



ORIGINAL ARTICLE

## Therapeutic procedures and use of alternating antipyretic drugs for fever management in children<sup>☆</sup>

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### KEYWORDS

Fever;  
Children;  
Treatment;  
Alternating therapy;  
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### Abstract

**Objective:** The evidence on the effectiveness of alternating antipyretics in fever management is scarce and indicates clinically negligible differences. The present study aimed to describe therapeutic procedures and the use of alternating antipyretics in children, and to evaluate associated factors.

**Methods:** This was a cross-sectional study with 692 children aged 0 to 6 years, living in Southern Brazil. Household interviews of the children's caregivers were conducted through cluster sampling using a structured questionnaire. A descriptive analysis was carried out, and the association between the use of alternating antipyretics and socio-demographic factors was evaluated. A total of 630 cases were analyzed (91.0%), corresponding to children with a history of fever.

**Results:** Approximately 73% of caregivers reported that the first measure adopted during the last fever episode was the administration of medication. The mean temperature considered as fever by caregivers was 37.4 °C, and as high fever, 38.7 °C. The use of alternating antipyretic therapy was reported by 26.7% of respondents, justified by the lack of response to monotherapy and medical indication, in most cases. The drugs most often used were dipyron and paracetamol. Children whose primary caregiver was a parent with higher socioeconomic status and higher educational level received more alternating medications. Approximately 70% of the doses used were below the minimum recommended dose for the treatment of fever.

**Conclusions:** The use of medication to control fever is a common practice, including alternating antipyretic regimens. Most caregivers consider as fever temperatures lower than those established and they reported lack of response to monotherapy and medical indication as the main reasons for alternating medication.

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**PALAVRAS-CHAVE**

Febre;  
Crianças;  
Tratamento;  
Terapia alternada;  
Antipiréticos

## Condutas terapêuticas e uso alternado de antipiréticos no manejo da febre em crianças

### Resumo

**Objetivo:** As evidências sobre a eficácia do uso alternado de antitérmicos no manejo da febre são escassas e apontam diferenças clinicamente desprezíveis. O objetivo do estudo foi descrever condutas terapêuticas e uso alternado de antipiréticos em crianças, e avaliar fatores associados ao uso alternado.

**Métodos:** Estudo transversal com 692 crianças de zero a seis anos, residentes no Sul do Brasil. Por meio de amostragem por conglomerados, foram realizadas entrevistas domiciliares com os cuidadores, utilizando questionário estruturado. Foi realizada análise descritiva e avaliada a associação entre o uso alternado de antipiréticos e fatores sociodemográficos. Foram analisados 630 casos (91,0%), correspondendo às crianças com histórico de febre.

**Resultados:** Cerca de 73% dos cuidadores informaram que a primeira medida adotada no último episódio de febre foi administrar medicamentos. A média de temperatura considerada febre foi de 37,4 °C, e febre alta, 38,7 °C. A utilização de terapia alternada com antipiréticos foi relatada por 26,7% dos entrevistados, justificada pela ausência de resposta à monoterapia e indicação médica, na maioria dos casos. Os medicamentos mais utilizados foram dipirona e paracetamol. Crianças cujo principal cuidador era um dos pais, com melhores condições socioeconômicas e maior nível educacional, receberam mais medicamentos alternados. Cerca de 70% das doses utilizadas estavam abaixo da dose mínima recomendada para tratamento de febre.

**Conclusões:** O uso de medicamentos para controlar a febre é uma prática comum, incluindo esquemas alternados de antipiréticos. A maioria dos cuidadores considera como febre temperaturas inferiores às preconizadas, e apontou não resposta à monoterapia e indicação médica como as principais razões para o uso alternado.

