Treatment of fever and associated symptoms in the emergency department: which drug to choose?

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Abstract. – **OBJECTIVE:** Fever is a frequent cause of admission to the Emergency Department (ED) worldwide. Although it can be caused by a wide range of conditions, the most effective treatment based on its etiology is still undetermined.

PATIENTS AND METHODS: This prospective, single-center, observational study enrolled adult patients who accessed the ED for fever. Physicians were free to administer paracetamol 1,000 mg (P), the combination paracetamol 500 mg/ibuprofen 150 mg (PI) or Ibuprofen 600 mg (I). The primary endpoint was both 1-degree and 1-point reduction in body temperature for all associated symptoms on the Numerical Rating Scale (NRS) after 1 hour (T1). The secondary endpoint was the reduction of at least 2 points on the NRS after two hours (T2). Adverse events, the need for rescue therapy, and the response based on the underlying etiology (bacterial, viral, or immune/neoplastic) were also evaluated.

RESULTS: 324 patients (170 males, mean age 71±6 years) were enrolled: 187 had bacterial, 80 viral, and 57 neoplastic/inflammatory fever. Fever was treated with Paracetamol 1,000 mg (P) in 189 patients and with Paracetamol/Ibuprofen 500/150 mg (PI) in 135 subjects, while none of the patients were primarily treated with I. Based on the fever etiology P was administered to 113 patients with bacterial fever (59.8%), 48 patients with viral fever (25.4%), and 28 subjects with neoplastic/inflammatory fever (14.8%). PI was administered to 74 patients with bacterial fever (54.8%), 32 patients with viral fever (23.7%), and 29 subjects with neoplastic/inflammatory fever (21.5%). The primary endpoint was achieved by 126 patients, 70 of them (37.0%) were treated with P and 56 (41.5%) with PI (p=0.418). The secondary endpoint was achieved by 295 patients, 171 (90.5%) of them treated with P and 124 (91.9%) treated with PI (p=0.669). No significant differences were found between groups treated with P and PI concerning rescue therapy (15 vs. 6 patients; p=0.893). Interestingly, PI was more effective than P in patients with bacterial fever at T1 (P 33.6% vs. PI 48.6%; p=0.040), while efficacy of P and PI was similar at T2 for all kind of fever.

CONCLUSIONS: Paracetamol 1,000 mg represents the first choice for the treatment of fever in the ED, followed by Paracetamol/Ibuprofen 500/150 mg. Interestingly, Paracetamol/Ibuprofen combination resulted in being more effective in patients with bacterial fever one hour after its administration.

Key Words:
Fever, Paracetamol, Emergency department, Paracetamol/Ibuprofen, NRS, COVID-19.

Introduction

Fever is a medical condition defined by an increase in the body's temperature set point. In normal circumstances, body temperature is the result of an interaction between peripheral nerve receptors, mostly located in the skin and the hypothalamus. Body temperature usually increases when a chemical substance, called pyrogen, stimulates those warm/cold receptors and then the hypothalamus. Pyrogens may be a constitutional peptide of infection agents, or inflammatory substances released not only as a consequence of infections but also during inflammatory diseases or tumors[1]. Fever is a common cause of admission to the Emergency Department (ED)[1]. However, there are no data at all concerning the best treatment available, based on the underlying disease, in the emergency setting. The few studies[2] available on this topic, have been published in the pediatric population, showing, however, conflicting results. In fact, a therapy exclusively based on paracetamol in febrile pediatric patients[3] is effective depending on the underlying condition, while in some cases, the simultaneous or alternated administration of paracetamol and a non-steroidal anti-inflammatory drug, such as ibuprofen, may be a good option in reducing body' temperature[4]. Since no data are still available regarding the best treatment for febrile adult patients admitted to the ED, we have designed a study aimed at identifying the most appropriate and effective treatment for controlling body temperature and all associated symptoms in the emergency setting.

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Objectives of the Study

This study is aimed to assess the efficacy and safety of the most common antipyretic drugs used in the ED, such as paracetamol (P), ibuprofen (I), and the combination paracetamol/ibuprofen (PI) in adult patients with fever. Emergency doctors were free to choose the most appropriate antipyretic drug to administer to patients enrolled in the study.

The primary endpoints were:

a) identification of the most prescribed antipyretic drug in the ED;

b) treatment efficacy according to the etiology of the fever. Concerning this endpoint, patients were divided into three groups: 1) fever due to bacterial etiology; 2) fever due to viral etiology; 3) fever due to immune/oncological etiology. A simultaneous reduction of at least 1 degree (°C) in body temperature and at least 1 point on the NRS scale for one or more associated symptoms after 1 hour (T1) from drug administration was considered.

