












# Guideline for managing fever in the context of pharmaceutical care

## *Diretriz de manejo da febre no contexto do cuidado farmacêutico*

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Receipt date: 12/01/2023

Publication date: 03/01/2024

### ABSTRACT

**Objective:** To systematize, through evidence-based practice, the management of self-limiting cases of fever in the context of Pharmaceutical Care. **Methods:** To prepare the guideline, the ADAPTE method was adopted as a structured process for reviewing the literature and constructing the document. The AGREE II and GRADE tools were also used to analyze the practice guidelines selected during the process and to categorize the evidence, respectively. **Results:** After elaboration, it was observed that the pharmaceutical anamnesis is an important step in confirming whether the fever is just an episode or whether it is associated with a state of disorientation in the patient; persistent tachycardia; tachypnea, hypertension and/or postural hypotension, as well as its duration for referral purposes. Among the non-pharmacological measures, fluid intake is the most recommended in order to avoid the risk of dehydration, as well as health education actions to avoid external methods of lowering the temperature, such as cold baths or baths with alcohol, as well as recommending cool environments, correct temperature measurement and the disposal of thermometers. Pharmacological treatment should be carefully evaluated, as it is only indicated for relieving signs of discomfort, giving preference to Ibuprofen and Paracetamol. **Conclusion:** Despite being a beneficial physiological process, caution is needed in vulnerable populations, such as the first three months of a child's life, pregnant women, puerperal women and patients taking medications such as corticosteroids, immunosuppressants or polypharmacy and the elderly.

**Keywords:** Management of Self-Limited Health Problems; Community pharmacy; Clinical.

### RESUMO

**Objetivo:** Sistematizar, por meio da prática baseada em evidências, o manejo de casos autolimitados de febre no contexto do Cuidado Farmacêutico. **Métodos:** Para elaboração da diretriz foi adotado o método ADAPTE como processo estruturado de revisão da literatura e construção do documento. Foram ainda utilizadas as ferramentas AGREE II e GRADE para análise dos guias de prática selecionados durante o processo e para categorização das evidências, respectivamente. **Resultados:** Após elaboração, observou-se que a anamnese farmacêutica é passo importante para confirmar se a febre é apenas um episódio isolado e autolimitado, se está associada a um contexto de “febre fobia” ou se inspira cuidados assistenciais mais intensivos; a duração da febre e sintomas associados, como desidratação, taquicardia persistente, taquipneia, hipertensão, são alguns sinais para encaminhamento. Dentre as medidas não farmacológicas, a ingestão de líquidos é a mais recomendada a fim de evitar desidratação. Além disso, recomendam-se ações de educação em saúde para coibir métodos inadequados de diminuição da temperatura, como banhos gelados ou com álcool, e incentivar práticas adequadas, como manter o paciente em ambiente fresco, aferir corretamente a temperatura e descartar adequadamente termômetros. Em relação ao tratamento farmacológico, deve-se avaliar com atenção a condição clínica do paciente, uma vez que o uso dos antitérmicos é indicado exclusivamente para alívio de sinais de desconforto, dando preferência ao Ibuprofeno e Paracetamol. **Conclusão:** Apesar de ser um processo fisiológico benéfico, a febre requer cautela em seu manejo, principalmente em relação às populações vulneráveis, como crianças nos primeiros três meses de vida, gestantes, puérperas, idosos e outras pessoas em uso de medicamentos como corticoides, imunossupressores ou em polifarmácia.

**Palavras-chave:** Manejo de Problemas de Saúde Autolimitados; Farmácia Comunitária; Farmácia Clínica

## Introduction

Fever is defined as a body temperature above the normal range, characterized by a controlled physiological response to infection, disease, or trauma.<sup>1-4</sup> The internal body temperature, under normal circumstances, is maintained between 36°C and 37.5°C, but it can vary due to the time of day, the instrument used for measurement, the environment in which the individual is located, and the patient's age. Generally, however, the average body temperature is 37°C.<sup>1-4</sup>

Children have a higher average body temperature than adults. In newborns, the average rectal temperature is 37.5°C, which can reach 38°C. On the other hand, older adults tend to have a lower average body temperature. The World Health Organization (WHO) and the *Society of Critical Care Medicine* (SCCM) define fever as a rectal temperature greater than 38°C or an axillary temperature greater than 37.5°C in adults or children. In the geriatric group, fever is considered to be an oral temperature greater than 37.8°C or a rectal temperature greater than 37.5°C, or an increase of more than 1.1°C from the baseline temperature recorded in previous measurements. Among the three main sites for measuring temperature (rectal, oral, and axillary), the rectal site is the most accurate for defining body temperature, although the axillary measurement is the most convenient method. Factors such as sweating, ambient temperature, humidity, and hair in the armpit can interfere with the accurate measurement of this physiological parameter.<sup>1,5</sup>

