

Pyrexia in the critically ill

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Abstract

Temperature change is a conserved physiological response to infection. In animal studies cytokine responses associated with body temperature changes have been elucidated. In humans with sepsis, hypothermia appears to be associated with higher TNF-alpha concentrations and has a significantly higher mortality. However, the presence of pyrexia does not appear to influence outcome from infection. The routine use of

antipyretic agents remains controversial and studies in patients with viral infections suggest that their use may be associated with an anti-inflammatory effect with prolonged time to viral clearance – and surprisingly, little evidence of improvement in symptoms. In one ICU study it would seem that ibuprofen when used in the sub-group of patients with hypothermia and sepsis is associated with an improvement in outcome.

Keywords: Pyrexia, hypothermia, sepsis, antipyretics

Introduction

Sepsis necessitates acquiring an infection and the physiological changes which occur in the host are then a result of the infection with that organism. Response is often to pathogen components. Some of these physiological changes are an attempt to eradicate the pathogen while others are often unwanted side-effects of being infected. For example, coughing is clearly designed to expel invading micro-organisms from the respiratory tract. However, cyanosis, for example, is a side-effect of compromised gas exchange resulting from the pneumonia caused by the invading organism and probably has little beneficial effect in eradicating the organism from the host. Much of the physiological response is conserved through evolution.

The basic physiological response to inflammation is reflected in the well known criteria for the systemic inflammatory response (SIRS):

Temperature > 38 or < 36°C

Heart rate > 90 bpm

Respiratory rate > 20 bpm; or IPPV

WBC > 12,000 or < 4,000 cells/ml

Pyrexia or hypothermia is one component of the definition and would therefore be expected to be an important determinant in outcome from infection. A recently described study [1] used a multi-dimensional neural network analysis of 382 patients with septic shock to define parameters dictating outcome. Systolic and diastolic blood pressure and platelet count were the three most highly correlated variables. Notably respiratory rate and temperature were unimportant. Even more surprisingly some treatments – notably catecholamine use were also unimportant. This new predictive scoring system – the MEDAN RRT, performed better than all other scores tested. The authors concluded that any beneficial physiological change should be associated with an improved outcome and from the results obtained pyrexia did not affect outcome. Moreover, blood pressure is indeed an important determinant of outcome in septic shock, but treatment of the blood pressure does not necessarily improve the score and outcome? Perhaps the pyrexia or hypothermia seen in sepsis may be an epiphenomenon or is acting peripheral to the main physiological changes. Some authors have suggested that while some physiological changes are a *defence*, others may actually be considered a *defect*.

Pyrexia as a defensive physiological change

Pyrexia is a phylogenetically ancient host response to infection and it is found in fish, reptiles, birds as well as

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mammals. Fever reduces mortality from infection in cold-blooded animals. However, in man, is pyrexia adaptive or maladaptive? Moreover, is hypothermia protective or detrimental and is it worse than pyrexia? If we accept that pyrexia may be beneficial then is the use of antipyretic agents associated with an altered response to infection or mortality?

Body temperature is carefully regulated even during fever – the thermostat is merely set at a higher temperature. For instance, cold-blooded lizards when infected seek out warmer areas to raise their body temperature by around 2°C; rats with a 2° fever when placed in a very hot cage activate their cooling mechanisms; rats with a 2° fever when placed in a very cold cage activate their heat conservation mechanisms. In all cases the core temperature returns to the same higher level.

Outcome and pyrexia

Julius Wagner-Jauregg won the Nobel prize for physiology and medicine in 1927 for his studies relating to fever. Knowing that malaria could be controlled with quinine and having observed that patients with some nervous disorders improved after infections with fever, he induced malaria to treat syphilis patients who had central nervous system disorders. He was thus able to control an incurable and fatal disease. Although antibiotics eventually replaced this treatment for syphilis, it led to the development of fever therapy.

A recent study sought to determine the incidence of hyperthermia (>38.3) and hypothermia (<36.0) in ICU [2]. This was a prospective, observational study in a thirty-one bed, medico-surgical intensive care. All adult patients admitted consecutively to the ICU for at least 24 h, during a 6 month period were studied. Fever 139 (28.2%) patients and hypothermia in 45 (9.1%) patients, at some time during the ICU stay. Fever was present in 52 of 100 (52.0%) infected patients without septic shock, and in 24 of 38 (63.2%) patients with septic shock. Hypothermia occurred in 5 of 100 (5.0%) infected patients without septic shock and in 5 of 38 (13.1%) patients with septic shock. Patients with hypothermia and fever had higher sequential organ failure assessment (SOFA) scores on admission (6.3±3.7 and 6.4±3.3 versus 4.6±3.2), maximum SOFA scores during ICU stay (7.6±5.2 and 8.2±4.7 versus 5.4±3.8) and mortality rates (33.3% and 35.3% versus 10.3%; which was significantly different p<0.01). Among the septic patients those that were hypothermic were older than febrile patients (69±9 versus 54±7 years). Patients with septic shock had a higher mortality if they were hypothermic than if they were febrile (80% versus 50%, statistically different with p<0.01). The authors conclude that both hypothermia

and fever are associated with increased morbidity and mortality rates. However, those with hypothermia have a worse prognosis than those with fever.