Secondary endpoints were:

a) to evaluate the number of patients (%) who obtained a reduction of at least 2 points on the NRS scale, in at least one of the symptoms associated with fever 2 hours after the antipyretic administration (T2);

b) to identify the number of patients who needed a rescue therapy (additional drug therapy, administered to patients following the ineffectiveness of the previous intake of antipyretics), stratified according to the dosage of antipyretics and the etiology of fever;

c) to identify the percentage of adverse events.

Patients and Methods

Study Design

This was an observational, prospective, monocentric study conducted at the Fondazione Policlinico Universitario A. Gemelli, IRCCS of Rome, from July 2021 to June 2022.

The emergency physicians were free to administer oral drugs with antipyretic action (P, I, or PI) to all patients eligible for enrollment. This study was approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli, IRCCS of Rome (#ID3710), and conducted according to the Helsinki Declaration of Human Right.

Study Population

We enrolled 324 patients with fever admitted to the ED of Fondazione Policlinico Universitario A. Gemelli, IRCCS of Rome. Fever was defined as a tympanic body temperature >37.8°C, based on the international accepted definition in the critical care setting[5]. Inclusion criteria were: adults with fever with/without associated symptoms who had given their consent to participate in the study. Therefore, patients with age <18 years old, with contraindications or allergies to P, I, or PI, who were unable to take oral drugs, or who did not express their consent to participate in the study were excluded.

Methods

We collected data concerning the body temperature and the pain perceived by patients in relation to any associated symptoms listed below, using a Numerical Rating Scale (NRS) scale (from 0=no pain to 10=maximum intensity of pain). The symptoms considered were: headache, sore throat, arthralgia, and muscular pain. These data were recorded upon arrival in the ED (T0) and after 1 hour (T1) and 2 hours (T2) from the administration of antipyretic therapy. Moreover, the use of rescue therapy and the onset of any adverse effects were also collected, together with the type of analgesic used in relation to the diagnosis, anamnestic data, any previous intake of antipyretics, blood tests, complete blood count with formula, chest X-ray and nasal swab performed.

Statistical Analysis

Statistical analysis was performed using Chi-square test, t-test, and multivariate analysis, including any confounding factors. The efficacy of the different drugs used on both fever and associated symptoms were evaluated. A p-value lower than 0.05 ($p \leq 0.05$) was considered statistically significant. Data were analyzed using SPSS for Windows™ version 25.0 software (IBM Corp., Armonk, NY, USA).

Results

Patients' Characteristics

Of 324 adult patients, 170 (52.4%) were male, 154 (47.6%) were female. Their overall median age is 71±6 years. Stratifying the enrolled patients according to gender and chosen treatment (Table I):

- of 170 men, 107 (56.6%) were treated with P, while 65 of them (47.9%) received PI;

- of 154 women, 82 (43.4%) were given P, and for the remaining 70 (52.1%), PI was preferred.

Stratifying the enrolled patients according to the etiology of fever (Table II):

Table I. Patients enrolled and treatments.

			Paracetamol	Paracetamol-Ibuprofen	Total
SEX	F	Count	82	70	154
		% in therapy group	43.4%	52.1%	47.6%
	M	Count	107	65	170
		% in therapy group	56.6%	47.9%	54.4%
Total		Count	189	135	324
		% in therapy group	100.0%	100.0%	100.0%

- 187 (57.7%), 101 males and 86 females, resulted with fever of bacterial origin (for example, caused by pneumonia, urinary tract infections, cholangitis, etc...).

- 80 (24.6%), 41 males and 39 females of viral origin (we refer exclusively to Sars-CoV-2 infection).

- 57 (17.7%), 28 males and 29 females, with immuno-oncological etiology (pancreatic carcinoma, leukemia, etc.).

Patients treated with P included 113 patients with bacterial fever (59.8%), 48 with viral etiology (25.4%), and 28 with inflammatory/neoplastic fever (14.8%). Patients treated with PI included 74 patients with bacterial fever (54.8%), 32 with viral (23.7%), and 29 with inflammatory/neoplastic fever (21.5%) (Table III).

