asthma. Measurements of fractional exhaled nitric oxide, forced expiratory volume in 1 second, Tiffenau index, and forced expiratory flow between 25% and 75% were not significantly different between the 2 groups (fractional exhaled nitric oxide $P = .14$; forced expiratory volume in 1 second $P = .87$; Tiffenau index $P = .53$; forced expiratory flow between 25% and 75% $P = .48$).[32]

In a systematic review, Heintze et al[33] proposed that the previous studies suggesting an association between paracetamol and asthma might be affected by confounding variables and bias, such as the lack of adjustment for indications for

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paracetamol in the cross-sectional studies. A recent meta-analysis of 6 studies evaluated the paracetamol intake in the first 2 years of life and the development of asthma.[34] The comparison between any paracetamol and no paracetamol administration showed a significant correlation with asthma (OR 1.56, 95% CI 1.07 and 2.26; adjusted for respiratory tract infection: OR 1.41, 95% CI 0.96 and 2.08). In the 3 studies stratifying for frequency of intake, an increased risk of asthma was observed in children who received a higher number of doses (OR 1.15, 95% CI 1.00 and 1.31). After adjustment for respiratory tract infections, it was not significant (OR 1.06, 95% CI 0.92 and 1.22), suggesting likely confounding by indication.[34]

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

Discussion

Overall, the recent available literature is mainly in accordance with the previous recommendations and support their continued applicability in clinical practice. Implementation and periodic update of available guidelines are pivotal to affecting appropriate clinical behavior of pediatricians regarding the management of fever in childhood. ■

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Appendix

Italian Pediatric Society Panel for the Management of Fever in Children includes:

Writing Committee—Elena Chiappini, PhD, Elisabetta Venturini, MD, Giulia Remaschi, MD, Filippo Festini, RN, Luisa Galli, MD, Maurizio de Martino, MD, Francesca Bonsignori, MD, and Alessandro Mugelli, MD (University of Florence, Florence, Italy); Nicola Principi, MD, and Susanna Esposito, MD (Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy); Riccardo Longhi, MD (Sant'Anna Hospital, Como, Italy); Pier-Angelo Tovo, MD (University of Milan, Milan, Italy); Paolo Becherucci, MD (Primary Care Practice, Florence, Italy); Bice Lucchesi, RPh (Health Authority 1, Massa, Italy); Gian Luigi Marseglia, MD (Istituto di Ricovero e Cura a Carattere Scientifico Foundation, Pavia, Italy).

Other participants in the Italian Pediatric Society Panel on the Management of Fever in Children—

Andrea de Maria, MD (University of Genova, Genova, Italy); Giacomo Faldella, MD (University of Bologna, Bologna, Italy); Paola Pecco, MD (Children's Hospital Regina Margherita, Turin, Italy); Simona Squaglia, MD (Health Authority C, Rome, Italy); Paolo Tambaro, MD (primary care pediatrician, Caserta, Italy); Pasquale Tulimiero, (President of the Parents' Association Noi per Voi, Florence, Italy); and Giorgio Zavarise, MD (Hospital Sacro Cuore-Don Calabria, Verona, Italy).

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 Pediatric Nursing Sciences, and the parents' association Noi per Voi.

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