# Fever: beneficial and detrimental effects of antipyretics

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Although various forms of therapy have been used, since antiquity, to lower the temperature of febrile patients, it is still not known whether the benefits of antipyretic therapy outweigh its risks. Justifications for the use of antipyretic drugs, and the evidence pertaining to these rationales, are examined. Antipyretic therapy in sepsis, and adverse effects of antipyretic medications, are also reviewed. Curr Opin Infect Dis 15:241–245.


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**Current Opinion in Infectious Diseases** 2002, 15:241–245

**Abbreviations**

| | |
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| **COX-2** | cyclooxygenase-2 |
| **NSAID** | non-steroidal anti-inflammatory drug |


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## Introduction

Humans have probably always treated fever. Prior to his death in 323 BC, Alexander the Great suffered from a febrile illness which his physicians treated with cool baths [1]. Plant products such as willow leaves, which contain salicylic acid, were used by the ancient Assyrians, Romans, and Chinese to alleviate pain and fever [1]. The Native Americans did likewise [1]. Following the advent of aspirin in 1899, numerous other antipyretics have been developed and used widely to suppress fever. Despite the popularity of this therapy among both healthcare workers and the general public, it is still not known whether the benefits of antipyretic therapy outweigh its risks. Consequently, rational guidelines for suppressing fever have been slow in coming.

Those who employ antipyretic therapy assume that fever is, at least in part, noxious, and that suppression of fever will eliminate or reduce the noxious effects [2]. Neither assumption has been validated experimentally.

## Rationales for antipyretic therapy

Reasons cited for the usage of antipyretic medication include relief of discomfort, reduction of morbidity and mortality, prevention of febrile seizures, reduction of cognitive impairment, and improving outcome in patients with stroke or brain injury.

### Relief of discomfort

A common justification for suppressing fever is the relief of discomfort. In fact, there have not been any randomized clinical trials designed to determine the efficacy of antipyretic medications in improving patient comfort. Several studies investigating external cooling measures, however, have secondarily addressed patient comfort. They showed that although sponge baths lowered body temperature at a faster rate than antipyretic drugs, patient discomfort increased from the baseline when external cooling was used to treat fever [3–6]. Patients in the medication groups of these studies were not assessed for changes in comfort levels. The fact that most antipyretic medications are also analgesic agents complicates the question of whether the suppression of fever, *per se*, or the analgesic effects of the medications improve patient comfort. However, in a recent randomized trial [7•] comparing external cooling with the absence of antipyretic treatment in febrile patients, comfort levels were not significantly different between the groups. This study suggests that lowering of fever alone does not enhance the comfort of febrile patients.

### Reduction in mortality

Antipyretics are also given because of the common perception among physicians, nurses and patients that fever is intrinsically harmful [8]. This perception has not been validated scientifically. In fact, considerable data suggest that fever has a beneficial effect on the outcome of many, although not all, infections [9]. For example, a survey of patients with community-acquired pneumonia showed that those with temperatures above 37.8°C and a leukocyte count above 10 000 cells/mm$^3$ had a 4% mortality rate, which compares with a mortality rate of 29% for patients with neither fever nor leukocytosis [10]. Improved survival has also been shown in febrile patients with *Escherichia coli* bacteremia [11] and *Pseudomonas aeruginosa* sepsis [12] relative to afebrile patients. By comparison, hypothermia has been shown to be a significant predictor of mortality in a large prospective study of trauma patients [13•]. Numerous animal studies have shown an inverse correlation between mortality and temperature during serious infection. In one such experiment, the survival rate increased from 0% to 50% in mice with *Klebsiella pneumoniae* peritonitis when their temperatures were raised artificially from normal to febrile levels [14]. Although none of these studies proves that fever lowers mortality, they at least suggest that fever does not worsen survival and, in fact, might enhance survival in serious infections.

### Reduction of morbidity

The prevention of fever-related morbidity has also been proposed as a justification for antipyretic therapy. The available clinical data, however, offer scant support for such reasoning. For instance, children with chickenpox who are treated with acetaminophen have been shown to have a longer time to total crusting of lesions than do placebo-treated control subjects [15]. In addition, adults with rhinovirus infections exhibit a longer duration of viral shedding and increased nasal signs and symptoms when treated with antipyretic medications [16]. In a study of children with bacterial meningitis, Bonsu and Harper [17] compared those treated empirically with antibiotics (for a non-cerebrospinal infection) within 1 week of diagnosis with those not receiving empirical antibiotics. They found that in *Streptococcus pneumoniae* meningitis, children who had received antibiotics prior to their diagnosis of meningitis had a longer duration of fever but fewer meningitis-related complications than the children who had not received empirical antibiotics. All of the children were treated with appropriate antibiotics after a diagnosis of meningitis was made. Of course, it is unclear whether the prior administration of antibiotics, the longer duration of fever, or both resulted in the lower complication rate. However, this investigation, like the others mentioned, provides indirect evidence that fever itself is not a cause of infection-related complications.