The average temperature at T0 was 38.4°C for paracetamol and 38.2°C for paracetamol/ibuprofen. At T1 we registered a 1-point temperature reduction in 143/324 patients (44.2%): specifically, 81 (42.9%) among those treated with P, 62 (46.0%) with the combination PI. At T2 we registered a further 0.5-point temperature reduction in 256/324 patients (79.3%): specifically, 118 (62.6%) among those treated with P, 89 (66.4%) with the combination PI. These results are showed in Figure 1.

As for the NRS scale at admission, patients presented a value between 4 and 6. After 1 hour from the administration of the therapy (T1) we obtained an average value of 2 with P and 4 with PI.

At T1 there was a reduction of 1 NRS point in 291 patients (90.08%), of which 172 (90.05%) were treated with P and 119 (88.10%) with PI. At T2, we found a value of NRS 0 with P and 2 with PI (Figure 2).

We observed that the primary endpoint (the concomitant reduction of at least 1 degree in body temperature and at least 1 point on the NRS scale for associated symptoms after 1 hour of administration (T1) was reached by 126 patients. Of these, 70 (37.0%) were treated with P and 56 (41.5%) with PI

Table II. Patients enrolled and etiology of fever.

			AGE	NRS T0	NRS T1	NRS T2	T (°C) at the inlet	T (°C) at 1 hour
Bacterial	N	Valid	187	187	187	187	187	187
	Median		71.0	4.0	3.0	1.0	38.0	37.3
	Percentiles	25	60.0	.00	.0	.0	37.8	37.0
		50	71.0	4.0	3.0	1.0	38.0	37.3
		75	79.25	6.0	4.0	3.0	38.5	37.6
Viral	N	Valid	80	80	80	80	80	80
	Median		65.5	5.0	3.0	.0	38.05	37.3
	Percentiles	25	48.0	.0	.0	.0	37.8	37.0
		50	65.5	5.0	3.0	0.0	38.05	37.3
		75	78.0	6.0	5.0	3.0	38.5	37.6
Immuno-oncological	N	Valid	57	57	57	57	57	57
	Median		68.5	5.0	2.5	.50	38.0	37.3
	Percentiles	25	58.0	2.0	.0	.0	37.8	36.85
		50	68.5	5.0	2.5	0.50	38.0	37.3
		75	77.0	6.0	4.0	2.25	38.4	37.6

Numerical Rating Scale (NRS); arrival in the ED (T0); after 1 hour (T1); 2 hours (T2).

**Table III.** Etiology of fever and treatment.

			Paracetamol	Paracetamol-Ibuprofen	Total
Pathology group	Bacterial	Count	113	74	187
		% in therapy group	59.8%	54.8%	57.7%
	Viral	Count	48	32	80
		% in therapy group	25.4%	23.7%	24.6%
	Inflammatory-Neoplastic	Count	28	29	57
		% in therapy group	14.8%	21.5%	17.7%
Total		Count	189	135	324
		% in therapy group	100.0%	100.0%	100.0%

(p=0.418). The secondary endpoint (the reduction of at least 2 points on the NRS scale in at least one of the associated symptoms two hours after the administration of the therapy) was reached by 295 patients, of which 171 (90.5%) treated with P and 124 (91.9%) with PI (p=0.669) (Table IV). 15/324 patients (4.6 %) required a "rescue therapy", in particular, 9 (4.8%) were treated with P, and 6 (4.4%) were treated with PI. Stratifying results according to the etiology of fever, 11 with bacterial fever required rescue therapy, and only 1 with viral fever.