In this context, three important concepts need to be distinguished. Fever, or pyrexia, is a mechanism regulated by the hypothalamus in response to a pyrogen, which is generally beneficial for the individual and serves as a warning signal. Hyperpyrexia, on the other hand, occurs when this “fever” is extremely high, above 41.5°C, which implies a likelihood of a more serious health issue, typically caused by sepsis or intracranial hemorrhage, and can result in severe physical and neurological consequences. Lastly, hyperthermia can be defined as an exacerbated increase in temperature, caused by a hypothalamic failure to maintain the body's homeostasis, resulting in uncontrolled temperature elevation and

excluding the possibility of fever caused by pyrogens. This condition is extremely harmful, requires differentiated and emergency treatment, as it does not respond to the use of antipyretics.<sup>2,3,5-7</sup>

It is also important to highlight the concept of “*feverphobia*”, which refers to a tendency that affects parents from all socioeconomic backgrounds and healthcare professionals, who treat the assessment and management of this sign in children with extreme concern. It is observed that people seem to believe that fever alone can cause serious and irreversible harm, leading to anxiety, emergency consultations in hospitals, and the unnecessary or incorrect use of antipyretic treatments.<sup>6-8</sup>

In the management of fever, studies show that one quarter of parents would give antipyretics to children with temperatures below 37.8°C; 85% also report waking their children to continue antipyretic treatment.<sup>7</sup> There is also a high incidence of medication errors, with the most frequent being overdosing.<sup>7,9</sup> The most commonly cited reason for the use of antipyretics was the reduction of the risk of febrile seizures, brain damage, and disease progression, indicating that the reduction of temperature is the primary expected outcome.

Therefore, the pharmacist can contribute to the support of managing this sign by guiding the rational use of medications through clear and reliable information, thereby reducing outpatient visits in acute and nonspecific cases.<sup>3,9</sup>

## Methods

For the development of this guideline, the **ADAPTE** method was used as the theoretical foundation, divided into three consecutive phases: (i) configuration, (ii) adaptation, and (iii) finalization. This method consists of a structured process for constructing practice guidelines based on pre-existing documents in the scientific literature. In this case, the following documents were selected as references: (i) orientation guides from evidence synthesis databases; (ii) clinical guidelines on the subject; (iii) systematic reviews on treatments; and (iv) specific guides or articles on pharmaceutical care.<sup>10-11</sup>

The searches were conducted between November 2020 and March 2021, using the MeSH terms

and boolean operators “Fever”[Title] OR “Hyperthermia”[Title] OR “Pyrexia”[Title]. Searches were performed in the evidence synthesis databases Best Practice, DynaMed, and UpToDate; on the websites of guideline developers such as the *National Institute for Health and Care Excellence* (NICE) and the Federal Council of Pharmacy (CFF); and finally, in the Cochrane, PubMed, Scopus, and Virtual Health Library (BVS/MS) databases.

Inclusion criteria were established for publications written in English, Portuguese, or Spanish that addressed mild and nonspecific fever in adults, children, and the elderly, as well as treatments with non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, acetylsalicylic acid (ASA), and dipyrene. Exclusion criteria included publications about fever as a symptom of specific diseases or infections by specific viral agents; fever with neutropenia; fever in hospital settings; fever in individuals with secondary comorbidities; fever in sepsis; malignant/chronic fever; and documents that exclusively addressed treatment suggestions with low scientific evidence.

For the preliminary evaluation of the guidelines identified in the literature and as a model for defining the sections and writing this Guideline, the *AGREE II* tool (*Appraisal of Guidelines for Research & Evaluation*) was used.<sup>12-14</sup>

An analysis of the quality of the evidence found regarding potential pharmacological and non-pharmacological interventions was also conducted using the **GRADE** tool (*Grading of Recommendations Assessment, Development and Evaluation*). It is noteworthy that GRADE is internationally used for categorizing recommendations and assisting in decision-making. Following this method, the interventions were classified according to their level of evidence as: (i) high, (ii) moderate, (iii) low, and (iv) very low, and regarding the degree of recommendation as (i) strong or (ii) weak.<sup>15,16</sup>

## Results

After searching the databases, 2,632 references were identified, and after the removal of duplicates, 88 documents were selected for title and abstract reading. A total of 36 studies were chosen following

the application of the selection criteria for full text reading. The guideline is composed of the following sections presented below:

- Objectives of Pharmaceutical Care
- Pharmaceutical Evaluation and Anamnesis
- Non-Pharmacological Interventions
- Pharmacological Interventions
- Warning Signs and Referrals
- Monitoring of Results

### Objectives of Pharmaceutical Care

Support the patient regarding the correct pharmacological management of fever at home, alleviating discomfort related to the signs and symptoms presented;<sup>3,9,17</sup>