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## Introduction

Fever is a common clinical entity in childhood, accounting for most of the emergency consultations and visits to the emergency pediatrics department. Although considered benign and desirable for a better host response against possible infection,<sup>1,2</sup> parents and guardians still regard it as a disease in itself and a risk for major complications, such as seizures or brain damage, creating a fear described as “fever phobia”.<sup>3-5</sup> This term, introduced in the literature in 1980s, regards the exaggerated concern, by many parents, of low and moderate fever. The belief that even mild fevers can cause neurological damage and that, without medication, the temperature could rise to 43 °C, may lead to the aggressive management of fever with antipyretics.<sup>6</sup>

Studies with parents and caregivers have shown that the main measure taken in the presence of a febrile episode is the use of drugs; non-pharmacological methods are used before the medication or associated with it.<sup>7,8</sup> Some parents, however, simply add a different drug to the pharmacological regimen, motivated by the alleged failure of the first one or because the child remains febrile, due to medical advice or fears regarding the effects of the fever,<sup>9,10</sup> thus alternately administering two antipyretic drugs.

Evidence on the effectiveness of alternating schemes, compared to monotherapy, are scarce and indicate clinically

negligible differences;<sup>6,11,12</sup> besides, alternating schemes add risks of poisoning and adverse effects.<sup>13,14</sup> Experts from several countries have advised against this practice.<sup>6,12,15-17</sup>

In Brazil, studies on the use of medications to treat different medical conditions in children have shown that antipyretics are one of the most frequently used drugs in pediatrics.<sup>18,19</sup> Few studies have specifically investigated the pattern of antipyretic use during febrile episodes in population samples,<sup>19,20</sup> and none of the studies assessed the use of alternating antipyretics.

The aim of the present study was to describe therapeutic procedures and the use of alternating antipyretics by caregivers of children from 0 to 6 years during febrile episodes. The association between the use of alternating antipyretics and sociodemographic characteristics, fever diagnosis, and fever management were also evaluated.

## Methods

The research was carried out in the city of Bagé, located in the state of Rio Grande do Sul, Southern Brazil, 396 km from the state capital. Its population in 2009 was approximately 115,000 inhabitants, with 81.92% of them residing in urban areas, according to data from the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística - IBGE). During the study period, the estimated

population of children aged 0 to 5 years of age was 11,221.<sup>21</sup> The municipal human development index (HDI-M) in 2000 was 0.802, above the national index (0.766).

The study had a cross-sectional design. Using a structured questionnaire, interviews were conducted with the parents or guardians of children aged 6 years or younger, who lived in the urban area of Bagé, from April 13 to May 25, 2009. For the purposes of this study, the term 'caregiver' is used to refer to the person responsible for decision-making regarding the child's health care, and who answered the questionnaire. When in doubt, the interviewers asked the following question: "Who is the person in the household that most often makes the decisions regarding the health care of <NAME OF CHILD>?" If the child's caregiver was not available at that time, another visit was scheduled at a more convenient time.

The sample calculation for a confidence level of 95% and an estimated use of alternating antipyretics scheme in previous studies of 60% resulted in 369 children. Cluster sampling was performed, with a raffle of 30 census sectors. The blocks of each sector were numbered and the first block to be covered was drawn, with a corner point of departure also randomly chosen by drawing lots. The interviewer approached all the houses in the raffled block, looking for children who met the study's inclusion criteria, i.e. those born after April 13, 2003.

If it were not possible to carry out the interview or schedule it with the caregiver after three attempts to contact him/her on different days and times, the child was considered as lost data. If there were two or more eligible children in the same household, data was collected for one randomly selected child. Exclusion criteria were children with serious health problems and caregivers with communication difficulties.

The caregivers' behavior during febrile episodes and use of medications to treat fever was investigated. Regarding the caregivers' behavior in the diagnosis and management of fever, the following was investigated: how often the fever was measured with a thermometer upon suspicion of fever (never/rarely/almost always/always), part of the body where the thermometer is placed (axilla/ mouth/ rectum/ear), which temperatures were considered as fever and high fever (in degrees Celsius), and procedures taken during the last febrile episode (gave medication, sought medical care, gave tea, applied cold compresses, gave warm bath, waited, others). The alternating use of antipyretics was investigated through the question: "Have you ever given <NAME OF CHILD> two different drugs on the same day to treat fever?" In case of affirmative answer, the caregiver was asked about the reason for the alternating use (no response, ran out of one of the drugs, doctor prescribed it, other), the doses of each drug (in mL, drops, suppository, or tablet), and the intervals between doses in hours.

