Fever and antipyretic therapy in the septic patient in the intensive care unit: an update

Alejandro Donoso* and Daniela Arriagada

Unidad de Paciente Crítico Pediátrico, Hospital Clínico Metropolitano La Florida, Santiago, Chile

Abstract

Fever is a very common sign to observe in critically ill children during their Intensive Care Unit stay, which should be understood as an evolutionary biological response of normal adaptive character from the host to physiological stress. It is the result of a complex response to pyrogenic stimuli, resulting in the generation of cytokines and prostaglandins. The molecular mechanisms involved in the onset of fever are not yet fully specified. Therefore, difficulties in the knowledge of the exact pathophysiological processes involved are created, so it is necessary to elaborate an adequate and specific therapeutic strategy. Experimental studies conclude that fever and inflammation are beneficial to the host. However, antipyretic therapy is commonly employed, and human studies on the presence of fever and its treatment for the prognosis of critically ill septic patients are inconclusive. Up-to-date information on the physiology of human thermoregulation, the effect of temperature on the febrile range over multiple biological processes involved in host defense, and thermoregulatory interventions in the septic patient are essential to know by the critical care physician.

Key words: Temperature. Fever. Cytokines. Antipyretics. Sepsis. Intensive care.

Fiebre y terapia antipirética en el paciente con sepsis en la unidad de cuidados intensivos: actualización

Resumen

La fiebre es un signo frecuente en el niño críticamente enfermo durante su estadía en la unidad de cuidados intensivos, y debe ser entendida como una respuesta biológica evolutiva, de carácter adaptativo normal del huésped al estrés fisiológico. Es el resultado de una compleja respuesta a estímulos pirogénicos, resultando en la generación de citocinas y prostaglandinas. Los mecanismos moleculares implicados en el inicio de la fiebre aún no están totalmente precisados, originando dificultades en el conocimiento de los procesos fisiopatológicos exactos involucrados y, por ende, necesarios para elaborar una adecuada y específica estrategia terapéutica. Estudios experimentales concluyen que la fiebre y la inflamación son benéficas para el huésped; no obstante, la terapia antipirética es comúnmente empleada y estudios en humanos sobre la presencia de fiebre y su tratamiento para el pronóstico del paciente crítico con sepsis no son concluyentes. Para el médico intensivista es esencial disponer de información actualizada referente a la fisiología de la termorregulación humana, el efecto de la temperatura en rango febril sobre múltiples procesos biológicos involucrados en la defensa del huésped y las intervenciones termorreguladoras en el paciente con sepsis.

Palabras clave: Temperatura. Fiebre. Citocinas. Antipiréticos. Sepsis. Cuidados intensivos.

Correspondencia:

*Alejandro Donoso

E-mail: adonosofuentes@gmail.com

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Introduction

"Humanity has three great enemies: fever, famine, and war; of these by far the greatest, by far the most terrible, is fever." (William Osler)

Although the temperature is a primary vital sign, its assessment in the critical patient has received little attention compared to other signs since infectious diseases, unlike those signs, occasionally affect the thermoregulatory system.

In the Intensive Care Unit (ICU), fever frequently occurs in both adults¹ and the pediatric² patients, although its origin can be diverse, sepsis is its leading cause, reaching 74% in hospitalized patients³, while in the pediatric population infectious pathologies represent 80%⁴. Fever should be regarded as an essential component of the host systemic inflammatory response, being an important defense and resistance mechanism against infections, by which the organism itself undergoes temporal thermal stress as a global regulatory mechanism⁵.

There is important experimental evidence in animals regarding the benefit of fever^{6,7}; however, its presence has a deleterious effect in patients with acute brain damage, neuropsychiatric alteration and in patients with limited cardiorespiratory reserve (shock) or those who present metabolic instability⁸.

There are misconceptions about fever and its treatment both in the general population as well as in the medical one⁹⁻¹⁴. Usually, fever is treated in many ICUs broadly and systematically, and it is common for the patient to receive non-pharmacological and pharmacological therapy since a putative risk to health is attributed to this condition; however, there is no conclusive evidence in favor of its routine treatment¹⁵.