Identify patients with acute fever who can be treated at home and patients with high-risk fever who require specific treatment and referral;<sup>3,9,17</sup>

Analyze the factors that promote fever to determine if they are results of long-term treatments, comorbidities, active immunization, inflammation, and/or unidentified infections;<sup>3,9,17</sup>

Provide guidance on measures to prevent infections, routine observation of fever, and non-pharmacological care;<sup>3,6</sup>

Reduce “*feverphobia*” through parental education, providing management information for children and decreasing anxiety related to the febrile state.<sup>7,9</sup>

### Pharmaceutical Evaluation and Anamnesis

Fever occurs as a result of the interaction of external pyrogens (e.g., infectious agents or toxins) or internal pyrogens (e.g., immune cytokines) at the hypothalamic set point that regulates body temperature. Cytokines are transported via circulation to the anterior hypothalamus, where they induce a sharp increase in the production of prostaglandins, especially prostaglandin E2 (PGE2), which raises the set point in the hypothalamic center. Thus, the thermoregulatory center, recognizing the body temperature as too low, triggers a series of mechanisms to increase it until the new equilibrium is reached.<sup>1,2</sup>

Starting from the stimulation of the hypothalamic vasomotor center, vasoconstriction is initiated,

reducing peripheral blood flow to decrease heat loss and sometimes inducing shivering, which increases heat production. This process continues until the temperature of the blood passing through the hypothalamus decreases the hypothalamic set point (e.g., with antipyretic drugs), thereby reversing heat to loss through sweating and vasodilation.<sup>2,3</sup>

Data has shown that hospitalized patients with infectious diagnoses and fever up to 39.4°C have a more positive prognosis than those who remain normothermic, highlighting that fever is not a disease but rather a defense mechanism of the body in combating acute infections, resulting in a beneficial final effect for the individual.<sup>2,7</sup> The increase in body temperature decreases the replication of bacteria and viruses that infect humans, as well as enhances the defense of white blood cells by increasing the speed at which they reach infection sites, the production of neutrophils, and the proliferation

of T lymphocytes.<sup>2</sup> Conversely, fever is associated with other signs and symptoms that lead to patient discomfort and increased metabolic demand, which can be detrimental when there is impairment of cardiac or pulmonary function.<sup>1,2,7,18</sup>

The causes of a febrile illness are often unidentified. Generally, fever is caused in reaction to inflammatory and/or infectious diseases. Acute fever, which is more common, usually results from some type of self-limiting infection and can often be easily treated at home. However, in addition to being associated with significant discomfort for the individual, fever can also be an indicator of bacterial infections or severe diseases.<sup>3,6,19</sup>

The pharmaceutical anamnesis should be conducted to analyze whether the self-limiting health problem reported by the patient is confirmed or if it may be an issue that requires greater attention (**Chart 1**).

**Chart 1.** Pharmaceutical Anamnesis in Patients with Fever (INDICO Strategy)<sup>20-28</sup>

Domain	Questions/Investigation*	Important Notes
Patient Identification	What is the patient's <b>age</b> ? Is the patient in <b>good general condition</b> ? Are they eating well? Do they have any <b>difficulty speaking, walking, or sleeping</b> ?	In children, parental reports or professional observations of the general condition are essential to assess the severity of the fever.
Nature of Signs and Symptoms	Does the patient have any <b>signs or symptoms associated</b> with the febrile episode? Do they experience discomfort, headache, chills, body aches, runny nose, congestion, or cough? Is the fever continuous or intermittent?	Investigate recent travels to regions that may have ongoing epidemics. Be alert to signs and symptoms that suggest more serious illnesses and signs of dehydration.
Duration	When did the patient's <b>febrile state</b> begin? Is it recurrent? Have they <b>traveled abroad recently</b> ? Have they been <b>in contact</b> with anyone showing flu-like symptoms?	Persistent fever for more than 3 days requires medical referral in children over 2 years and adults, as well as recurrent febrile episodes within a 6-month period.
Started any treatment	Has the patient taken any medication during this episode? If so, was there any improvement? What <b>medications</b> have been used <b>previously</b> ? Does the patient have any treatment references?	Lack of response to antipyretics over a three-day period requires medical referral. It may also be important to prescribe medications that the patient reports as effective previously.
Comorbidities	Have they recently used antibiotics? What is the <b>vaccination history</b> ? Does the patient have any chronic diseases? Are they <b>immunocompromised</b> ?	Investigate drug-induced fever or fever caused by vaccinations. Some chronic diseases limit the use of certain medications. Patients with immunodeficiency should be referred to a physician.
Other Special Situations	Is the patient <b>pregnant</b> or breastfeeding?	Fever in postpartum women can be caused by mastitis and should be evaluated by a physician. In pregnant women, the use of medications is limited.