The following data regarding the child were also collected: gender, age (in years), and number of siblings. Caregiver data were collected regarding parental relationship (mother, father, grandmother (grandfather), aunt (uncle)/,other), age (years), self-reported ethnicity (white, black, mixed-race, Asian, Native Brazilian), level of schooling (grade), occupation, and whether he/she had health insurance, as

well as data on the family's socioeconomic classification, according to the Brazilian Economic Classification Criterion (Critério de Classificação Econômica Brasil - CCEB), which estimates the family's purchasing power.

The adequacy of the doses used in the alternating regimen was assessed by comparing the doses reported by caregivers with those recommended for each drug, according to the literature,<sup>22</sup> considering the drug concentration in the available commercial form of the medication and the child's age and weight at the last febrile episode.

The data were digitized by Teleform Workgroup V10, stored and analyzed using the Statistical Package for Social Sciences (SPSS) version 18.0 for Windows and STATA version 11.2. Data were expressed as absolute and relative frequencies, means and standard deviations. Estimates of the prevalence ratio (PR) for the use of alternating therapy were calculated by Poisson regression with robust variance. At the first stage of model construction, the child's characteristics (gender, age, self-reported ethnicity, number of siblings), the caregiver's characteristics (parental relationship, age, education, occupation, health insurance), family characteristics (economic class), and fever management (temperature measured with a thermometer, temperatures considered as fever and high fever) were tested. The variables that showed statistical significance, defined as  $p < 0.20$  in individual analyses, were selected for the second stage, in which all variables were included in the initial multivariate model. After that, variables with  $p > 0.20$  were eliminated one by one in the multivariate model.

The project was submitted to the Ethics Committee of Universidade Federal do Rio Grande do Sul, and approved at the 16<sup>th</sup> meeting, record No. 96 of October 11, 2007. An informed consent was read and signed before the start of the interview; two copies were provided.

## Results

The sample consisted of 692 interviews. The total number of children per census sector that met the inclusion criteria was not found in five sectors. There were six losses due to refusal to cooperate or due to the fact that the house was empty in three attempts at contact. The sample corresponds to 6.2% of the population aged 0 to 6 years of the city of Bagé in 2009.<sup>21</sup>

Interviews related to children with at least one fever episode to date were analyzed, totaling 630 cases. The main characteristics of children and caregivers are summarized in Table 1. Children with no history of fever ( $n = 56$ ) had significantly younger mean age ( $16.62 \pm 14.67$  months) than the other groups ( $19.86 \pm 40.03$  months) and a higher percentage of mothers as the caregivers (89.3%), compared to the group of children who had fever (77.6%). There were no other differences in child characteristics (gender and number of siblings), caregiver characteristics (age, education, job, health insurance), and family characteristics (economic class).

The caregivers' behavior regarding the diagnosis and management of fever are shown in Table 2. Most caregivers said they measured temperature using an axillary

**Table 1** Sociodemographic characteristics of children and caregivers residing in the urban area of Bagé, Rio Grande do Sul, Brazil, 2009 (n = 630).

Characteristic	Variable/Range	n*	%/Mean	95% CI
<i>Child</i>				
Child's gender	Male	317	50.3	46.4-54.2
	Female	313	49.7	45.8-53.6
Child's age (months)	2.14-80.03	630	40.1	38.5-41.6
Number of siblings	Only child	239	37.9	34.1-41.7
	One or more siblings	370	58.8	55.0-62.6
<i>Child's caregiver</i>				
Who cares for the child	Mother	489	77.6	74.3-80.9
	Father	60	9.5	7.2-11.8
	Others	81	12.9	10.3-15.5
Age (years)	13-79	630	32.9	32.1-33.7
Self-reported ethnicity	White	490	77.8	74.6-81.0
	Non-white	140	22.2	19.0-25.4
Schooling, in years	0 to 8	256	40.6	36.8-44.4
	9 to 11	236	37.5	33.7-41.3
	12 or more	136	21.6	18.4-24.8
Has a job	Yes	259	41.1	37.3-44.9
	No	357	56.7	52.8-60.6
	Not reported	14	2.2	1.0-3.3
Has medical insurance	Yes	256	40.6	36.8-44.4
	No	362	57.5	53.6-61.4
	Not reported	12	1.9	0.8-3.0
Family's economic class	High (A1, A2)	53	8.4	6.2-10.6
	Middle (B1, B2, C1)	286	45.4	41.5-49.3
	Low (C2, D, E)	263	41.7	37.9-45.6
	Not reported	28	4.4	2.8-6.0

