

Italian Experts' Statements on Paracetamol/Ibuprofen in Children Fever/Pain

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Fever and pain are challenging symptoms in children and adolescents and are common reasons for consultations in primary care and hospital. Paracetamol and ibuprofen are currently the only recommended drugs for treating fever in Italy, but the therapeutic approaches are discrepant in the different settings.

Keywords: fever ; pain ; children ; primary care ; hospital ; emergency department

1. Introduction

Fever and pain are challenging symptoms in children and adolescents ^{[1][2][3]} and are common reasons for consultations in primary care and hospital admissions. The therapeutic approaches are discrepant with the evidence-based recommendations in the various settings ^{[4][5][6][7]}. The management of fever is characterized by overtreatment, often owing to “fever phobia” ^[8], whereas pain is undertreated ^[7], leading to untimely and inadequate analgesia.

In Italy, there are incorrect dosages and low adherence to the above-mentioned guidelines by healthcare professionals and caregivers, and these practices can be dangerous for the health of children ^{[6][8]}, with regional differences that may mirror the varied backgrounds of pediatricians. In the absence of a clear and univocal definition of discomfort ^[1], the prevalent approach to febrile patients still focuses on lowering the temperature by antipyretics ^[8].

Pain management is still suboptimal and uneven, especially in emergency departments (EDs), with inadequate evaluation and treatment ^{[7][9][10]}. The approach to pain in primary care is heterogeneous ^[4], yet pain management requires systematic approaches ^[11]. Although paracetamol and ibuprofen are the most prescribed analgesics for acute mild–moderate pain in children, their use is inappropriate in most pediatric cases in Italian EDs ^{[10][12]}.

For the treatment of febrile children, paracetamol and ibuprofen are currently the only recommended drugs in Italy ^[13]; paracetamol is indicated since birth, whereas ibuprofen is indicated starting from three months of age ^{[13][14]}.

2. Italian Experts' Statements on Paracetamol/Ibuprofen in Children Fever/Pain

Communication was acknowledged as a priority, since it is often insufficient, underused, or heterogeneous. Information is essential for the family, but also for healthcare providers (HCPs) such as pediatricians, nurses, and pharmacists. This priority is due to the different views among HCPs in the various settings in the same territory that may disorient parents. Fever phobia—recently amplified during the COVID-19 pandemic—is detectable in parents and HCPs who manifest hyper-sensibility or limited tolerance to fever.

It was suggested to enhance communication, especially for parents, taking advantage of social media and using coherent messages in simple language, especially regarding general recommendations about the use of drugs and specific guidelines for the administration of paracetamol and ibuprofen. Educational activities should be extended to schools and television programs.

The experts underlined the paramount importance of the continuous education of all HCPs and suggested that pediatricians should train other HCPs in favoring homogeneity and agreement. It is essential to align the messages between hospital and territory settings. Educational activities should be geared toward each territory and macro-area, with a uniform approach within the same administrative area (city, region, or local healthcare administration). The central–southern panel underlined the importance of spreading coherent educational messages based on simple concepts (no

physical tools and no preventive administration of drugs). These messages should be shared between territory and hospital settings.

Currently, the antipyretic dose is calculated according to either the age or the weight range. Instead, the dose must be recommended according to the weight of each child. The dosage of paracetamol for infants, even according to the Italian guidelines, is not univocal.

The opinion of the expert panel was that the alternated or combined use of ibuprofen and paracetamol is often improper. The administration routes are critical and regard the personalization of the dose; yet, a distinction between drops, syrup, and suspension is lacking.

The opinion of the expert panel was that a misconception about a superior efficacy and manageability of the rectal route has been spread among parents. The rectal route has limitations in administering the correct dose, given the variable gut absorption ^[15]. The opinion of the expert panel was that parents perceive ibuprofen as more effective than paracetamol. This perception may be due to the use of ibuprofen at maximum dosage compared to paracetamol, which is often underdosed, especially when administered through the rectal route. Consequently, the rectal route should never be the first-line choice but prescribed only in the presence of vomiting. Moreover, this misconception can explain the increased use of ibuprofen as a first-line treatment in the territory and EDs.

Fever prevention during convulsive crisis is not in compliance with the guidelines; thus, HCPs detect shortcomings in the management of these patients.

The critical issues linked to caregivers are self-medication, self-management of drugs, tendency to observe the degree of temperature as being more than the general status, pursuing the lowering of the temperature, and lacking knowledge of the different side effects of drugs (ibuprofen has different side effects).