\*Suggestive questions. They are not for diagnostic purposes but rather for better understanding of the case and identification of potential warning signs for referral.

The clinical manifestations related to fever are non-specific and do not occur in all individuals. However, they are associated with the discomfort experienced by the patient in a febrile state, evidenced by: general discomfort and malaise; headache; excessive sweating; chills; tachycardia; arthralgia; myalgia; and irritability.<sup>3,6</sup>

A study using the *Fever Assessment Tool* (FAST) questionnaire to determine the signs and symptoms related to fever shows that, in addition to common symptoms, it can also manifest in association with generalized body pain, drowsiness, cough (even in the absence of cold symptoms), and difficulty breathing in most symptomatic patients. Furthermore, a substantial portion of patients were asymptomatic during febrile episodes.<sup>29</sup>

In the anamnesis of children, measuring vital signs can be important for screening for more serious illnesses. However, this population generally has a good tolerance to febrile states. The evaluation of a child over six months should, therefore, not be based solely on high temperatures but rather on the overall impression of their clinical status, whether they are alert or disoriented, and on the information provided by their caregivers. The Traffic Light System can be used for assessing a child with fever (**Chart 2**).<sup>6,8,17,30,31</sup> Tachycardia is

common in febrile children, as long as it is not persistent.

Signs of tachypnea, hypertension, and postural hypotension suggest the presence of other more serious comorbidities, such as systemic disorders, inflammatory conditions, or severe infections.<sup>31</sup>

Fever induced by the use of medications typically appears between the seventh and tenth day of treatment but can also occur after a prolonged treatment period. It may be caused by hypersensitivity reactions or may result from alterations in thermoregulation caused by the substance. In contrast, fever associated with vaccination occurs within two days following vaccination and is characterized by a mild fever. The incidence of drug-related fevers in outpatient settings is unknown, but in hospitalized patients, it can reach up to 10% of cases.<sup>3,6,31,32</sup>

In the context of the medicalization of society, the practice of “prophylaxis” for fever during vaccination has become increasingly common. In a randomized controlled study evaluating this practice, it was observed that, although febrile reactions significantly decreased in the intervention group (using paracetamol), the routine prophylactic administration of antipyretic medications at the time of vaccination should not be recommended, as it reduces antibody responses to various vaccine antigens.<sup>33</sup>

**Chart 2.** Traffic Light System for Assessing a Child with Fever<sup>30,34</sup>

Signs and Symptoms	Green - Low Risk	Yellow - Intermediate Risk	Red - High Risk
Color of Skin, Lips, and Tongue	Normal	Pallor	Pallor Mottled skin Cyanosis
Activity	Normal cognitive response Child smiles Awake or wakes up easily Strong crying or absence of crying	Abnormal cognitive response Does not smile Awakens only with vigorous stimulation Decreased activity	No cognitive response Appearance weakened Does not wake up or remain awake Continuous or weak crying
Respiration	Normal Respiratory Rate* Infants ( <b>20-40</b> breaths per minute) Children ( <b>20-25</b> breaths per minute)	Tachypnea - Rapid breathing: <b>More than 40</b> breaths per minute Oxygen saturation <b>less than 95%</b>	Child grunting or moaning Tachypnea + <b>60</b> breaths per minute Intercostal retractions
Circulation and Hydration	Normal skin and eyes Moist mucous membranes	Tachycardia Dry mucous membranes Low appetite Reduced urine output.	Abnormal skin turgor
Others	None of the yellow or red symptoms	Temperature greater than 39°C or fever for several days Chills Swelling in a limb or joint Inability to bear weight on one leg	Rash that does not fade with pressure Bulging fontanelle Nuchal rigidity Status epilepticus Neurological focal signs Focal seizures

\*Source: Author's own work. \*Values may vary depending on the reference used (adults generally have a rate below 20 breaths per minute).

## Non-Pharmacological Interventions

Physical measures for reducing temperature (such as baths, compresses, and others) are generally not recommended or have limited effectiveness when used in isolation.<sup>3,18</sup> Similarly, covering with warm clothing or heavy blankets, as well as alcohol baths or the use of ice<sup>3,7</sup> and other body cooling techniques<sup>18</sup>, are also ineffective and should not be recommended. Patients often employ these strategies until antipyretics begin to take effect, with the intention of reducing discomfort related to symptoms.<sup>3,6</sup> However, external cooling of the body does not alter the hypothalamic physiological changes as antipyretics do, and therefore has little utility in the treatment of mild and acute fever.<sup>4,6</sup>

Cold water baths are used in patients with hyperthermia and hyperpyrexia for rapid reduction of body temperature.<sup>6</sup> However, although febrile patients may experience a decrease in axillary temperature, the resulting arterial constriction from cooling methods can increase internal heat conservation, leading to an increase in rectal temperature and consequently worsening the fever. These techniques may also be associated with an increase in shivering.<sup>35</sup>