It should be kept in mind that the fever treatment will always intervene with the inflammatory process that undergoes in the host⁵. On the other hand, pharmacological agents to reduce fever can cause undesirable hemodynamic effects (arterial hypotension)¹⁶, platelet dysfunction and gastrointestinal bleeding¹⁷ or hepato-renal dysfunction in the dehydrated patient or the one with associated morbidities¹⁸⁻²⁴.

Finally, for various specific conditions, it is not yet defined if fever or the physiological response to it causes morbidity and mortality and whether its treatment confers any benefit. In the septic patient, the thermal control, as well as its purpose, remain under debate^{8,25,26}.

The objective of this review is to provide an update on the thermoregulatory mechanisms and fever development

from an evolutionary perspective, in its physiopathology and the available evidence of its beneficial and harmful effects. Specifically, the role of fever and the use of antipyretic therapy on infections in the critically ill patient are analyzed. There was no systematic review of the subject.

Body temperature regulation

Endothermy is a characteristic of all mammals and birds^{27,28}, which regulates body temperature through the balance between heat generation and heat loss. The heat is produced by the metabolic activity and depending on the environmental temperature it can be acquired from or lost to the environment. In response to infection, many animals temporarily increase their temperature between 2°C and 4°C by altering the balance between heat generation and heat loss²⁹.

In mammals, homeostatic control of body temperature (thermoregulation) is essential and is strictly regulated ($\pm 0.2^\circ\text{C}$), it is obtained through autonomic, endocrinological, metabolic, and behavioral mechanisms^{30,31}. Unlike other mammals, humans have a high protective capacity against heat, produced through autonomic thermoregulation of cutaneous blood flow and transpiration.

The thermoregulation system comprises a network of peripheral and central location thermoreceptors (sensory afferent pathway), a control center (hypothalamus) and effector mechanisms of body heating and cooling, which include the regulation of peripheral blood flow, shivers production, and sweating (evaporative cooling) (Fig. 1).

It should be noted that the autonomic thermoregulatory activity is similar in children and adults under neutral environmental conditions; however, there are some unique patterns in infants³² and children, who present a lower adaptation to extreme environmental temperatures (higher body surface/mass ratio and less evaporative loss)³³ as well as in pre-pubertal adolescents³⁴. The neonatal patient presents thermoregulatory instability during the first 2-3 days of life, then achieving an adequate homeothermia³⁵.

The accepted normal range for body temperature is from 36.1°C to 37.8°C³⁶, presenting variations with physical activity and environmental factors³⁷. The central temperature is higher in the pediatric patient than in the adult³⁸.

In addition to the strict control of temperature, there is a rhythmic variability in periods of 24 h, which is associated with the sleep-wake cycle (morning nadir)³⁹. This circadian rhythm is altered in the critically ill patient⁴⁰.

Figure 1. Human thermoregulatory system: the thermoregulation system comprises a network of peripheral and central thermoreceptors (sensory afferent pathway), an integrating center (hypothalamus) and effector mechanisms of body heating and cooling, which include regulation of peripheral blood flow, shiver production, and sweating (evaporative cooling).

Definition of fever, febrile response, and hyperthermia

The definition of fever is arbitrary since it depends on the method used for its measurement⁴¹, the studied population (infection and post-resuscitation care) and the purpose for which it is determined⁴².

Fever is understood as the regulated elevation of the central temperature as a consequence of a complex inflammatory process, which originates in the thermoregulatory center. Fever is often, but not necessarily, part of the host's defensive response to infectious and non-infectious stimuli recognized as pathogenic or strange⁴³. As a result, rapid and stereotyped response of the innate immune system⁴⁴ to infections occurs, where the body temperature rarely exceeds 41°C and does not cause tissue damage.

It should be noted that fever is one of the components of the febrile response, which is understood as a physiological reaction mediated by cytokines and characterized by the elevation of the thermostatic set point, involving the generation of acute phase reactants, and

activation of central nervous, autonomic, immune and endocrine systems, in addition to a component of behavioral change^{30,45-47}.

Finally, fever should be distinguished from hyperthermia (> 41°C), which corresponds to an increase in body temperature not caused by a shift in the hypothalamic thermostatic set point that does not have diurnal variation, which is potentially harmful and where pyrogenic cytokines are not involved directly. Hyperthermia is due to an alteration in the mechanisms that control the production and loss of heat (excessive environmental temperature, neuroleptic malignant syndrome, and severe thyrotoxicosis).