95% CI, 95% confidence interval.

\*Differences in the total of each variable result from absent data.

thermometer. The mean temperature that caregivers considered as fever was 37.4 °C (SD 1.5; mode 38 °C and median 37.5 °C) and as high fever was 38.7 °C (SD 1.4; mode and median 39 °C) (Table 2). Alternating use of antipyretics was confirmed by almost a third of respondents; the main reasons for the use of another drug was the "lack of response" to the drug when used alone (monotherapy) and medical indication. The alternating antipyretic drugs mentioned by respondents are shown in Table 3; paracetamol and dipyron were the most widely used drugs.

Regarding the adequacy of antipyretic doses used in alternating schemes, it was observed that 9% of doses were above the recommended dose, and 70.5% were below the recommended minimum dose. This distribution was maintained for all drugs except diclofenac, which was used at a higher dose than the recommended. In 13 cases, the dose of at least one of the alternately used drugs was not mentioned by the respondents, accounting for 7.8% of cases. The more frequent dosing intervals were every 4 hours (35.6%) and every 6 hours (28.1%). In 25.3% of cases, intervals < 4 hours were mentioned. The intervals were not mentioned by 8 respondents (4.8% of cases).

Table 4 shows the estimates of crude and adjusted PR for each variable. In the crude analysis, the use of alternate

therapy was positively associated with child's age > 1 year, father or mother as the caregiver, parental education less than 9 years, self-reported white ethnicity, having health insurance, middle and high socioeconomic class, and temperature measurement. In the adjusted analysis, these characteristics remained positively associated with the use of alternating therapy, except for health insurance and temperature measurement, which lost statistical significance.

## Discussion

The present study evaluated the behavior of caregivers regarding the use of alternating antipyretic therapy to treat fever in children aged up to 6 years. As it was a population-based study and used a representative sample of children living in a Brazilian city, the findings of this study provide new data for discussion of a common, but little investigated therapeutic practice in Brazil.

To evaluate the percentage of alternating therapy found in this study (26.7%), it is necessary to consider that findings from previous studies vary widely (from 4% to 67%), and that many have limited the use to alternating therapy with acetaminophen and ibuprofen. The alternating use

**Table 2** Conducts in the diagnosis and management of fever in children residing in the urban area of Bagé, Rio Grande do Sul, Brazil, 2009 (n = 630).

Characteristic	n*	Mean temperature/%	95% CI
<i>Fever temperature (°C)</i>	612	37.44	37.3-37.6
<i>High-fever temperature (°C)</i>	612	38.67	38.6-38.8
<i>Uses thermometer</i>			
Always	281	44.6	40.7-48.5
Almost always	146	23.2	19.9-26.5
Sometimes	132	21	17.8-24.2
Rarely	30	4.8	3.1-6.5
Never	39	6.2	4.3-8.1
Not reported	2	0.3	0.0-0.7
<i>Gave the child medication</i>			
Yes	469	72.9	69.4-76.4
No	171	27.1	23.6-30.6
<i>Body site where temperature was measured</i>			
Axilla	588	93.3	91.3-95.2
Mouth	3	0.5	0.0-1.0
<i>Alternating medication</i>			
Yes	168	26.7	23.2-30.1
No	461	73.3	69.9-76.8
<i>Reasons for alternating medication</i>			
No response	101	60.5	56.7-64.3
Doctor prescribed	62	37.1	33.3-40.9
Ran out of medication	2	1.2	0.3-2.0
Others	2	1.2	0.3-2.0

95% CI, 95% confidence interval; C, degrees Celsius.

