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## **Management of fever and associated symptoms in children and adults: an Italian national survey**

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**Availability of data and materials:** the datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## **Abstract**

An advisory committee of Italian experts conducted a national, cross-sectional, web-based survey in June 2024 to describe the current management of fever and associated symptoms in different settings, including primary care, emergency departments, and hospital wards in pediatric and adult patients. The survey covered two domains: participants' features and questions about the main drugs prescribed to treat fever and associated symptoms. A total of 832 questionnaires were analyzed. Paracetamol was the most prescribed drug to treat fever. Most participants were influenced by related symptoms when choosing the most appropriate drug. Almost all participants selected the oral route as their preferred one. This survey

provides a current state of fever management among physicians in different settings throughout Italy. It highlights a trend in treating fever with antipyretics at appropriate doses and evaluating pain through validated scales.

## **Introduction**

Fever and associated symptoms are a challenging issue in both adults and children. They represent common reasons for primary care visits and hospital admissions.<sup>1</sup> Fever is caused by a disruption of thermal homeostasis and thermal setpoint caused by pyrogenic cytokines. It is an essential part of the inflammatory response to avoid the reproduction of bacteria and viruses and boost the immunological response.<sup>2</sup> As a result of a defensive mechanism, fever should not be treated directly and drastically; instead, the main focus should be on the underlying cause. Although most fevers are viral in origin, approaching a febrile patient is always a concern, and there is a significant gap between current practice and scientific evidence.<sup>3</sup> Overtreatment is common, often due to “fever phobia.”<sup>4</sup> A wide range of symptoms may be associated with fever, including headache, muscle ache, sweating, chills, loss of appetite, and fatigue.<sup>5</sup> Their treatment and relief with antipyretics are strictly connected to the management of pain in different age groups.<sup>3</sup> Not assessing appropriately for pain leads to underestimation and subsequent undertreatment. Patients who are non-verbal or who have mental impairments are at higher risk. Standardized reliable assessment scores stratified by age are available but not always sufficient if used alone.<sup>6</sup> An overall approach should be adopted, including the patient’s quality of life, sleep pattern, social relations, and daily activities to ensure appropriate management. As with the management of other conditions<sup>7</sup>, and despite a remarkable body of evidence,<sup>8</sup> a standardized treatment of fever and associated symptoms cannot be recognized yet in adults or children.

The primary goal of this nationwide survey is to provide an overview of the current management of fever and associated symptoms in various healthcare settings, including primary care, emergency departments, and hospital wards for pediatric and adult patients.

## **Materials and Methods**

Potential items for the online questionnaire were identified by an advisory board of Italian experts, either primary care or hospitalists, who are among the authors of the present paper. All possessed extensive knowledge of current literature and expertise on this topic, with some specializing in adult patients and others in pediatric care. Therefore, the items used for this survey resulted from discrepancies or gaps in literature and clinical practice that were collectively deemed relevant by the advisory board. This study is a national, cross-sectional, web-based survey. The questionnaire was distributed in June 2024 to 2000 physicians nationwide, with half primary care physicians and the other half hospitalists, including emergency physicians and ward physicians. Pool selection was assumed to provide a valid representative sample of the hospital and the territory. To boost the return rate, four reminder emails were sent along the planned time frame. Participants in the study provided their informed consent before starting the survey upon their free and voluntary assent on the first page. One thousand one hundred forty recipients did not provide informed consent and were excluded from the study. The enrollment flow chart is shown in Figure 1.

The estimated time to complete the questionnaire was 5 minutes. The questions were created with multiple-choice answers. For some questions, a free-text answer was requested. Overall, the questionnaire was composed of 11 items. Please take note of the following information:

The survey included two main areas: i) Basic information on the participant, such as gender and current role (resident, hospital doctor, emergency doctor, primary care). Participants were also asked to specify if they are members of a medical group practice and the estimated number of patients they treat for fever per year; ii) Questions about the primary medications prescribed for treating fever and associated symptoms. This included details about dosage, reported side effects, and the use of scales to evaluate pain when it was associated with fever. The whole survey document is included in a supplementary file. The survey detailed the symptoms associated with fever, including fatigue, warmth, headache, loss of appetite, muscle aches, chills, sweating, nausea, irritability, and arthralgia. The survey was created with no personal identifying information requested from the participants, using an available online application, the SurveyMonkey platform.