According to the World Health Organization, fever is defined as a $\geq 37.5^{\circ}\text{C}$ rectal temperature³⁷ in children. Clinically, fever is the appearance of a 1°C or higher increase in the body temperature compared to the average temperature of the place where it is evaluated. The levels accepted as fever are $\geq 38^{\circ}\text{C}$ for rectal and $\geq 37.4^{\circ}\text{C}$ for axillary temperature⁴⁸. The importance of the increase of at least 1°C more than the average

Figure 2. The phylogenetic relationships between fever, heat shock, innate, and adaptive immunity. Animals today use fever as a strategy to cope with an infection. The approximate phylogenetic origin of fever (600 million years) and the related biological processes are also shown.

temperature lies in the diurnal variation of the normal body temperature, which is higher in the afternoon (17–19 h). These fluctuations are greater in children than in adults and more pronounced during febrile episodes⁴⁸.

Fever mechanisms: an evolutionary strategy

From an evolutionary perspective, fever has risen as an additional host response to infection, before the onset of adaptive immunity, but in the setting of already well-established heat shock and innate immunity responses in major animals. Thus, fever is a primitive and phylogenetically preserved immune response in mammals and birds⁴⁹, dating back probably to 600 million years ago^{5,50} (Fig. 2). This response is generally considered limited to homeothermic animals; however, many poikilothermic animals such as minor vertebrates⁵¹, arthropods⁵², and annelids develop a similar process, increasing their core temperature in the presence of infection by seeking a warmer environment.

Fever has been documented in the two main divisions of animals: deuterostomes and protostomes, suggesting that the increase in core temperature in response to infection is a conserved survival strategy, which evolved from the separation moment of both evolutionary lines⁵. On the other hand, fever can be blocked by inhibition of the enzyme cyclooxygenase (COX) in various species of poikilotherms^{53,54} and homeotherms, which suggests the possibility that the fever development mechanisms may have evolved from a common ancestor.

Although the normal body temperature of a mammal is determined by the climatic temperature when it first appeared on our planet⁵⁵, a recent study calculated that the optimal central temperature of a mammal is approximately 36.7°C, derived from the compensation between bacterial spread by hypothermia and the metabolic cost increase of hyperthermia⁵⁶.

Molecular and cellular bases

Fever development requires that various communication pathways between the nervous and immune systems propagate the inflammatory response to the central nervous system immediately after the peripheral activation of the innate immune system⁵⁷ (Fig. 3).

In the classical model of infection-induced fever, the exogenous pyrogen lipopolysaccharide (LPS)⁴⁴, a prototype of a pathogen-associated molecular pattern (PAMP), is identified by the pattern recognition receptors or Toll-like receptor-4 in what we can call a “first wave”⁵⁸. These receptors are located in circulating peripheral immune cells (monocytes and macrophages) and resident cells (hepatic Kupffer cells), causing genetic transcription, synthesizing and releasing endogenous pyrogens such as interleukin (IL)-1, tumor necrosis factor- α (TNF- α)⁵⁹ and others such as IL-6 and interferon γ (Table 1). These cytokines, together with the PAMPs, will trigger a “second wave” of activation, which originates a communication between immune and nervous systems through vagal receptors (brainstem nucleus of the solitary tract), in the blood–brain barrier (BBB) and in the circumventricular organs,

Figure 3. Proposed mechanism of the generation of fever in sepsis. The stimulation of sentinel cells by exogenous pyrogens produces endogenous pyrogens, which stimulate the fever production in the hypothalamic preoptic area (POA), through second messengers such as PGE₂ and ceramide. PGE₂ is also produced in Kupffer cells, in the liver, in response to the stimulation of LPS, which additionally stimulates the POA through the vagus nerve. OVLT: organum vasculosum of the lamina terminalis; LPS: lipopolysaccharide; PGE₂: prostaglandin E₂. (Modified from Walter et al.¹⁵⁷).

specifically the Organum Vasculosum of the Lamina Terminalis (OVLT). The OVLT is located in the optic recess of the anteroventral region of the third ventricle and connects with the preoptic hypothalamic nuclei^{44,60,61}.