\*Differences in the total of each variable result from absent data.

**Table 3** Antipyretic regimens utilized in alternating therapy used by caregivers of children residing in the urban area of Bagé, Rio Grande do Sul, Brazil, 2009 (n = 168).

Alternating medications	n*	%	95% CI
Dipyron + paracetamol	80	48.2	40.6-55.8
Paracetamol + ibuprofen	46	27.7	20.9-34.5
Dipyron + ibuprofen	27	16.3	10.7-21.9
Dipyron + acetylsalicylic acid	7	4.2	1.2-7.2
Paracetamol + acetylsalicylic acid	5	3	0.4-5.6
Diclofenac + acetylsalicylic acid	1	0.6	0.0-1.8

95% CI, confidence interval.

\*One caregiver answered paracetamol + paracetamol and another did not report which antipyretics were used.

of paracetamol and ibuprofen was reported by 26% of caregivers interviewed in a London hospital outpatient clinic<sup>3</sup> and by 52% of Australian parents who answered a mailed questionnaire.<sup>23</sup> In the United States, Crocetti et al.<sup>24</sup> found that 27% of caregivers, interviewed in two pediatric clinics in Baltimore, mentioned the use of alternating therapy, at a lower percentage than that reported by caregivers whose children were attended to at a hospital emergency room in Alabama (67%).<sup>25</sup> In another study in the United States, in a study carried out

with Hispanic parents, only 4% reported use of alternating acetaminophen and ibuprofen.<sup>26</sup>

The most commonly used drug in alternating therapy was paracetamol, followed by dipyron, while studies carried out in the United States and England show ibuprofen as the main antipyretic used interchangeably with paracetamol.<sup>3,24,25</sup> In this study, it was observed that dipyron was the drug most often used in this treatment regimen, possibly due to its lower cost when compared to ibuprofen and greater availability in Brazil, considering

**Table 4** Crude and adjusted prevalence ratio (PR) of the use of alternating therapy according to sociodemographic variables, diagnosis, and fever management by caregivers in children residing in the urban area of Bagé, Rio Grande do Sul, Brazil, 2009 (n = 630).

Variables	n	Alternating therapy %	Crude PR PR (95% CI)	Adjusted PR PR (95% CI)
<i>Child's gender (n = 629)</i>				
Female	312	24.3	0.84 (0.65-1.09)	
Male	317	29.0		
<i>Child's age (n = 629)</i>				
> 1 year	566	28.3	2.23 (1.15-4.31)	2.72 (1.24-5.98)*
1 year	63	12.7		
<i>Firstborn (n = 617)</i>				
Yes	247	30.4	1.21 (0.93-1.56)	
No	370	25.1		
<i>Caregiver (n = 629)</i>				
Parents	548	28.5	1.92 (1.12-3.29)	2.05 (1.19-3.54)*
Others	81	14.8		
<i>Age of caregiver, in years</i>				
<i>Years of schooling (n = 627)</i>				
≥ 9 years	372	33.6	2.04 (1.50-2.79)	1.49 (1.06-2.10)*
≤ 8 years	255	16.5		
<i>Self-reported ethnicity (n = 629)</i>				
White	489	30.3	2.12 (1.38-3.25)	1.52 (1.11-2.07)*
Non-white	140	14.3		
<i>Has a job (n = 615)</i>				
Yes	258	30.2	1.24 (0.96-1.61)	
No	357	24.4		
<i>Has health insurance (n = 617)</i>				
Yes	256	30.9	1.33 (1.02-1.72)	
No	361	23.3		
<i>Socioeconomic classification (n = 601)</i>				
High	53	43.4	2.48 (1.66-3.72)	1.65 (1.14-2.41)*
Middle	285	31.6		
Low	263	17.5		
<i>Measures temperature (n = 627)</i>				
Always/almost always	426	30.0	1.55 (1.13-2.13)	
Sometimes/rarely/never	201	19.4		
<i>Fever (n = 611)</i>				
< 37.4 °C	195	26.1	0.94 (0.71-1.24)	
≥ 37.4 °C	416	27.9		
<i>High fever (n = 611)</i>				
≤ 39.4 °C	496	28.8	1.38 (0.94-2.02)	
> 39.4 °C	115	20.9		

\*Significant results after analysis adjusted by Poisson regression with robust variation. 95% CI, confidence interval; PR, prevalence ratio.

that the drug is not sold in many countries, including the United States and England.

