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Fever effects and treatment in critical care: Literature review

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ABSTRACT

Considering that the incidence of fever may reach up to 75% among critically ill adults, healthcare professionals employed in the Intensive Care Unit (ICU) are called to evaluate and manage patient temperature elevation on a daily basis. This literature review synthesizes the evidence about the effects of fever and antipyretic treatment in ICU patients. Although the febrile response acts protectively against infections, noxious effects are possible for patients with cerebral damage, neuropsychiatric disorders or limited cardiorespiratory reserve. Observational studies on ICU populations have reported associations between fever magnitude and patient mortality. Especially recent findings indicated that infected patients may significantly benefit from temperature elevation, while high fever may be maladaptive for non-infected ones. Aggressive antipyretic treatment of ICU patients has not been followed by decreased mortality in randomized trials. However, fever suppression and return to normothermia improved outcomes of septic shock patients. Antipyretic treatment should begin with drug administration and proceed with external cooling in case of refractory fever, but adverse effects of both antipyretic methods should always be considered. This article concludes by providing implications for antipyretic treatment of critically ill adults and suggesting areas for future research.

Introduction

Patient care for fever has traditionally been a core competency for nurses employed in the Intensive Care Unit (ICU).[1] Besides temperature monitoring and evaluation, nurses also participate in antipyretic treatment decisions. However, despite the considerable amount of evidence, beneficial and detrimental effects of fever and fever suppression remain inconclusive for the majority of ICU patients.[2,3] Thus, published guidelines about fever have been limited to the evaluation of temperature elevation.[4] Although previous authors have attempted to outline evidence-based recommendations for antipyretic treatment, the low level of evidence for antipyretic interventions has been highlighted.[5,6] In this context, questions on which patients will benefit from antipyretic treatment, when this treatment should be initiated and which antipyretic method should be preferred, have not been answered yet. Thus, the aim in reviewing the literature was to explore, synthesize and discuss the existing evidence about beneficial and detrimental effects of fever and antipyretic treatment in critically ill adults.

Search methods

Articles published between January 1995 and April 2012 in English-language peer-reviewed journals indexed by the Cumulative Index for Nursing and Allied Health Literature (CINAHL) and PubMed (National Library of Medicine) were searched for clinical

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studies on fever and antipyretic treatment in adult ICU patients. Searches initially took place at the first week of March 2012 and were updated at the first week of May 2012. Additional articles were retrieved through hand-searching, from reference lists of the online found literature. A combination of the following terms was used in the search: fever, pyrexia, temperature, hyperthermia, antipyresis, antipyretic treatment, mortality, outcomes, ICU/CCU, critically ill. At the first stage, possible beneficial and detrimental effects of fever and antipyretic treatment were investigated; thus, selected articles were not limited to the ICU population. At the second stage, studies reporting on mortality of febrile patients treated in critical/intensive care settings were selected; these included observational or experimental design studies, as well as meta-analyses of relevant studies. Studies conducted in pediatric ICU patients or in adults not admitted to the ICU were excluded.

Retrieved studies were screened for inclusion by two independent reviewers (P.K. and D.A.), initially by using titles and abstracts and then by obtaining and reading the full text when necessary. Eligibility for inclusion was jointly determined by both reviewers. Data extracted from selected studies were categorized according to fever effects, antipyretic treatment effects, fever-mortality associations, mortality differences according to antipyretic treatment, and present practice in antipyretic treatment.

Ten observational studies reporting on fever-mortality associations of ICU patients, three experimental studies investigating the effect of antipyretic treatment on mortality of ICU patients, and two meta-analyses of relevant experimental studies were considered appropriate for inclusion. Main characteristics of observational and experimental studies and appraisal criteria for quality were summarized in tables.

Beneficial and detrimental effects of fever

Despite its metabolic cost, fever is followed by significant benefits. As part of the acute phase response, fever has evolved to provide adaptive advantages during infection.[7] Exposure to febrile temperatures can be directly cytotoxic for pathogens or inhibit their growth. Fever induces the expression of heat shock proteins, which protect host cells and regulate immune responses.[8] The heat shock response also inhibits the activation of NF-κB, which acts as an upstream modulator of the proinflammatory cytokine response, and its activity is positively correlated with mortality in septic shock patients.[9] Laboratory studies conducted on animals have demonstrated the positive effect of fever manifestation on host survival.[10] Retrospective studies in hospitalized adults with bacterial infections have also reported increased mortality rates in those who fail to develop fever.[11]