It should be noted that the exact mechanism by which circulating cytokines (hydrophilic molecules) reach the neural tissue has not been fully elucidated. Several hypotheses have been proposed, such as a BBB alteration in the OVLT area, active transport of cytokines, or activation of cytokine receptors in the endothelium of the neural vasculature⁶².

OVLT synthesizes intracerebral prostaglandin E₂ (PGE₂), which is the terminal critical mediator⁶³, through inducible COX-2 enzyme and microsomal prostaglandin E₁ synthase^{64,65}. In experimental animal models, it has been demonstrated that the COX-2 transcription mechanism exhibits upregulation at the endothelial level and in

perivascular cells of the cerebral microvasculature between 90 min and 12 h after the LPS administration⁶⁵⁻⁶⁸.

Through the cyclic AMP, intracerebral PGE₂ acts in the preoptic nucleus reducing the firing frequency of heat-sensitive neurons, causing a response that has the aim of decreasing heat loss and increasing its production until the body reaches a new hypothalamic temperature set-point, which once achieved, will be sustained by the same mechanism used in the regulation of normal body temperature.

PGE₂ is actively removed from the brain by the organic anion transporter-3, but the relationship between its brain clearance rate and the fever duration has not yet been established⁶⁹.

The lipid derivative ceramide can act as a second messenger independently of PGE₂, being of particular importance in the early stages of the fever generation⁷⁰.

Table 1. Main endogenous pyrogens, antipyretic mediators and their action.

Mediator	Role in fever
IL-1	The most potent endogenous pyrogen in humans
TNF- α	Endogenous pyrogen. Inflammatory mediator
IL-6	Endogenous pyrogen
IL-8	Endogenous pyrogen
IFN- γ	Endogenous pyrogen
MIP-1 β or CCL4	Chemokine of monocytes and T lymphocytes, among other immune cells
NF- κ B	Transcriptional factor that controls endogenous pyrogens expression
AP-1	Transcriptional factor that controls endogenous pyrogens expression
IL-1 RA	Endogenous antipyretic cytokine
IL-10	Endogenous antipyretic cytokine
TNF- α -BP	Endogenous antipyretic cytokine
AVP	Endogenous antipyretic
α -MSH	Endogenous antipyretic
Glucocorticoids	Endogenous antipyretic
ACTH	Endogenous antipyretic

IL-1: interleukin-1; TNF- α : tumor necrosis factor alpha; IL-6: interleukin-6; IL-8: interleukin-8; IFN- γ : interferon gamma; MIP-1 β : macrophage inflammatory protein-1 β ; CCL4: C-C motif chemokine 4; NF- κ B: nuclear factor-kappa b; AP-1: activator protein-1; IL-1 RA: IL-1 receptor antagonist; IL-10: interleukin-10; TNF- α -BP: tumor necrosis factor binding protein; AVP: arginine-vasopressin; α -MSH: alpha-melanocyte-stimulating hormone; ACTH: adrenocorticotrophic hormone.

It should be highlighted the existence of a negative feedback mechanism mediated by glucocorticoids, through nuclear factor-kappa B and activator protein-1. Moreover, the febrile response is also regulated by specific antipyretic cytokines (Table 1).

There is evidence in numerous experimental models of the COX-2 participation in the neural vasculature for the fever generation⁷¹. Thus, COX-2 knockout mice are not capable of producing a febrile response⁷², and in humans, the use of selective COX-2 inhibitors reduce fever^{73,74}. However, pyrogenic cytokines stimulate PGE2 production and can also contribute to the fever development through alternative pathways (PGE2-independent)⁷⁵, which could explain the therapeutic failure of COX-2 inhibitors in some patients.

Metabolic consequences of fever

The stimulation of the hypothalamic preoptic area by pyrogenic mediators in the septic patient causes a sympathetic activation⁷⁶ inducing tachycardia (adrenergic stress)⁷⁷. However, this can also occur in the presence of sympathetic activity blockade⁷⁸. Hence, a role of humoral mediators (prostanoids) and metabolic factors on cellular receptors of the cardiac pacemaker is attributed⁷⁹.

The body temperature increase causes an increment in heart rate (10 beats/min for each degree Celsius)^{80,81}, cardiac output and oxygen consumption (VO₂)⁸², in addition to the enhanced production of carbon dioxide (VCO₂)⁸³ and catecholamines⁸⁴.