The analysis of doses used indicates a high percentage of drug underdosing for all mentioned drugs, with the exception of diclofenac. No studies were found with data on the doses used in alternating schemes for comparison with the present findings. In clinical trials published on alternating therapy, the doses and intervals between doses vary, although all of them used full doses recommended in monotherapy (12.5 to 15.0 mg/kg of paracetamol and 5 to 12.5 mg/kg of ibuprofen, according to the age group).<sup>11</sup>

It appears that the caregivers' lack of knowledge or poor advice given to them regarding the recommended doses for treatment of fever extends to the temperature considered to be fever. Considering the variability of measurements obtained by various thermometers and site of measurement, the natural oscillation of body temperature according to the time of day, environmental factors, age, and individual variability, the definition of fever according to body temperature is arbitrary.<sup>6</sup> When necessary for diagnosis and counseling to parents, the most common values in the literature indicate the lower limit for

moderate fever an axillary temperature of 38.5 °C, and of 39.5 °C for high fever.<sup>6</sup> Using these limits as a parameter for comparison with the present findings, it is possible to suggest that the medians of 37.5 °C for fever and 39 °C for high fever verified in this study show that a significant portion of caregivers consider as high fever values below the recommended ones.

The administration of low doses of antipyretics, and temperature values used for the diagnosis of fever below the recommended values suggest a lack of advice given to caregivers, and their fever phobia. The anxiety that affects parents and the lack of knowledge on the time necessary for the start of antipyretic effect could explain, in part, the use of doses at intervals of less than four hours and the supposed lack of response to the first drug used, reported by caregivers as justification for the use of alternating therapy.

Considering that most caregivers reported using a second antipyretic drug due to “failure” of the first one, the correct guidance on the dose to be used could have prevented the use of a second drug and consequent exposure to the risk of adverse effects inherent to these drugs. Although many professionals postulate that the alternating use of antipyretics does not present obvious risks for children, misunderstandings can occur due to different drug doses, formulations, concentrations and administration forms,<sup>25</sup> generating non-response or delay in the desired antipyretic effect. During consultations with the pediatrician by phone, a routine behavior for segment of the population that uses health insurance plans, the risk of dosing errors due to misunderstandings may be even greater.<sup>27</sup>

Noteworthy, as a limitation to this study, is the possibility of recall bias regarding the last febrile episode, and the drugs and doses administered. To reduce this bias, caregivers were asked about the number of febrile episodes in the previous year, and then asked about the last febrile episode. It should also be noted that the drug doses used are usually prescribed as drops or mL per kilogram of the child, and that it is more important that the caregiver remembers the amount of drug administered (in drops or mL) that the exact weight of the child during the febrile episode, thus reducing the bias. From this perspective, weight gains of less than a kilogram between the last febrile episode and the date of the interview would not change the recommended dose.

This study did not assess the fears or reasons why caregivers treat body temperature increase in their children, as a quantitative approach was chosen. Walsh et al.<sup>23</sup> developed, after several studies on “fever phobia” in Australian parents, a scale to assess this fear in any community. However, the instrument has yet to be validated in other countries, such as Brazil.

It can be concluded that the use of drugs in the management of fever is a common practice for caregivers of children up to 6 years, including the use of alternating antipyretics. Most caregivers considered as fever temperature values below those recommended and indicated the non-response to monotherapy and medical indication as the main reasons for the use of alternating antipyretic drugs. Educational measures, clarifying to the public about what fever is, and when and how to treat it, may assist in the proper use

of drugs and prevent excessive demand for unscheduled medical consultations and emergency room visits.

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## Conflicts of interest

The authors have no conflicts of interest to declare.

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