2.1. Acute Mild–Moderate Pain in Primary Care Settings

The loco-regional difference in managing acute mild–moderate pain in children may be ascribable to the different backgrounds of the pediatricians. We should consider management in terms of pain assessment and treatment, since the appraisal of pain is as valuable as the efficacy of the treatment. The real-life experience of the expert panel is that the systemic aspect of pain is under-evaluated in all Italian regions—only topical therapy is often adopted. The use of scales for pain assessment and re-assessment is incorrect or lacking. The software and computerized medical records used in hospitals generally do not have sections for measuring pain. However, insisting the use of pain scales is paramount because the current methods are based on empirical and indirect measurements is.

The management of pain treatment is often inadequate or missing for prophylaxis, as is the repeated treatments during the day without considering the entire daily dose and in the planned treatment of continuous acute mild–moderate pain (otitis, pharyngitis, etc.). The on-demand approach is frequently used instead of the planned use of drugs.

Similar to fever, the experts underlined the need for reinforcing educational activities through meetings and training with other HCPs (pediatricians, orthopedics, otolaryngologists, etc.) that can increase the awareness of pain in children. In particular, the objective is to increase orthopedics' attitudes toward evaluating and treating pain in children. Since pain scales are not routinely used, the expert panel recommended that use of scales with strong evidence be more promoted in the primary care setting ^[16]. Particular attention should be paid to the management of disabled children since they are not able to express their pain.

2.2. Fever and Acute Mild–Moderate Pain for Specific Patient Profiles in Primary Care Settings

The risk of dehydration in the management of fever and pain in children in primary care is not always considered, and improper use of ibuprofen in children with Kawasaki's disease is still detectable, as well as in patients with pneumonia and varicella (Kawasaki's disease is not a common diagnosis and can be detected after several days of a fever).

The risk of hemorrhage is not considered in at-risk patients (a lack of awareness of pediatricians about the risk of hemorrhage with NSAIDs).

Moreover, caution is required for subjects with acute viral or bacterial infections, underlying chronic pathologies (comorbidities), infants, gastrointestinal diseases, hemorrhage, and risk of dehydration and acute gastroenteritis.

In children with several pathologies, self-prescription by the families must be opposed and the therapy must be decided and prescribed by doctors.

2.3. Fever and/or Acute Mild–Moderate Pain in General and in Specific Patient Profiles in Hospital Care Settings

Children with fever or pain are among those patients who most frequently access Eds and can present different levels of complexity. The critical issues in hospital are the same as those found in the primary care setting. Additional critical issues in hospital are the improper use of paracetamol for fever by the intravenous injection route rather than by oral administration and the alternating use of paracetamol and ibuprofen. More attention on comorbidities and other pathologies is required. Not all EDs are specialized in pediatrics which can explain this picture and can lead to the inadequate management of pediatric patients.

The reference hospital center should highlight, sensitize, and share the risk factors of each child with all HCPs, e.g., writing the risk factors on the dismissal letter. Children with chronic and complex diseases deserve special attention.

Training about prophylaxis for predictable pain, such as that related to procedures, is needed even for ED-based HCPs.

It is essential to also sensitize parents to pain and its best management. In particular, the central–southern panel highlighted the excessive use of self-prescribed ibuprofen by the family for fever in children with dehydration and gastroenteritis, possibly explained by an over-prescription of this drug by pediatricians.

The Italian guidelines show that the efficacy of ibuprofen is not superior to that of paracetamol, and highlight their similar safety profiles, yet the types of adverse events are different. Therefore, in light of precision medicine, it is possible to identify the patient categories for whom the two drugs are most appropriate.

3. Statements

Statement 1

Recommendations for the use of paracetamol and ibuprofen in primary care and emergency settings should overlap (agreement necessary regardless of the setting).*

- Infants require particular attention in terms of fever management;
- Fever should be distinguished from pain;
- It would be helpful to underline certain concepts: not alternating ibuprofen and paracetamol therapy; the guidelines are not consistent everywhere.

According to a recent systematic review, although combined or alternating therapy reduces the temperature more effectively than monotherapy, the benefit on child discomfort was not clinically meaningful ^[17]. This evidence cannot bolster the combined or alternating use of the two drugs compared to monotherapies, in agreement with the majority of international recommendations ^{[13][17][18]}.

Statement 2

The guidelines suggest that the efficacies of paracetamol and ibuprofen are comparable (in terms of efficacy, a 15 mg/kg dose of paracetamol overlaps a 10 mg/kg dose of ibuprofen).*

- There is no difference in superiority in terms of efficacy between paracetamol and ibuprofen ^{[13][14]};
- The safety profiles of the two drugs are similar but differ according to the type of reported adverse events for the treatment of fever and pain in children. Given the widespread use and the evidence, paracetamol and ibuprofen are associated with rare and specific side effects at the recommended doses ^{[19][20]}.