## ***Statistical analysis***

Descriptive statistics were performed using IBM SPSS for Windows (Version 24.0, IBM Corp). Comparison analyses for categorical variables (survey items) between independent groups

(participants' current positions) were performed using the Chi-square test. Statistical significance was considered at  $p < 0.05$ .

## Results

A total of 832 questionnaires were analyzed, of which 717 were fully completed and 115 partially completed. The descriptive characteristics of the participants are reported in Table I. The answers were stratified according to their current positions. The figures showing the responses according to the current positions of the contributors are reported in Figures 3 and 4 and in a supplementary file. When asked to express the estimated number of patients with fever treated per year, most participants (38, n=289) referred 400-800 patients, whereas minor amounts referred less than 400 patients (22%, n=168) and more than 1200 (22%, n=168).

Paracetamol was the most prescribed drug to treat fever (84%, n=645,  $p < 0.00001$ ), followed by the association paracetamol-ibuprofen (8%, n=62) and ibuprofen (7%, n=50) as shown in Figure 2. Associated symptoms influenced most participants (86%, n=656) in choosing the most appropriate drug. Almost everyone (95%, n= 763) preferred the oral route (Figure 4). The preferred dose was 1000-3000 mg in 24 hours for paracetamol and 600-1200 mg in 24 hours for ibuprofen. Most physicians, particularly pediatricians, preferred to prescribe medication based on the patient's weight. Many respondents (70%, n=507) reported that neither drug consistently caused adverse effects. Ibuprofen was associated with adverse effects in a small percentage of cases (25%, n=180) and paracetamol in an even smaller percentage (2%, n=18). Pain was assessed by scales continually, frequently, rarely, and never respectively, in 16, 38,36, and 10% of cases. The full data on drug choice are reported in Table 2.

## Discussion

Fever is a nearly universal phenomenon; it is safe to say that practically everyone has had a fever at one time or another and its physiology has been extensively studied.<sup>9</sup> There is no universally shared threshold for fever, since body temperature changes by individual, daytime, and way of assessment. On the basis of daily temperature fluctuations, a morning temperature  $>37.2^{\circ}\text{C}$  or an afternoon temperature of  $>37.7^{\circ}\text{C}$  could be considered fever.<sup>10,11</sup> A conventional threshold of temperature  $>37.8^{\circ}\text{C}$  or  $>38^{\circ}\text{C}$  is

frequently used.<sup>12,13</sup> When handling a febrile patient most healthcare providers consider infection as a first hypothesis, and rightly so. However, it should be considered that any condition that promotes the release of pyrogenic cytokines by monocytes will result in fever. Besides infection, these conditions include activity, inflammation, increased metabolism, injury, and exposure to toxins.<sup>14</sup> Since fever is a main item of a complex immunological defensive system it should not be treated straight away, rather the temperature should be analyzed along with clinical conditions to find the underlying cause. An increasing number of point-of-care tools may integrate physical examination to assess objectively the clinical scenario.<sup>15</sup> "Fever phobia" can sometimes lead to frequent, unnecessary visits to the emergency room or clinic, resulting in unplanned doctor visits, inappropriate treatments, and unexpected financial costs.<sup>16</sup> During the SARS-CoV-2 pandemic, emergency department and primary care visits dropped to low numbers without distinctions among pathologies,<sup>17,18</sup> but are now rising again.

Since managing fever and associated symptoms in adult and pediatric patients is a main issue in emergency and primary care, we developed a survey to provide current data on this topic in the Italian Health Service.