Treatment of Fever in COVID-19 Patients

Eighty patients with fever were COVID-19-positive, 33 (26.1%) of whom were women, and 47 (73.9%) were men. Their average body temperature at T0 was 38.50°C, which decreased to 37.3°C and 37.0°C, respectively, at T1 and T2. The initial NRS value was 5, which decreases to 3 at T1 and to 0 at T2. Patients treated with P were 48 (25.4%), and patients treated with PI were 32 (23.7%). We registered a reduction of at least 1°C at 1 hour after administration in 39 patients (27.0%), out of 143 patients who had this reduction, considering all etiologies; of these, 26 (54.2%) with P paracetamol group, and 10 (31.25%) with PI. Regarding NRS, the reduction of one point on the NRS scale at T1 was found in 68 patients, of which 42 (87.5%) were treated with P and 26 (81.25%) with PI. The results are
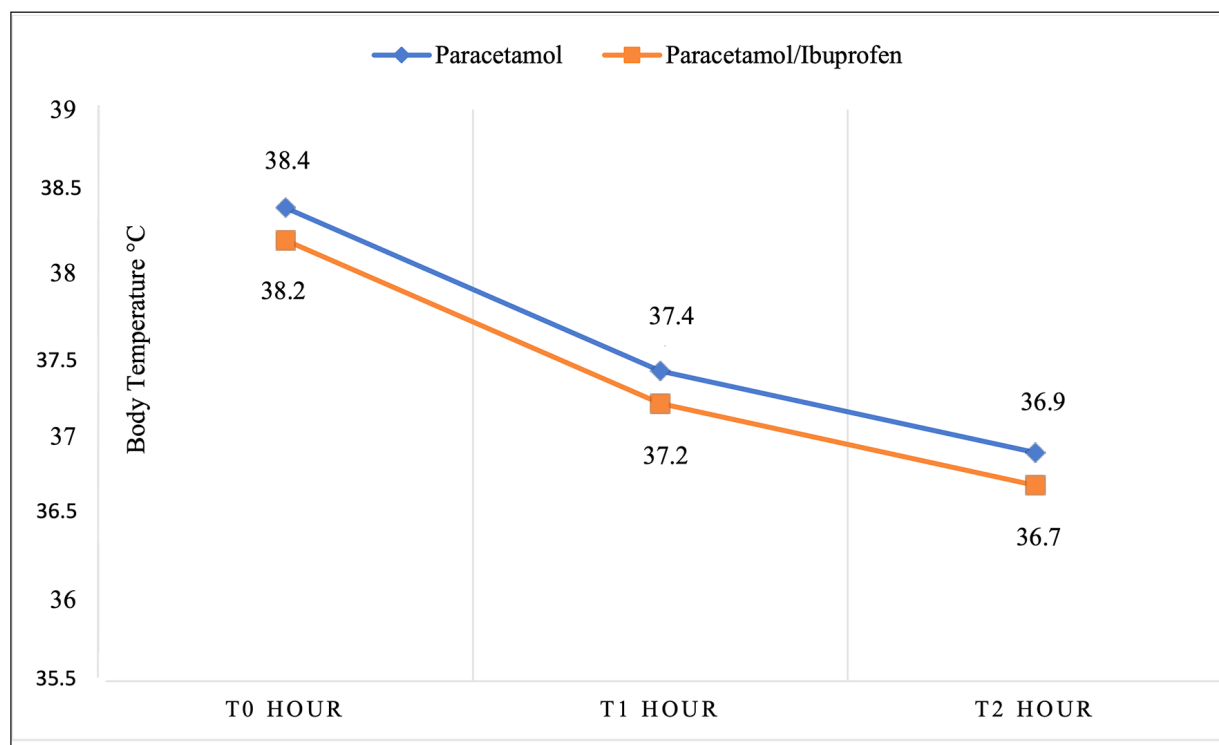
Figure 1. Reduction of body temperature according to the treatment.
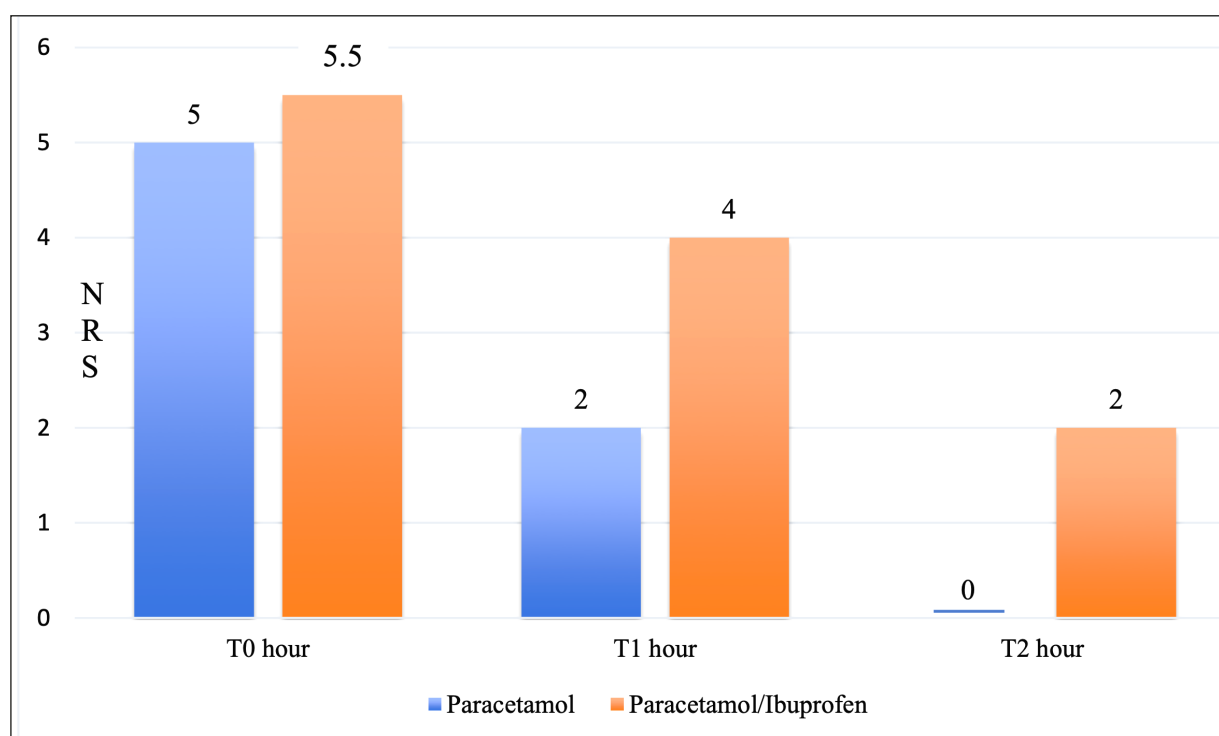
Figure 2. Reduction of NRS according to the treatment.