Statement 3

Paracetamol showcases a good safety profile when used at the recommended dose of 15 mg/kg 4 times/day maximum (not to overstep the daily dose of 60 mg/kg; the route of administration and the age of the child are important, e.g., in neonates and infants, the dose should be adjusted to 12.5 mg/kg every 6 h if given by the IV route)*

- The dosing of paracetamol must be established according to body weight;
- The maximum recommended dose of paracetamol is safe and cautious. For pain, the toxicity threshold dose of paracetamol (single dose) can be 120 mg/kg [21].

For febrile children, the AGREE II method appraises the guidelines of the Italian Society of Pediatrics, as those with the highest-quality score in terms of methodology, applicability, and transparency [1].

Compared to ibuprofen, at the recommended doses, the liver toxicity of paracetamol is more predictable and liver injury occurs when a dose of 80–100 mg/kg/die is exceeded. At the recommended doses, paracetamol can be safer than NSAIDs for patients with advanced liver disease, but dose adjustments are advised [22]. A dose of 120–150 mg/kg is a potentially toxic dose. A dose of 60 mg/kg/day is the recommended therapeutic dose in children over three months of age or weighing more than 7 kg [13][21][23].

Statement 4

The use of paracetamol is more appropriate in specific conditions: Children at risk of dehydration or dehydrated children and children with varicella, pneumonia, Kawasaki's disease, and coagulation disorders (dehydration is a frequent condition in infants with fever).*

- In patients with hepatic impairment, paracetamol is recommended for fever and pain management;
- Dehydration is common in febrile children. However, if correctly hydrated, a febrile child should not be considered as under specific conditions. In hospital, the hydration of febrile infants is under control, but at home, paracetamol is advisable;
- The risk of dehydration due to fever is higher in younger than older children;
- For dehydrated children, the administration of ibuprofen is not necessary and not indicated by the Italian Society of Pediatrics [1].

The inappropriate use of antipyretic drugs for fever or acute mild–moderate pain in children or adolescents can lead to an increased risk of toxicity, especially for specific patients' profiles.

The expert panels agreed upon identifying specific children's conditions most amenable to paracetamol or ibuprofen. In conclusion, the opinion of the expert panel was that paracetamol is not only more appropriate for children with specific clinical conditions, but it should also be considered, when required/necessary, the first-line treatment for fever and acute mild–moderate pain.

As an additional suggestion, optimizing the pre- and in-hospital management of fever is desirable. Dehydration, which is common in febrile children [24], should always be addressed.

Furthermore, the maximal daily dose of paracetamol to avoid toxicity is 80–100 mg/kg (the recommended dose is “not to exceed a daily dosage of 60 mg/kg”; the route of administration and the age of the child are important, e.g., in neonates and infants, the dose should be adjusted to 12.5 mg/kg every 6 h if given by the IV route) [1]. Paracetamol (as well as other drugs) poisoning is a common reason of admission in poison centers; therefore, drugs must be kept far out of reach of children.

References

1. Chiappini, E.; Bortone, B.; Galli, L.; de Martino, M. Guidelines for the symptomatic management of fever in children: Systematic review of the literature and quality appraisal with AGREE II. *BMJ Open* 2017, 7, e015404.
2. Eccleston, C.; Fischer, E.; Howard, R.F.; Slater, R.; Fargeron, P.; Palermo, T.M.; Birnie, K.A.; Anderson, B.J.; Chambers, C.T.; Crombez, G.; et al. Delivering transformative action in paediatric pain: A Lancet Child & Adolescent Health Commission. *Lancet Child Adolesc. Health* 2021, 5, 47–87.
3. Murphy, A.; McCoy, S.; O'Reilly, K.; Diez, J.; Crispino, G.; Wakai, A.; O'Sullivan, R. A prevalence and management study of acute pain in children attending emergency departments by ambulance. *Prehosp. Emerg. Care* 2016, 20, 52–58.