In line with other studies<sup>19,20</sup> paracetamol was the preferred drug to treat fever and associated symptoms ( $p < 0.00001$ ), partly considering the side effects of NSAIDs. Ibuprofen is the only other antipyretic recommended in febrile children.<sup>13</sup> In a recent systematic review, Narayan *et al.*<sup>21</sup> stated that there is little evidence supporting the superiority of paracetamol or ibuprofen to treat fever in children since both drugs are effective and safe. According to international guidelines the choice of the drug should rely on the child's characteristics, while the alternate use of the two drugs is controversial. Alternating therapy might be more effective than monotherapy in reducing body temperature, but the benefit appears modest and probably not clinically relevant.<sup>22</sup>

Most physicians in this survey stated that associated symptoms influence their drug choice. Fever is a part of a complex immunological defensive mechanism, so therapy is not aimed simply at reducing it but rather at managing fever-related symptoms. In adults, fever therapy has not shown a significant reduction in mortality.<sup>23</sup>

The oral route of drug administration was the most selected. Analyzing the stratification of answers according to current positions, most emergency physicians selected the intravenous route. In emergency settings, a peripheral intravenous line is routinely placed to obtain a blood sample and administer intravenous fluids when needed. This is probably why the intravenous administration of antipyretics was preferred in this setting. Yet, this widespread practice deserves special attention. As widely reported in

the literature, this route is not more effective than the oral one and should not be preferred due to its cost and invasiveness. It should be limited to patients who cannot tolerate oral medications, when a faster effect is desired, or when drugs are poorly absorbed by the gastrointestinal tract.<sup>24</sup>

Few family pediatricians still chose the rectal route. A recent French study showed that parents and healthcare providers use paracetamol suppositories also for non-vomiting or older children.<sup>19</sup> This may be explained by the practical nature of suppositories and by some disadvantages of the oral formulation, such as poor taste, short storage time after opening, and transportability issues.

Roughly half of the physicians, many of whom were pediatricians, dosed the drugs according to the patient's weight. The more frequent daily dose for adults was 1000-3000 mg for paracetamol and 600-1200 mg. While this responded to prescription standards for paracetamol, it was underdosed for ibuprofen. Underdosing of ibuprofen is in line with what Milani et al.<sup>25</sup> reported in more than 60% of children presenting to the Emergency Department. Although most responders reported no adverse effects associated with antipyretic drugs, concerns about the toxicity of non-steroidal anti-inflammatory agents probably underlays underdosing of oral ibuprofen. A list of adverse effects of ibuprofen is reported in the supplementary file. The argument on which is the most effective antipyretic persists.<sup>26</sup> A recent meta-analysis stated that ibuprofen is marginally more effective than paracetamol for fever reduction, but only focused on children under 2 years.<sup>27</sup> The clinical implications of these findings are unclear. As previously mentioned, antipyretics are used in febrile children with the therapeutic goal of improving the patient's overall comfort. Because discomfort was not universally recorded as an inclusion criterion in this study and data on pain outcomes were largely lacking, it was difficult to assess any clinical impact.<sup>27,28</sup>

Pain assessment through scales is important to appropriately treat pain. In this survey pain evaluation by scales was performed always or frequently in more than 50% of cases, in line with the data of a recent survey among pediatricians by Marseglia et al.<sup>29</sup> Interestingly in our survey emergency physicians reported a high rate of use of algometric scales.

Our study had several limitations and strengths. The first one is intrinsic to the nature of the survey that is based on self-reporting. Furthermore, the survey was not targeted to a specific population, including residents, hospitalists, and family doctors. Yet, this study is one of the few surveys that investigated fever management in hospitals and in outpatient clinics.

Another limitation is that we did not get information on how the purported relevance of associated symptoms determined the drug choice. Since in the open-ended section, many participants indicated



that they would prefer ibuprofen in the presence of an inflammatory condition, we can assume that this might apply to the wider number of those who did not justify their criteria of choice.

A final notable limitation is that there was no prespecified threshold to define fever. As a consequence, we could not assess whether participants would treat mild fever or febricula (temperature < 38°C) We believe that most of them would probably choose not to treat this condition, but we do not have enough data to confirm this assumption.