Conversely, body cooling in the sedated and ventilated febrile patient reduces energy expenditure⁸⁵, and in the critically ill patient it reduces VO₂ by 10% for each degree Celsius decreased in the core temperature as well as VCO₂^{3,86}. From the above, it seems evident that any beneficial effect of fever should always be evaluated individually and according to the metabolic cost caused by it, especially in patients with low cardiorespiratory reserve (high doses of inotropes and vasopressor agents and patient-ventilator asynchrony).

Immunological consequences of fever

Fever induces the production of heat shock proteins (HSPs), which are highly preserved between different organisms⁸⁷ and are expressed in response to various stimuli or stress conditions^{88,89}, these proteins are essential for cell survival⁹⁰; their function is to provide thermotolerance to the cell^{29,91-93}.

In the presence of fever, the neutrophils transendothelial extravasation⁹⁴ and the phagocytosis capability are optimized⁹⁵. Moreover, the L-selectin-mediated binding of the human lymphocyte to the vascular endothelium is improved with the temperature in a febrile range, which favors the lymphocyte migration to the site of tissue inflammation. However, neutrophils and macrophages present a significant decrease in their functioning at temperatures of 41°C⁹⁶. Finally, the increase in temperature causes acceleration of caspase-dependent apoptosis in human neutrophils, a process that plays a role in limiting inflammation and tissue damage during infection⁹⁷.

Pharmacological consequences of fever

Fever can affect the absorption, distribution, and elimination of some drugs used in critical patients. Few

Figure 4. The balance of the evidence from the experimental studies that support the beneficial effects versus the detrimental effects of fever.

studies have been conducted in humans⁹⁸, and alteration in the pharmacokinetic profile has been described for some antibiotics⁹⁹. Thus, there is still no certainty about the effects of fever on the drug's pharmacokinetics and pharmacodynamics that eventually allow pharmacological therapy to be modified in febrile septic patients.

Importance of fever in animals with infection

A subject of debate for many decades has been whether the development of fever represents a beneficial or risky response to the host,¹⁰⁰ and there is still no unappealable answer available. Perhaps the most powerful argument to support its beneficial effect has teleological bases^{7,50}. As noted above, fever is present in ectothermic vertebrate animals (reptiles, amphibians, and fish) and endotherms (mammals and birds), as well as in some invertebrates. Given the significant metabolic-energetic and nutritional cost of the febrile response⁸³, its persistence in such a large group of organisms gives us evidence of its evolutionary advantage⁷, which has been demonstrated by various experimental animal models. For example, the pioneering studies of Kluger et al.¹⁰⁰ concerning the heat-seeking behavior in infected lizards and their effect on survival are important^{7,53,101}.

The artificial temperature increase has proven to increment the mice survival to infection produced by herpes simplex virus¹⁰², poliovirus¹⁰³, coxsackievirus¹⁰⁴, rabies virus¹⁰⁵, and in an experimental model of bacterial peritonitis due to *Klebsiella pneumoniae*¹⁰⁶. However, it should be noted that this thermal increase is not homologous to the febrile response in endothermic animals.

In an animal model of septic shock, longer survival was demonstrated in the experimental group (fever > 39°C), while the use of antipyretic therapy was associated with lower HSP70 circulating levels¹⁰⁷.

Moreover, a meta-analysis on the effect of the use of antipyretic drugs in animals infected with influenza virus showed that its use was associated with a higher risk of mortality¹⁰⁸. Similar findings have been demonstrated for bacterial infections^{53,109,110}.

Although considerations derived from an evolutionary point of view support the protective effect of fever, these are not necessarily applicable to the critical patient at present, in whom the elimination of pathogens is pharmacologically supported.

In summary, although there is no uniform answer from experimental studies on the benefit of fever in critical illness, the balance subtly leans toward its beneficial value (Fig. 4). However, the protective effects of these experimental findings have not yet been manifested in the clinical context.

Table 2. Proposed criteria for the selection between pharmacological and non-pharmacological antipyretic therapy for the septic patient.