A systematic review by Meremikwu and collaborators (2003)<sup>35</sup> included seven studies with evident methodological issues, comparing physical cooling methods with placebo or no treatment. The data obtained were inconclusive in confirming or refuting the recommendation of most of these techniques. Sponge baths with lukewarm water showed beneficial effects for patients in some small studies, but most guidelines on the topic do not recommend the routine use of this technique, as it may cause discomfort and shivering.<sup>1,3,6,17,30</sup>

The patient should only be kept in a cool environment, preferably at temperatures up to 25.6° C. Blankets and clothing that allow the individual to remain comfortable should be used, without attempting to excessively raise or lower body temperature.<sup>3,6,17</sup>

Increased fluid intake (whether water or breast milk) should be recommended to avoid dehydration.<sup>3,6,17,30</sup> Adequate hydration, especially for children, should be strictly maintained during the

fever treatment period, with an intake of at least 2 liters of water per day.<sup>3,4</sup> This is because the elevation of body temperature due to fever increases the patient's perspiration, leading to greater water loss.<sup>3</sup>

It is suggested to avoid recommending treatments and other interventions (**Chart 3**) when the need for reducing body temperature is not clearly evident.<sup>3,17,18</sup> Fever is a natural defense mechanism of the body, and in some cases, both pharmacological and non-pharmacological management may be unnecessary.<sup>32</sup> The primary reason for treating febrile children is to improve their discomfort.<sup>1,17</sup> Therefore, it is possible to choose not to treat children (and adults) with mild fever without associated discomfort, favoring health education instead.<sup>3,17,19,30</sup>

A systematic review<sup>36</sup> including eight studies showed that ongoing and preventive education for parents and caregivers of children (before febrile episodes) about managing fever and common infections is beneficial for both the child and the healthcare system. In addition to reducing medical consultations and visits to emergency units, this intervention also contributes to optimizing medication management, with a decrease in the administration of inappropriate over-the-counter medications (OTCs) and incorrect dosages.

Thus, in cases of mild fever in children without warning signs, it is essential to ensure that parents understand that managing fever involves several important considerations. Firstly, it is vital to understand that fever itself does not increase the risk of seizures, brain damage, or death. Febrile seizures are rare, and the use of antipyretics does not prevent them. Monitoring the child while they sleep is sufficient, without the need to wake them to administer medication. The primary focus should not be on reducing temperature, but rather on the child's comfort, prioritizing hydration and overall well-being. Furthermore, attention should be paid to warning signs, and professional guidance should be sought if necessary. The use of complementary or herbal therapies should be avoided due to the lack of scientific evidence, and proper disposal of mercury thermometers is recommended to ensure safety.<sup>1,3,7,8,17,19,30</sup>

**Chart 3. Summary of evidence for non-pharmacological interventions for fever.**<sup>4,10,11,16-22,24,31-33</sup>

Conduct	Technical Foundation	GRADE	
		Level of evidence	Grade of Recommendation
Increase in fluid intake	The elevation of body temperature increases sweating and water loss from the body, making it extremely important for the patient to replenish fluids to avoid damage resulting from dehydration.	Very low *	Strong
Preventive education	Parents of febrile children tend to experience high levels of anxiety and administer treatment inadequately. Continuous preventive education for parents of febrile children and those with common colds has shown the ability to reduce medical consultations and visits to emergency units. It also demonstrates a significant improvement in medication management, with a decrease in the administration of inappropriate over-the-counter medications and incorrect dosages.	Moderate ***	Strong
Physical methods	The use of physical methods for cooling the body is commonly employed with the intention of increasing heat loss in febrile patients; however, it is also associated with the occurrence of uncomfortable and harmful adverse effects. The use of sponge baths with warm water may increase the risk of adverse effects, including chills, shivering, and crying in children. Other methods, such as cold baths and the application of alcohol, may provoke even more adverse effects. The use of alcohol to resolve fever is contraindicated due to the risks of irritation and intoxication from inhalation of the product.	Moderate ***	Weak

## Pharmacological Interventions

The pharmacological treatment of fever should be used only to alleviate significant patient discomfort and when the risk-benefit ratio is favorable. Reducing body temperature is not the primary goal of pharmacological therapy.<sup>1,4,18,30</sup> The over-the-counter medications (OTCs) available in Brazil for the treatment of fever include NSAIDs such as acetylsalicylic acid and ibuprofen, as well as the antipyretics paracetamol and dipyron (Chart 4).<sup>3,47</sup> The antipyretic effect of these medications typically begins after 1-3 hours of administration, lasting up to 6 hours,<sup>1,17</sup> and the treatment duration should not exceed three days.<sup>3,6</sup>