Despite the protective value of fever, detrimental consequences of elevated temperature have been identified for patients with cerebral damage, attributed to traumatic brain injury, intracerebral or subarachnoid hemorrhage, ischemic stroke or brain surgery.[12,13] In these cases, fever or hyperthermia exacerbates brain tissue damage and has been associated with neurological deterioration, poor functional outcome, and increased in-hospital mortality.[14] Suggested mechanisms for these associations include increased cerebral metabolic rate, decreased cerebral blood flow, brain edema exacerbation, excitotoxic neurotransmitter release and blood–brain barrier breakdown.[15] Although there is no consensus on the need for cerebral hypothermia,[16] maintaining core temperature of patients with cerebral damage within the normal range of 36.5–37.5 °C seems to be the best choice.

Fever has been identified as an independent risk factor for agitation or delirium in the critically ill.[17–19] However, it is unclear whether mental deterioration is triggered by increased temperature or by increased circulating cytokine levels. The latter has been followed by increased anxiety and depression and worsened memory in healthy volunteers,[20] having thus the potential to affect brain function of patients, especially the elderly. Even if increased temperature independently contributes to agitation or delirium, much more effective interventions for preventing neuropsychiatric disorders than fever suppression have been suggested, such as adequate administration of sedatives and analgesics, treating electrolyte disorders and helping patients be oriented in time and space.[21]

A core temperature increase from 37 °C to 39 °C results in a 25% increase in metabolic rate and subsequent increases in oxygen consumption, respiratory quotient, heart rate and cardiac output.[22] These increases mainly occur during the chill phase of fever, when shivering is manifested. Critically ill patients with limited cardiorespiratory reserve, e.g. in sepsis, may not adequately compensate for increased metabolic demands.[23] In these patients, fever suppression might decrease metabolic demands and prevent severe hemodynamic instability and hypoxic tissue injury. In surgical ICU patients, propacetamol administration has been reported to decrease oxygen consumption by 3–12% for 1 °C temperature decrease, without adverse hemodynamic effects.[24]

Magnitude and duration of fever can be important determinants of its adverse effects. Febrile temperatures rarely exceed 40.5–41 °C due to the activation of endogenous antipyretics.[25,26] These neuroactive substances, such as glucocorticoids, melanocortins and interleukin-10, suppress synthesis of pro-inflammatory cytokines, mitigate their potentially destructive actions, and provide central thermoregulatory control; thus, they restrain the intensity of the febrile response and control magnitude and duration of fever.[27] This highly regulated nature of fever implies that the febrile response can be maladaptive when this exceeds an upper limit or when this is of long duration. Besides metabolic rate increase, very high fever may aggravate immune function, by inhibiting apoptosis (death) of immune cells and perpetuating pro-inflammatory cytokine response.[28] Collateral tissue injury may also occur due to enhanced immune mechanisms, especially when cells are exposed to temperatures >39.5 °C.[11] Even higher temperatures can be followed by acid–base and electrolyte abnormalities, cell protein denaturation, impaired oxygen release to tissues and multisystem failure.[29]

Antipyretic treatment: methods and adverse effects

Antipyretic agents act by inhibiting conversion of arachidonic acid to prostaglandin-E_2, promoting the return of thermostatic set-point of hypothalamus to normal. On the contrary, physical antipyresis is mainly based on external cooling methods, which accelerate heat loss through the skin by conduction, convection or evaporation.[5] Antipyretic drug therapy carries a considerable risk for adverse effects, such as hypotension, gastrointestinal bleeding, renal and hepatic toxicity.[30] Likewise, adverse effects of physical antipyresis mainly include shivering, vasoconstriction, vasospasm of coronary arteries and rebound hypothermia.[3]

Physical antipyresis is opposed to normal thermoregulatory mechanisms, which try to maintain increased temperature during fever. Thus, its application is expected to result in increased heat production, metabolic rate and oxygen consumption.[24] For this reason, external cooling should not be used alone, but only after antipyretic drugs have started to lower the elevated thermostatic set-point. Antipyretic drug administration has therefore been recommended as the first-line treatment, with external cooling being added in cases of refractory fever or when rapid temperature decrease is considered necessary.[30] However, neither conventional external cooling techniques compared to antipyretic drugs, nor the combined use of pharmaceutical and physical antipyresis compared to antipyretic drugs alone, have been confirmed to be