## **Conclusions**

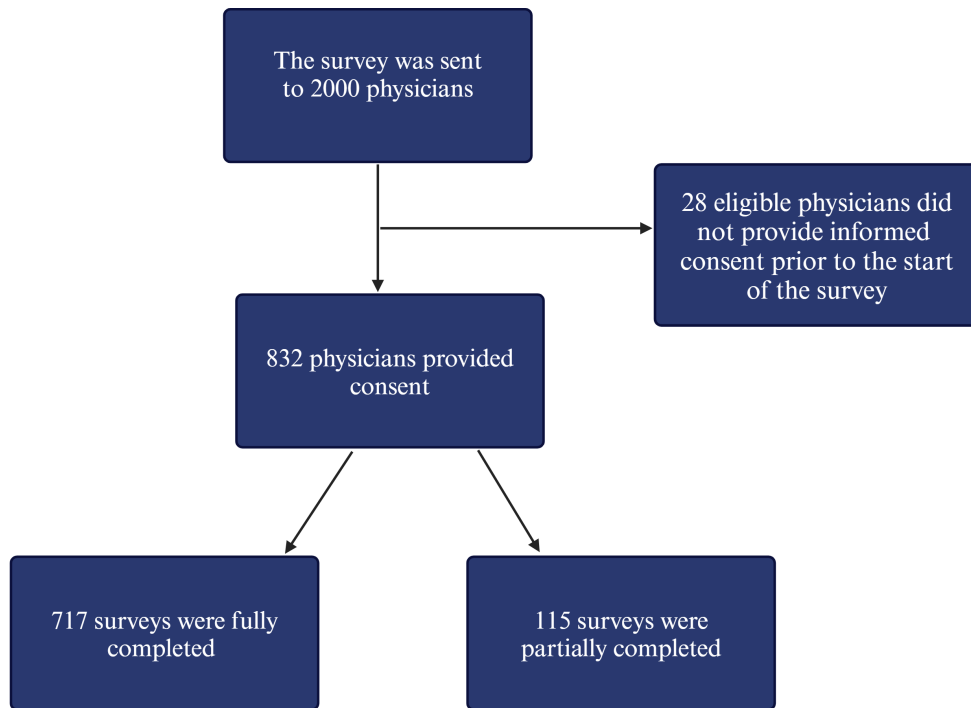
This nationwide survey provides a current state of the management of fever and associated symptoms by physicians working in different settings in Italy. It highlights a trend towards treating fever with antipyretics at appropriate doses and evaluating pain through validated scales.

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**Figure 1. The survey enrollment flow chart**

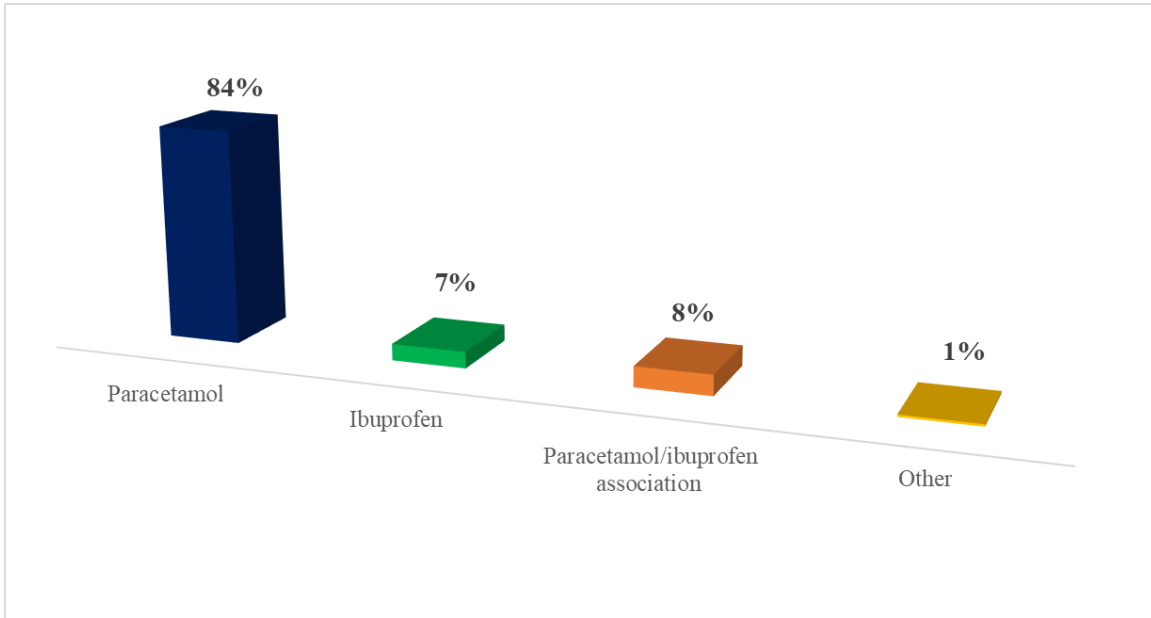


Figure 2. Drugs most prescribed for treating fever. Other includes non-steroidal anti-inflammatory drugs (NSAIDS), corticosteroids, and homeopathic products.