The antipyretic mechanism is mainly related to the inhibition of cyclooxygenases 1 and 2 (COX-1 and COX-2), enzymes responsible for the synthesis of PGE<sub>2</sub>. Paracetamol is a weak inhibitor of these enzymes in peripheral tissue; however, its metabolism in the brain leads to the antipyretic effect.<sup>5,32</sup> NSAIDs are associated with the alteration of a series of factors that lead to fever and inflammation. The inhibition of COX-2 in the brain is their primary antipyretic effect, but this class of medications also reduces the action of several other cytokines that can lead to an increase in body temperature.<sup>32</sup>

Drugs with the strongest evidence for use are ibuprofen and paracetamol.<sup>3,4,6</sup> Both are also consi-

dered the safest and most effective medications for use in children and are the most recommended and prescribed internationally. However, in Brazil, dipyron is also available, with authorization for use in children by Anvisa.<sup>3,7,17,30,48</sup> Despite the lack of evidence regarding dipyron due to its non-commercialization in some countries because of the risk of agranulocytosis, its use has proven to be safe.<sup>3,49</sup>

In Brazil, according to data from the largest population survey on access to medications (PNAUM), ibuprofen, paracetamol, and dipyron are the most consumed medications by children, with dipyron being the most widely used. The Pelotas Birth Cohort (2004), the largest and oldest in the country, also observes the priority consumption of this trio over the decades.<sup>50,51</sup>

At appropriate doses, paracetamol is nearly free of adverse effects. However, overdose caused by the medication is difficult to treat and can be fatal. Ibuprofen is associated with gastrointestinal and renal symptoms, but it is also considered safe at adequate doses.<sup>1,32</sup>

In a systematic review addressing the effects of antipyretics in adults (n = 5 articles) and children (n = 30 articles), the authors concluded that ibuprofen has superiority over paracetamol in half of the selected sources. Regarding safety, episodes ranging from mild (such as nausea) to severe intensity (such as pneumonia) were reported. However, only one

study in children indicated that paracetamol was more tolerable than ibuprofen. Therefore, ibuprofen appears to be as effective and safe as, or even more so than, paracetamol for both adults and children.<sup>38</sup>

Similarly, in another systematic review focused on children under two years of age, ibuprofen demonstrated greater effectiveness than paracetamol, without an increased risk of renal or hepatic issues. However, the effect was not superior when compared after a few hours.<sup>39</sup>

When evaluated, the combined or alternating use of ibuprofen with paracetamol proved effective in reducing temperature.<sup>8,17,30</sup> However, despite the benefits, from a clinical perspective, it is not possible to assess the safety of this practice, and its implementation does not appear to be relevant.<sup>52</sup> The effect on the child's discomfort and the number of doses of the medication was also modest. Additionally, the use of two medications to control an event deemed harmless by healthcare professionals can, in cases of managing fever in children, increase parental anxiety, contributing to feverphobia.<sup>7,8,53</sup> Therefore, the combined use of paracetamol and ibuprofen should only be considered if the individual use is ineffective. Furthermore, the treatment should be properly guided and monitored by a pharmacist to avoid complications arising from potential adverse events.<sup>1,19,30</sup>

The use of antipyretics in children to prevent febrile seizures is not recommended,<sup>8,17,30</sup> as they are ineffective in lowering the temperature during episodes that lead to seizures or in preventing the recurrence of such events.<sup>54</sup> Three studies comparing the prophylactic use of antipyretics found the same rate of seizure occurrence in both the intervention and placebo groups (22-24%).<sup>54</sup>

It is also recommended to avoid products with combinations for cough and cold in children, as they may increase the risks of overdose, adverse effects, and duplicate use of active ingredients.<sup>3,4,7,17</sup> Experimental studies show that medications containing a mixture of analgesics and antipyretics increase the chances of renal toxicity compared to isolated pharmaceutical forms.<sup>55</sup> Additionally, hepatotoxicity induced by paracetamol is often related to overdose from the concomitant intake of multiple medications containing the active ingredient.<sup>32</sup>

Another option available on the market is acetylsalicylic acid for treatment in adults. In children under 12 years old, its use is not recommended due to the risks of developing Reye's syndrome.<sup>3,17,32</sup> In a review, the effectiveness of acetylsalicylic acid in treating fever and colds was analyzed across different clinical trials.<sup>56</sup> The three clinical trials reviewed showed a significant reduction in body temperature, demonstrating effectiveness similar to other anti-inflammatory and antipyretic medications used in fever treatment. In a randomized clinical trial with adult patients experiencing acute fever,<sup>57</sup> both paracetamol and acetylsalicylic acid reduced body temperature by up to 1°C when 500 mg was used and by up to 1.4°C when 1000 mg was administered. This trial also concluded that the decrease in body temperature was accompanied by relief from discomfort and symptoms related to the febrile state.