Antipyretic drug	External cooling
Not sedated patient	Hypothalamic dysfunction
Simultaneous need of analgesia	Need for strict thermal control
	Patient with hemodynamic instability
	No response to pharmacological therapy

Fever in the patient with infection

Taking into consideration the previously described data (vide supra) the question should be the following. Under what conditions is it beneficial to treat a fever?

The effect of fever on the prognosis of the adult patient remains controversial, at least in part, because it has been reported the use of various definitions and different moments of fever assessment, making it difficult to identify a threshold for the development of relevant clinical consequences. Several studies in septic patients have reported a deleterious¹¹¹, neutral¹¹², or beneficial¹¹³ effect of fever. Recently, a large retrospective cohort study showed in non-neutropenic septic patients that the presence of fever is associated with lower mortality, a finding not evidenced in neutropenic patients, which could suggest a relationship between neutrophil activation during the febrile episode and mortality¹¹⁴.

In the pediatric population, few reports investigate the role of fever in the ICU patient. Gordijn et al.² pointed out in a retrospective observational study that 40% of the patients presented fever during their stay in the ICU, the majority within the first 48 h of admission and concerning the primary diagnosis. The fever that began after 48 h was associated with a longer stay.

The scientific literature indicates an increased risk related to the development of fever and reveals a relation between the fever magnitude (> 39.5°C), the severity of the disease and mortality. Therefore, it seems reasonable to assume that antipyretic treatment could improve the patient's prognosis; however, as noted below, this presumption is not as evident as it seems.

Antipyretic therapy to the patient with infection

Various approaches to fever control have been proposed:

- Treatment: a drug is administered when the temperature exceeds a predefined threshold
- Strict prevention of fever: temperature is maintained below the fever threshold
- Strict maintenance of normothermia: through targeted temperature management (TTM), where a predefined range of normothermia (36-37°C) is held.

Regarding the therapeutic strategies used in the febrile patient, there is no standardized practice, although its use is usually justified in terms of well-being assurance and reduction of cardiorespiratory physiological distress^{16,42,111,115}. However, most doctors start treatment when the temperature is > 38.5°C¹¹⁶. Data that prove the superiority of one modality of antipyretic therapy over another are not available for the septic patient¹¹⁷. Table 2 lists some criteria for the choice of antipyretic methods (pharmacological and non-pharmacological).

It is important to remark that antipyretic agents act at the hypothalamic temperature set-point, which suppresses the heat generating response and, therefore, to be effective they require the integrity of the thermoregulatory system. In contrast, surface cooling devices reduce body temperature but do not decrease heat production. Both present opposing mechanisms on vascular tone: the first one cause's vasodilation to improve heat loss, while body cooling produces vasoconstriction, which will produce a different hemodynamic repercussion in the septic patient¹⁶ and should be considered carefully.

At present, it is not possible to establish with certainty whether treating the fever in septic patients without neurological impairment is beneficial or risky for their vital prognosis^{117,118} (Fig. 5). However, the available evidence indicates that a temperature > 40°C must be treated in any case¹¹⁷. In support of the fever treatment, it is pointed out that the induction of systemic changes caused by it, such as the increase in oxygen and energy demand (the latter being especially hazardous in the septic patient with hemodynamic dysfunction), can be reduced by an antipyretic strategy¹⁶. Similarly, experimental animal models have shown that fever can worsen inflammatory lung damage^{119,120} and exacerbate the damage induced by mechanical ventilation¹²¹.

However, the treatment of fever can mask symptoms and signs for the early diagnosis of severe infection^{122,123} and delay the start of an appropriate antibiotic therapy,

Figure 5. Potential (extra neurological) risks produced by fever in the septic patient and therapeutic goals of their control. PK/PD: pharmacokinetics/Pharmacodynamics; CO₂: carbon dioxide.

which is associated with higher mortality¹²⁴. Furthermore, when deciding to treat fever indiscriminately, it should be considered that it improves cellular immune function¹²⁵, determines the growth rate of some bacterial¹²⁶ and viral¹²⁷ pathogens, influences the magnitude of parasitemia¹²⁸ and optimizes the bactericidal action of antibiotic therapy¹²⁹. Furthermore, clinical evidence indicates that the naturally hypothermic septic patient presents a worse

vital prognosis compared to those who generate a febrile response¹³⁰⁻¹³². Recently, a similar finding has been described for patients with acute respiratory distress syndrome¹³³. Moreover, a multicenter observational study confirmed that the use of antipyretic agents, whether nonsteroidal anti-inflammatory drugs or acetaminophen, increases mortality in septic patients¹¹². In the same line, the ongoing research, Fever and Antipyretic in Critically

ill patients Evaluation (FACE II trial)¹³⁴, will compare the safety and efficacy of two temperature control objectives (< 38°C vs. < 39.6°C) in patients' survival.