Cytokines and the temperature response to infection

Interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha) have been implicated as key mediators in inflammation, morbidity, and mortality associated with sepsis. These agents may be associated with the temperature changes seen in sepsis as well as survival. Leon and co-workers [3] studied these cytokines and outcome using a ceecal ligation and puncture (CLP) model in gene knockout mice. Wild-type mice developed an initial hypothermia and subsequent fever during sepsis. However, the IL-6 knockout mice did not develop fever; rather, they maintained a profound hypothermia during sepsis. TNF p55/p75 receptor (TNFR) knockout mice had attenuated hypothermia, but developed a virtually identical fever to the wild-type mice. Survival was significantly enhanced in the TNFR knockout mice compared with wild-type controls. Lack of IL-6 did not affect lethality. The authors conclude that IL-6 is a key mediator of fever, whereas TNF is responsible for the initial hypothermia and lethality of sepsis.

In further studies, [4] the effect of the anti-inflammatory cytokine interleukin-10 (IL-10) was studied. IL-10 inhibits the synthesis of pro-inflammatory cytokines known to be involved in fever, including IL-1, IL-6, and TNF-alpha. In this model, mice injected with recombinant murine IL-10 (rmuIL-10) were resistant to fever induced by a low dose of endotoxin (lipopolysaccharide LPS) (100 micrograms/kg, i.p.) and to the hypothermic and febrile effects of a high dose of LPS (2.5 mg/kg, i.p.). Injection of rmuIL-10 alone had no effect on body temperature. IL-10 knockout mice showed an exacerbated and prolonged fever in response to a low dose of LPS (50 micrograms/kg, i.p.) compared to their wild-type counterparts. These data support the hypothesis that IL-10 acts as an endogenous antipyretic during LPS-induced fever in mice and has a protective role in the lethal effects of LPS injection.

Antipyretics and fever

Antipyretics have been used since antiquity to lower the temperature in febrile patients. However, it is not known whether the benefits of such treatment outweigh the risks that may be involved by lowering the fever of a septic patient. It is not known if the core temperature ever reaches levels that are intrinsically noxious in an infected patient without attempts to lower the body temperature. There

have been very few studies in humans looking at the use of antipyretic agents in sepsis.

There have been at least two studies which have examined the use of antipyretics in patients with viral infections. Graham NM and co-workers conducted a double-blind, placebo-controlled trial to study the effects of over-the-counter analgesic/antipyretic medications on virus shedding, immune response, and clinical status in the common cold [5]. Sixty healthy volunteers were challenged intranasally with rhinovirus type 2 and randomized to one of four treatment arms: aspirin, acetaminophen, ibuprofen, or placebo. Fifty-six volunteers were successfully infected and shed virus on at least 4 days after challenge. Virus shedding, antibody levels, clinical symptoms and signs, and blood leukocyte levels were carefully monitored. Use of aspirin and acetaminophen was associated with suppression of serum neutralizing antibody response and increased nasal symptoms and signs. There was a concomitant rise in circulating monocytes suggesting that the suppression of antibody response may be mediated through drug effects on monocytes and/or mononuclear phagocytes. There were no significant differences in viral shedding among the four groups, but a trend toward longer duration of virus shedding was observed in the aspirin and acetaminophen groups.

Another study looked to see whether acetaminophen affected the duration or severity of childhood varicella [6]. Again this was a randomized, double-blind, placebo-controlled trial and 72 children between 1 and 12 years of age entered the study. Acetaminophen, 10 mg/kg/dose, was given at 8am, 12pm, 4pm and 8pm for 4 days. There was less time to total scabbing 5.6 days in the placebo group compared with 6.7 days in the acetaminophen group, and symptoms were also less in the placebo group (symptom score 2.9 versus 2.2). The authors conclude that acetaminophen did not alleviate symptoms in children with varicella and may actually prolong the illness.

There have also been a few studies in intensive care patients looking at temperature as a physiological response to infection. In one the clinical and physiologic characteristics of febrile septic patients were compared with hypothermic septic patients [7]. In addition, plasma concentrations of TNF-alpha and IL-6 were compared be-

tween hypothermic septic patients and febrile patients. Half of the patients were given ibuprofen treatment (10 mg/kg (maximum 800 mg) administered intravenously over 30 to 60mins every 6hrs for eight doses in a double blind fashion). 455 patients with severe sepsis were studied. Forty-four (10%) of the patients were hypothermic and 409 (90%) were febrile. The mortality rate was significantly higher in the hypothermic patients, 70% versus 35% for febrile patients. At study entry serum concentrations of TNF-alpha and IL-6 were significantly elevated in hypothermic patients compared with febrile patients. In hypothermic patients treated with ibuprofen, there was a trend toward an increased number of days free of major organ system failures and a significant reduction in the 30-day mortality rate from 90% (18/20 placebo-treated patients) to 54% (13/24 ibuprofen-treated patients). The authors conclude that hypothermic sepsis has an incidence of approximately 10% and an untreated mortality twice that of severe sepsis presenting with fever. When compared with febrile patients, the hypothermic group had an amplified response with respect to cytokines TNF-alpha and IL-6. Treatment with ibuprofen decreased mortality but only in this select group of septic patients. The changes in TNF-alpha fully support the animal data presented above.

Conclusions

Temperature change is a conserved physiological response to infection. However, the presence of pyrexia does not appear to influence outcome from infection. Hypothermia in septic patients is associated with a significantly higher mortality. Hypothermia appears to be associated with higher TNF-alpha concentrations in septic patients. The routine use of antipyretic agents remains controversial and studies with patients with viral infections suggest that their use may be associated with an anti-inflammatory effect with prolonged time to viral clearance – and surprisingly little evidence of improvement in symptoms. In one ICU study it would seem that ibuprofen when used in the sub-group of patients with hypothermia and sepsis is associated with an improvement in outcome.

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