The use of anti-inflammatory medications (ibuprofen and acetylsalicylic acid) during pregnancy can inhibit labor and, therefore, should not be used, as well as dipyron. Both during pregnancy and lactation, paracetamol should be the first choice of treatment.<sup>3,58</sup>

In elderly patients, it is essential to be mindful of polypharmacy, comorbidities, and clinical history.<sup>3</sup> Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and acetylsalicylic acid for fever in elderly individuals are contraindicated according to the Beers<sup>59</sup> criteria due to the increased risk of gastrointestinal bleeding and ulcers. These medications should also be approached with caution because of other potential adverse effects and the tendency of this population to have gastrointestinal, cardiovascular, and renal issues.<sup>58</sup> Therefore, paracetamol is also recommended as the preferred antipyretic.<sup>3,58</sup>

Another consequence of the use of NSAIDs is the elevation of blood pressure due to the inhibition of renal vasodilation;<sup>58</sup> therefore, their use should be avoided in patients with hypertension, as well as in heart and/or kidney failure, with a preference for the use of paracetamol.<sup>3</sup>

However, the prophylactic use of medications to prevent post-vaccination fever is not recommended due to the lack of studies demonstrating the effecti-

veness of this intervention.<sup>3,17,53</sup> Fever and local reactions should be regarded as normal reactions to the vaccine and are not harmful.<sup>17</sup> The immune response may be diminished with the prophylactic administration of paracetamol, and it should be used only if there is significant discomfort after vaccine administration.<sup>3,60</sup> The Ministry of Health recommends the administration of paracetamol, dipyrrone, or ibuprofen in children and adults in these cases.<sup>60</sup>

Patients diagnosed with dengue or those who live in or have traveled to endemic areas should not

use NSAIDs due to the risk of hemorrhagic complications.<sup>3,61</sup> The Ministry of Health recommends treatment with paracetamol or dipyrrone in cases of suspected arboviral infections.<sup>62</sup>

#### Warning Signs and Referral

Despite being a self-limiting health issue, certain warning situations require referral (**Chart 5**). For children under three months presenting with fever, evaluation by a pediatrician is recommended. This is necessary because, in this population, fever may be the only clinical sign of a serious infection.<sup>7,33</sup>

**Chart 4.** Summary of Pharmacological Interventions for Fever<sup>3,7,17,30,48,63-66</sup>

Medication	Standard Use	Patient Instructions	GRADE	
			Level of Evidence	Grade of Recommendation
Acetylsalicylic Acid MIP/SUS (tablet and extended-release tablet 500 mg)	<b>ADULTS:</b> 1 to 2 tablets of 500 mg. If necessary, repeat every 4 to 6 hours. Maximum dose: 4000 mg/day (8 tablets) <b>CHILDREN: Contraindicated for those under 12 years of age.</b>	“Take preferably after meals.” “Avoid alcohol use due to increased risk of gastric irritation.” “As with other NSAIDs, avoid high doses and prolonged use (+ of 5 days).” “Report any signs of excessive bleeding.”	Moderate ***	Strong
Paracetamol MIP/SUS (tablet 500 mg and 750 mg, oral suspension 100 mg/mL and 32 mg/mL, oral solution 200 mg/mL)	<b>ADULTS:</b> 1 to 2 tablets of 500 mg or 1 tablet of 750 mg. If necessary, repeat every 4 to 6 hours. Maximum dose: 4000 mg/day (8 tablets of 500 mg). <b>CHILDREN:</b> The recommended dose varies from 10 to 15 mg/kg/dose. A suitable dosing syringe should be used. If necessary, repeat every 4 to 6 hours. Maximum dose: 75 mg/kg/day (5 doses).	“Most tablets are coated; do not crush or chew.” “Preferred alternative for pregnant women and children, with caution.” “Effervescent formulas should be dissolved in at least half a glass of water.”	Moderate ***	Strong
Dipyrrone MIP/SUS (tablet 500 mg and 1 g, oral solution 50 mg/mL and 500 mg/mL)	<b>ADULTS:</b> 1 to 2 tablets. If necessary, repeat every 6 hours. Maximum dose: 4 g (8 tablets of 500 mg or 4 tablets of 1 g). <b>CHILDREN (above 3 months and 5 kg):</b> The recommended dose varies from 10 to 15 mg/kg/dose. A suitable dosing syringe or guidance on drops per kg in the package insert should be used. If necessary, repeat every 6 hours. Maximum dose: 60 mg/kg/day (4 doses).	“Avoid use in individuals with a history of drug allergies.” “Can be used in suspected dengue cases.” “Prefer other alternatives in frail elderly patients or those at risk of hypotension.” “May alter some laboratory tests, such as lipid profiles; alert the analyst.” “Avoid oral solution in patients with diabetes.”	Moderate ***	Weak
Ibuprofen MIP/SUS (tablet and capsules 200 mg, 300 mg, 400 mg, oral suspension 20 mg/mL, 30 mg/mL, 50 mg/mL, and 100 mg/mL)	<b>ADULTS:</b> 1 to 2 tablets of 200 mg or 1 tablet of 300 mg or 1 tablet of 400 mg. If necessary, repeat every 4 to 6 hours. Maximum dose: 1200 mg/day (3 tablets of 400 mg). <b>CHILDREN (above 6 months):</b> The recommended dose varies from 5 to 10 mg/kg. If necessary, repeat every 6 to 8 hours. Maximum dose: 40 mg/kg/day (4 doses).	“Take preferably with or after meals.” “In the oral suspension, shake well before measuring the dose.” “Avoid alcohol or smoking due to the risk of gastrointestinal bleeding.” “As with other NSAIDs, avoid high doses and prolonged use (+ of 5 days).”	High ****	Strong