There are potential risks of antipyretic therapy concerning the temporal course of the disease, which is being evidenced in experimental conditions *in vivo*, as in the excessive release of TNF from immune cells (by the inhibition of negative feedback by PGE₂)¹³⁵. At a clinical level, the use of acetaminophen has been related to the development of arterial hypotension¹³⁶, with the presence of sepsis being a risk factor for presenting this effect¹³⁷. Its use has also been associated with pyroglutamic acidosis in critical adult¹³⁸ and pediatric¹³⁹ patients. Recently, the role of this drug as an antioxidant in septic patients¹⁴⁰ has been evaluated, and clinical trials on safety and efficacy in adult critical patients^{141,142} are under development (NCT02280239-NCT01869699).

There are currently few randomized studies evaluating the efficacy of antipyretic therapy in critically ill adult patients. Bernard et al.¹⁴³ found no difference in mortality at 30 days with the use of ibuprofen for 48 h in septic patients with at least one organ dysfunction. Recently, Zhang et al.¹⁴⁴ noted that there is no mortality reduction with the use of antipyretic therapy in septic patients. It has been demonstrated that the use of intravenous acetaminophen every 6 h versus placebo (HEAT study) in patients with or suspected infection and temperature >38°C (20% with septic shock) was not effective in decreasing the number of ICU free-days and did not present any beneficial effect on mortality at 28 and 90 days¹⁴⁵⁻¹⁴⁷. Two important meta-analyses concluded that the use of antipyretic therapy showed no benefit regarding mortality in ICU patients with infection and without neurological disease^{148,149}. Although the use of antipyretic drugs^{143,150,151} reduces the temperature in the critical patient¹⁵², there is no conclusive evidence on its effectiveness in reducing mortality¹⁵³.

About the use of surface cooling to reach normothermia (TTM: 36.5-37°C) in the adult patient with febrile septic shock and assisted ventilation, a French multicentric study proved that it was safe and useful in decreasing the vasopressor requirements and produce a better survival at 14 days. However, there was a higher incidence of secondary infections in the treated group, and there was no difference in mortality at discharge from the ICU or the hospital¹⁵⁴. A *post hoc* analysis confirmed that the observed decrease in mortality was a direct effect of the reduction of body temperature and not by the heart rate

reduction¹⁵⁵. The use of external cooling measures hardly is tolerated by the conscious patient; recently, it was pointed out that its use can be risky in the septic patient¹⁴⁴.

Regarding the use of therapeutic hypothermia, the results of the Danish study named The Cooling and Surviving Septic Shock Study¹⁵⁶, which evaluates the effect of induced hypothermia (32-34°C) for 24 h followed by thermal control (36-38°C) for 48 h on the mortality of adult patients with septic shock, has not been reported.

In the future, the now inconsistent results in the use of antipyretic therapy in critical patients, the systematic reviews and the meta-analyses should establish whether fever in a specific population is a marker of disease severity or is an associated risk factor and whether its treatment could improve the vital prognosis.

Conclusions

Fever is an evolutionarily ancient and well-preserved, usually beneficial, response of the host to infection. However, the association between fever, its etiology, antipyretic treatment, and morbidity-mortality is particularly complex, and many questions are still present.

The continuous progress in knowledge about the pathophysiology of fever in the septic patient should lead to a better understanding of the reasons for employing a particular strategy of thermal control. Although there are currently no recommendations on a preferred method in the clinical practice, the physician does have precise, safe, and efficient options.

At present, there is no definitive evidence of a beneficial effect of the antipyretic therapy use in pediatric ICU septic patients. The evaluation of the biological response to a specific temperature control strategy will allow an individualized therapy, which should lead to more coherent management of the febrile patient and, eventually, an improvement in its prognosis.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors declare no conflicts of interest.

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