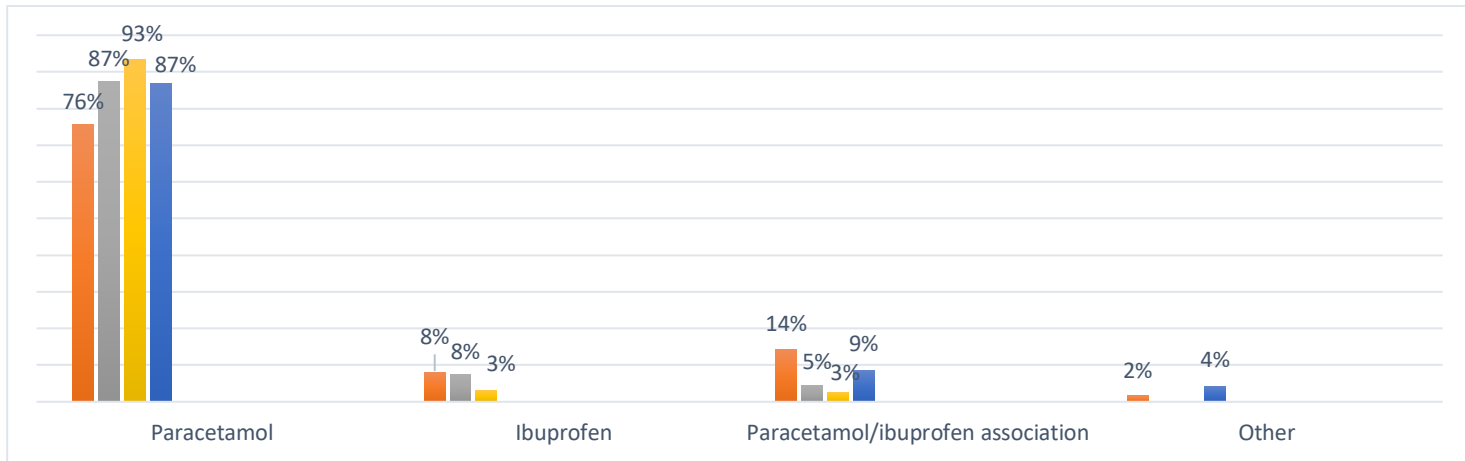
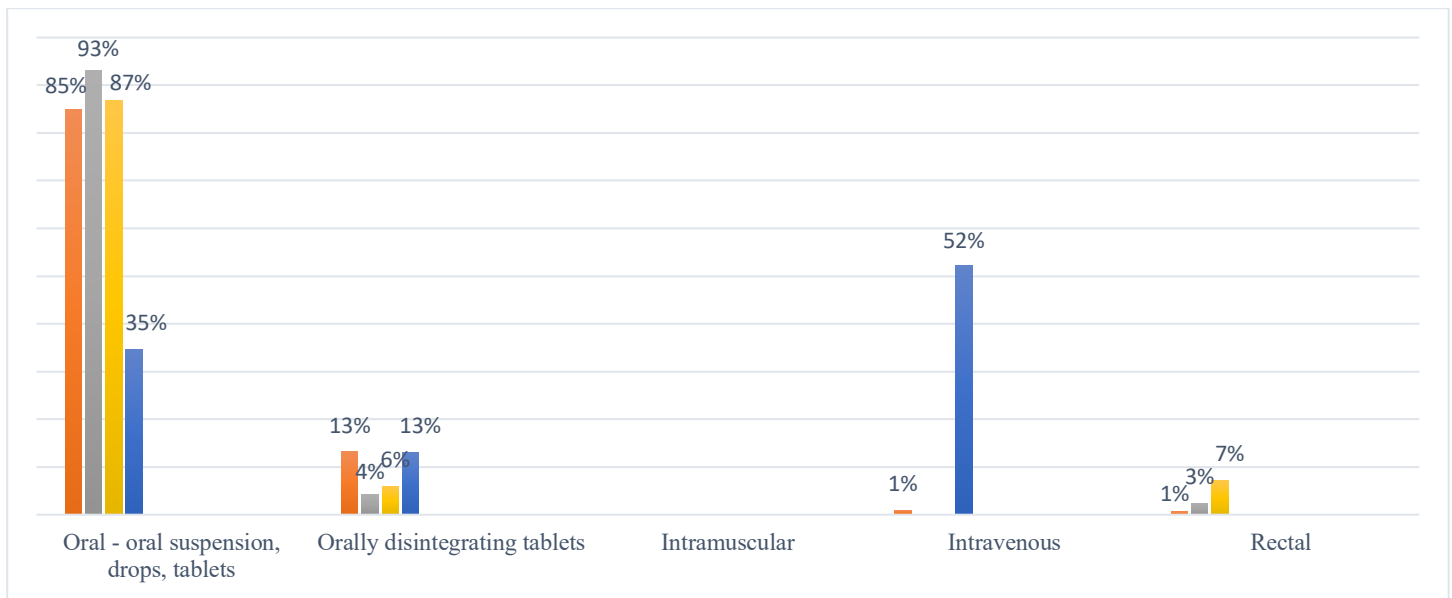