**Chart 5.** Warning Signs for Referral of Patients with Fever<sup>3,4,6,8,17,30</sup>

KEYWORDS	ALERT SIGNS
PERSISTENT OR RECURRENT FEVER	Persistent fever lasting more than three days in children and adults and more than 24 hours in infants under 2 years old. Lack of response to the use of antipyretics. Recurring febrile episodes over a period longer than six months.
CONTINUOUS DISCOMFORT	No resolution of symptoms related to fever, even with a decrease in body temperature after three days of treatment. Children with difficulty ingesting liquids or with vomiting, preventing oral treatment.
HIGH TEMPERATURES	Temperature above 40°C. Suspected hyperthermia. Infants under three months with a rectal temperature above 38°C.
SKIN, RESPIRATORY, OR NEUROLOGICAL CHANGES	Very debilitated appearance, altered mental state, and severely altered vital signs. Children with a history of seizures. Children with “yellow” or “red” signs such as skin changes, respiratory issues, mental confusion, signs of dehydration.
PREGNANT WOMEN AND PUERPERIUM	Fever in postpartum women. Pregnant women with persistent fever. Breastfeeding women showing signs of mastitis.
COMORBIDITIES	Drug-induced fever. Suspected underlying serious illness. Compromised immune system (use of corticosteroids, immunosuppressants, chemotherapy, HIV). Possible injury to the central nervous system (history of injuries or strokes).
CONFUSING SIGNS AND SYMPTOMS	Unusual signs or symptoms causing concern. Focal symptoms of an infection requiring medical treatment (e.g., urinary tract infection). Vomiting or diarrhea. Severe pain in the abdomen, back, or suprapubic region.

High exposure to febrile episodes in the first trimester of pregnancy may increase the chances of malformations, the occurrence of cleft palate, and other fetal damages. Additionally, the use of certain medications may also contribute to these issues.<sup>34</sup> Breastfeeding women, on the other hand, may experience fever related to mastitis, an inflammation of breast tissue characterized by redness, warmth, swelling, and pain.<sup>35</sup> Drug-induced fever can occur, especially in elderly patients, those on polypharmacy, and individuals living with HIV.<sup>36,37</sup>

## Monitoring of Results

The evaluation of the results of pharmacological and non-pharmacological therapy is carried out through a complete reassessment of the patient, analyzing adherence, safety, effectiveness of interventions, and the possible need for medical referral. The reduction in temperature with the use of antipyretics typically occurs shortly after the administration of the first dose. However, the effectiveness of the treatment should be assessed after at least one day of use to evaluate the actual decrease in temperature.<sup>36,10</sup>

In situations of self-monitoring, it is important to instruct the family on the correct way to measure temperature, considering the individual's age and preference regarding the method of measurement.

Remember to recommend that the temperature should always be measured with the same device and in the same location to ensure accurate comparison of temperatures throughout the day.<sup>3,6</sup>

Some studies have indicated that body temperature in children can be effectively measured using a tympanic thermometer (ear) as well as digital axillary thermometers. Oral thermometers are recommended only if the child is old enough to cooperate with the measurement procedure. The rectal route, while providing a more reliable temperature measurement, is an invasive method and is not routinely recommended. Non-contact thermometers (infrared) should be used with caution due to their higher potential for operational error, although they tend to be the most commonly used today and have seen a greater number of launches and innovations.<sup>1,17,53,67</sup>

## Contributions of Authors

APC, APOB, BMCSA, RMP, LBPB, FMQ, MMB, NGMJ, RFL, TMR, and RSS were responsible for the conception of the project, data analysis, and manuscript writing; RFL, TMR, and RSS were responsible for the revision and approval of the manuscript.

## Conflicts of Interest

The authors declare that there are no conflicts of interest regarding this work.

## Responsible Editor

Lindemberg Assunção-Costa.

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