shown in Figure 3. The primary endpoint was reached by 32 patients: 22 (45.8%) who received P and 10 (32.0%) who received PI. The reduction of at least two points on the NRS scale at T2 was obtained in 71 patients: 43 (89.6%) with P and 28 (87.5%) with PI. In conclusion, we found that P and PI had similar results in COVID-19 patients. No adverse effects were reported. Only 1 patient (6.6%) required rescue therapy out of the 15 total patients (if we consider all etiologies).

Discussion

Fever is a common cause of admission in the ED around the world and can be associated with a wide range of different conditions[1,2,6]. Fever is commonly treated with classic antipyretics drugs such as paracetamol[6], Ibuprofen[7], or a combination of those drugs[8]. Some studies[9] reported that this combination is more effective compared to monotherapy in pediatric patients with selected causes of fever. Indeed, the use of combinations may allow us to reduce the dosage of the active component of the drugs, thus reducing potential adverse effects[10], especially those of the GI tract[11-13]. At the same time, combining two different drugs in the same pill may reinforce its action, since two different components exert a different analgesic activity[14-16]. Concerning the combination of paracetamol/ibuprofen, previous studies[9,17-19] showed that there are no interactions between those molecules when taken simultaneously, but an increase in absorption of paracetamol may be observed. This effect has a potential benefit in relation to the onset of the analgesic

Table IV. Number of patients (%) who reached the primary and secondary endpoint.

	Paracetamol	Paracetamol/Ibuprofen	*p*
Total Patients	126	295	-
Primary Endpoint N. patients (%)	70 (37.0%)	56 (41.5%)	0.418
Secondary Endpoint N. patients (%)	171 (90.5%)	124 (91.9%)	0.669
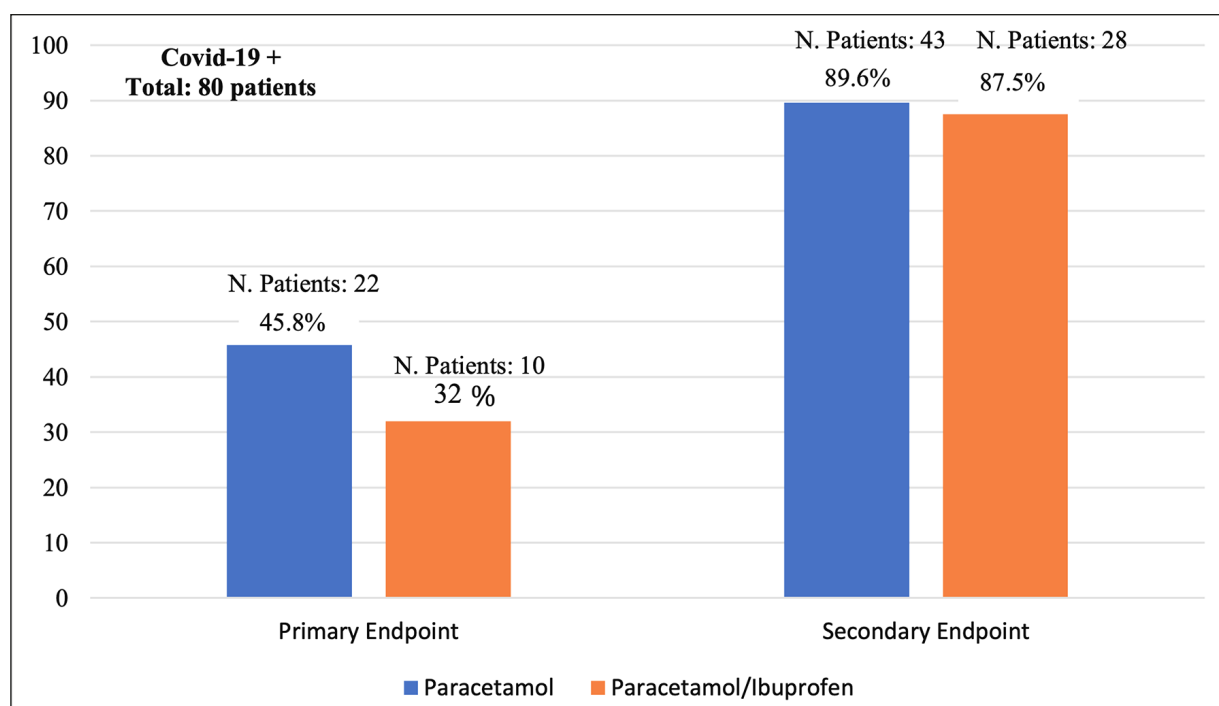
Figure 3. Primary and secondary endpoint in COVID-19 patients.