4. Raffaelli, G.; Orenti, A.; Gambino, M.; Peves Rio, W.; Bosis, S.; Bianchini, S.; Tagliabue, C.; Esposito, S. Fever and pain management in childhood: Healthcare providers' and parents' adherence to current recommendations. *Int. J. Environ. Res. Public Health* 2016, **13**, 499.
5. The Royal College of Emergency Medicine. Management of Pain in Children. In Best Practices Guideline; The Royal College of Emergency Medicine: London, UK, 2017; Available online: [https://www.rcem.ac.uk/docs/RCEM%20Guidance/RCEM%20Pain%20in%20Children%20-%20Best%20Practice%20Guidance%20\(REV%20Jul%202017\).pdf](https://www.rcem.ac.uk/docs/RCEM%20Guidance/RCEM%20Pain%20in%20Children%20-%20Best%20Practice%20Guidance%20(REV%20Jul%202017).pdf) (accessed on 7 June 2021).
6. Chiappini, E.; D'Elia, S.; Mazzantini, R.; Becherucci, P.; Pierattelli, M.; Galli, L.; de Martino, M. Adherence among Italian paediatricians to the Italian guidelines for the management of fever in children: A cross sectional survey. *BMC Pediatr.* 2013, **13**, 210.
7. Milani, G.P.; Benini, F.; Dell'Era, L.; Silvagni, D.; Podestà, A.F.; Mancusi, R.L.; Fossali, E.F.; PIERRE GROUP STUDY. Acute pain management: Acetaminophen and ibuprofen are often underdosed (Observational study). *Eur. J. Pediatr.* 2017, **176**, 979–982.
8. Chiappini, E.; Parretti, A.; Becherucci, P.; Pierattelli, M.; Bonsignori, F.; Galli, L.; de Martino, M. Parental and medical knowledge and management of fever in Italian pre-school children. *BMC Pediatr.* 2012, **12**, 97.
9. Benini, F.; Piga, S.; Zangardi, T.; Messi, G.; Tomasello, C.; Pirozzi, N.; Cuttini, M.; PIPER Study Group. Nationwide study of headache in paediatric emergency care. *Acta Paediatr.* 2016, **105**, e200–e208.
10. Benini, F.; Castagno, E.; Barbi, E.; Congedi, S.; Urbino, A.; Biban, P.; Calistri, L.; Mancusi, R.L. Multicentre emergency department study found that paracetamol and ibuprofen were inappropriately used in 83% and 63% of paediatric cases. *Acta Paediatr.* 2018, **107**, 1766–1774.
11. Fein, J.A.; Zempsky, W.; Cravero, J.P. Committee on Pediatric Emergency Medicine and Section on Anesthesiology and Pain Medicine. *Pediatrics* 2012, **130**, e1391.
12. Ferrante, P.; Cuttini, M.; Zangardi, T.; Tomasello, C.; Messi, G.; Pirozzi, N.; Losacco, V.; Piga, S.; Benini, F.; PIPER Study Group. Pain management policies and practices in pediatric emergency care: A nationwide survey of Italian hospitals. *BMC Pediatr.* 2013, **13**, 139.
13. Chiappini, E.; Venturini, E.; Remaschi, G.; Principi, N.; Longhi, R.; Tovo, P.; Becherucci, P.; Bonsignori, F.; Esposito, S.; Festini, F.; et al. Italian Pediatric Society Panel for the Management of fever in children. 2016 Update of the Italian Pediatric Society Guidelines for management of fever in children. *J. Pediatr.* 2017, **180**, 177–183.
14. NICE (National Institute for Health and Care Excellence). NICE Guideline; NICE: London, UK, 2019; Available online: www.nice.org.uk/guidance/ng143 (accessed on 7 June 2021).
15. Ziesenitz, V.C.; Zutter, A.; Erb, T.O.; van den Anker, J. Efficacy and safety of ibuprofen in infants aged between 3 and 6 months. *Pediatr. Drugs* 2017, **19**, 277–290.
16. Birnie, K.A.; Hundert, A.S.; Laloo, C.; Nguyen, C.; Stinson, J.N. Recommendations for selection of self-report pain intensity measures in children and adolescents: A systematic review and quality assessment of measurement properties. *Pain* 2019, **160**, 5–18.
17. Trippella, G.; Ciarcia, M.; de Martino, M.; Chiappini, E. Prescribing controversies: An updated review and meta-analysis on combined/alternating use of ibuprofen and paracetamol in febrile children. *Front. Pediatr.* 2019, **7**, 217.
18. Wong, T. Combined and alternating paracetamol and ibuprofen therapy for febrile children. *Evid.-Based Child Health* 2014, **9**, 675–729.
19. Kanabar, D.J. A clinical and safety review of paracetamol and ibuprofen in children. *Immunopharmacology* 2017, **25**, 1–9.
20. Barbagallo, M.; Sacerdote, P. Ibuprofen in the treatment of children's inflammatory pain: A clinical and pharmacological overview. *Minerva Pediatr.* 2019, **71**, 82–99.
21. De Martino, M.; Chiarugi, A. Recent advances in pediatric use of oral paracetamol in fever and pain management. *Pain Ther.* 2015, **4**, 149–168.
22. Malespin, M.H. Risk of nonsteroidal anti-inflammatory drugs and safety of acetaminophen in patients with advanced liver disease. *Clin. Liver Dis.* 2018, **12**, 85–88.
23. American Academy of Pediatrics. Committee on Drugs. Acetaminophen toxicity in children. *Pediatrics* 2001, **108**, 1020–1024.
24. Boutin, A.; Carceller, A.; Desjardins, M.P.; Snachez, M.; Gravel, J. Association between dehydration and fever during the first week of life. *Clin. Pediatr. Phila* 2017, **56**, 1328–1335.