Figure 3. Drugs most prescribed to treat fever and associated symptoms according to the current position of participants

- Adult primary care physician
- Hospital pediatrician
- Pediatric primary care physician
- Emergency physicians



**Figure 4.** Preferred route of administration according to the current position of participants.

- Adult primary care physician
- Hospital pediatrician
- Pediatric primary care physician
- Emergency physicians

**Table I. Characteristics of participants**

Characteristics of Participants	n (%)	<i>p</i> value
<b>1. Current position</b>		
Adult emergency department physician	23 (3)	
Pediatric emergency department physician	23 (3)	
Adult primary care physician	323 (39)	
Pediatric primary care physician	335 (40)	
Hospital pediatrician	119 (14)	
Resident	9 (1)	
Total	832 (100)	
<b>2. Member of medical group practice</b>		
Yes	353 (43)	$< 0.00001$
No	464 (57)	
Total	817 (100)	
<b>3. Gender</b>		
Female	401 (51)	
Male	385 (49)	

Prefer not to answer	3 (0)	< 0.00001
Total	789 (100)	
<b>4. Estimated number of patients with fever visited per year</b>		
<400	168 (22)	
400-800	289 (38)	
801-1200	141 (18)	
>1200	168 (22)	< 0.00001
Total	766 (100)	

**Table II. Drug choice to treat fever**

<b>Drug choice</b>	<b>n (%)</b>	<b>p value</b>
<b>1. Drug most prescribed to treat fever and associated symptoms</b>		
Paracetamol	645(84)	
Ibuprofen	50(7)	
Paracetamol/Ibuprofen association	62(8)	<0.00001
Other	7(1)	



Total	764(100)	
<b>2. Influence of associated symptoms on drug choice</b>		
Yes	656(86)	
No	107(14)	0.008
Total	763(100)	
<b>3. Route of administration preferred</b>		
Oral - oral suspension, drops, tablets	725(95)	
Intramuscular	0(0)	
Rectal	23(3)	
Intravenous	15(2)	< 0.00001
Total	763(100)	
<b>4. Dose of paracetamol administered to treat fever</b>		
1000 mg in 24 hours	34(5)	
1000-3000 mg in 24 hours	292(39)	
Less than 1000 mg in 24 hours	12(2)	< 0.00001
mg/Kg in pediatric patients	402(54)	
Total	740(100)	
<b>5. Dose of ibuprofen administered to treat fever</b>		
Less than 600 mg in 24 hours	41(6)	
600-1200 mg in 24 hours	244(33)	
1200-1800 mg in 24 hours	71(10)	< 0.00001
mg/Kg in pediatric patients	373(51)	
Total	729(100)	
<b>6. Drug most associated with adverse effects</b>		
Paracetamol	18(2)	
Ibuprofen	180(25)	

None	507(70)	0.06
Both	19(3)	
Total	724(100)	
<b>7. Use of scales to assess pain</b>		
Always	115(16)	<0.00001
Frequently	276(38)	
Rarely	257(36)	
Never	73(10)	