effect. In a randomized, comparative and parallel study[15,20-22] conducted in 2014 on 99 children with fever, authors demonstrated that the combination of paracetamol/ibuprofen had the same efficacy on the control of the body temperature than paracetamol alone up to 4 hours after their administration. On the other hand, the association showed improvement in some clinical manifestations associated with fever compared to paracetamol alone. Despite data available in the pediatric population, there are no studies designed to identify the best treatment option for fever in adults in the emergency setting. Our study tried to clarify this issue and demonstrated that the most used drug in subjects accessing the ED for fever is paracetamol 1,000 mg, followed by the combination paracetamol/ibuprofen 500/150 mg, while, surprisingly, ibuprofen alone was never prescribed. One of the explanations for this phenomenon is that paracetamol is the antipyretic drug associated with the lowest rate of contraindications and side effects compared to NSAIDs. Paracetamol, in fact, may be safely administered at all ages, including in fertile women or during lactation. This drug shows very few contraindications, such as allergy, liver or renal failure, hemolytic anemia, or deficit of glucose-6 phosphate dehydrogenase[23,24]. On the other hand, NSAIDs show a high

variety of contraindications, including allergy, liver or renal failure, GI diseases including bleeding, allergic asthma, cardiovascular diseases, pregnancy, and lactation[25,26]. This is why, especially in overcrowded facilities, such as the ED, doctors may be more confident in administering drugs associated with a higher level of safety, such as paracetamol alone. An interesting finding of this study also derives from the administration of the association paracetamol/ibuprofen 500/15 mg. In particular, while this association showed similar effects of paracetamol in reducing fever and associated symptoms in patients with viral disease, including COVID-19 and immune/neoplastic conditions, it showed superiority in fever of bacterial origin at least 1 hour after its administration. One of the possible explanations is that in bacterial fever, there is a lower but progressive increase of inflammatory activity compared to viral fever; therefore, introducing an anti-inflammatory drug together with paracetamol may be the best choice, at least in those cases.

Conclusions

In conclusion, paracetamol 1,000 mg represents the first choice for the treatment of fever in the ED.

On the other hand, paracetamol/ibuprofen 500/150 mg is more effective within the first hour of administration in patients with bacterial fever. Further randomized and multicentric studies are now needed in order to confirm our findings and to standardize protocols for the treatment of fever in the ED.

Conflict of Interest
All the authors declare no conflict of interest.

Informed Consent
All patients signed an informed consent.

Ethics Approval
This study was approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli, IRCCS of Rome (#ID3710), and conducted according to the Helsinki Declaration of Human Rights.

Authors' Contributions
Conceptualization, F.F.; methodology, M.Co., and M.C.; validation, V.O., and M.C.; investigation and data collection, C.L., A.C., and A.N.; writing-original draft preparation, A.S., and F.F.; writing-review and editing, A.S., F.F., and M.Co.

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