### Prevention of febrile seizures

Fever, regardless of the etiology, has long been known to be associated with seizures in children. Unfortunately, antipyretic therapy has never been shown to prevent febrile seizures [18]. The most recent randomized trial of antipyretic therapy in the prevention of febrile seizures compared ibuprofen with a placebo. It found no difference in the recurrence rates for such seizures in the two treatment groups [19]. Studies of acetaminophen have likewise failed to demonstrate a reduction in the recurrence rate of febrile seizures by prophylactic antipyretic therapy [20,21].

### Reduction of cognitive impairment

Antipyretic therapy might be beneficial in reducing the mental dysfunction sometimes observed in patients with fever. An early study of young volunteers infected with sandfly fever virus showed that aspirin with propoxyphene lessened fever-associated cognitive impairment [22]. More recently, Reichenberg and colleagues [23•] demonstrated that there was increased anxiety and depression, as well as worsened memory, in volunteers with *Salmonella abortus equi*-induced temperature elevation relative to controls. Unfortunately, these authors did not examine the capacity of antipyretic therapy for preventing such fever-associated cognitive and emotional disturbances.

### Improving outcome for patients with stroke or brain injuries

Lowering of the temperature of patients with stroke or brain injuries has been advocated as a means of improving cognitive and behavioral outcomes. The induction of hypothermia in humans, by means of external cooling, has been shown in several small studies to be effective in this regard [24,25]. However, a recent large randomized trial in stroke patients demonstrated no differences in the poor outcomes (defined as severe disability, vegetative state, or death) between those treated with induced hypothermia and controls [26••].

A recent meta-analysis demonstrated an association between elevated body temperature and poor outcome in stroke patients [27]. Unfortunately, the analysis did not distinguish between fever and hyperthermia. Hyperthermia is an unregulated rise in core temperature that is not mediated by pyrogenic cytokines and which is usually unaffected by standard antipyretic medications [2]. Fever, by comparison, is a cytokine-mediated rise in core temperature accompanied by a host of associated immunological and physiological reactions [28]. The relationship between stroke and infection-induced fever has been examined in animals. In one experiment in which rats were injected with *E. coli* lipopolysaccharide prior to the induction of global brain hypoxia, fever was associated with increased neural damage [29]. Retro-

spective data also indicate that stroke patients with preceding bacterial infections have poorer neurological and behavioral outcomes than do uninfected counterparts [30,31]. Such studies suggest that fever, like hyperthermia, adversely affects the course of acute stroke, at least in some patients. Unfortunately, studies of the effects of antipyretic therapy on outcomes in such patients are presently lacking. Thus, the role of antipyretic therapy in patients with strokes and brain injuries has yet to be defined.

## Antipyretic therapy in sepsis

Sepsis is a condition characterized by multiple organ dysfunction. Many people believe that fever potentiates tissue injury during sepsis and should, therefore, be suppressed. In fact, encouraging results obtained in animal models have raised hopes that antipyretic therapy can be used to improve outcomes in patients with sepsis [32]. However, to date, only one randomized clinical trial has studied this question in humans. It found that ibuprofen did not improve survival in patients with sepsis, even though the drug did have a salutary effect on core temperature and metabolic rate [33]. Recent data demonstrating fever-induced expression of several heat-shock proteins protective against oxidative injury raise the concern that, by suppressing the expression of such proteins, antipyretic therapy might actually potentiate the adverse effects of sepsis in some situations [34,35].

Fever affects metabolism in several ways. During the ascending phase of fever, activation of the sympathetic nervous system causes peripheral vasoconstriction and an associated increase in mean arterial blood pressure [36]. Oxygen consumption increases, as does carbon dioxide production [37]. Reduction of the fever by using external cooling attenuates these effects, but only if shivering is prevented by inducing paralysis [38]. However, external cooling is uncomfortable. More importantly, it has the potential to cause vasospasm of diseased coronary arteries by activating a cold pressor response [39], and is, therefore, best avoided in critically ill patients.

Although fever (i.e. elevation of core temperature above the normal range), *per se*, has yet to be shown to be deleterious in patients with sepsis, or for that matter in any infection, considerable data suggest that the pyrogenic cytokines mediating the febrile response are also the mediators of the septic process. The febrile response, of which fever is only one component, is a complex response involving activation of immunological, endocrinological and other physiological systems. The response is generally beneficial. Polymorphonuclear cell, macrophage, and T lymphocyte function are all enhanced during fever in at least some experimental models [40–42]. Presumably, such effects promote clearance of pathogenic microorganisms, and hence improve outcome during infection. Antipyretics, by lowering the core temperature, might mitigate, if not abrogate, the beneficial effects. However, pyrogenic cytokines – the proteins mediating the stimulatory effect of fever on the immune system – have the potential to be harmful as well as beneficial during the course of infection. Their activity is influenced by temperature in complex ways that depend upon the magnitude and timing of the temperature variation and the specific cytokine examined [32]. Numerous animal studies have shown a protective effect of pyrogenic cytokines against a variety of viral, bacterial, fungal, and parasitic infections (reviewed in [2]). However, pyrogenic cytokines have also exhibited detrimental effects on outcomes in certain experimental infections [43]. Recent reports suggest that, under certain conditions, they function as bacterial growth factors [44•] and contribute to the anxiety, depression, and diminished memory of patients with infectious illnesses [23•]. Most importantly, they appear to play a central role in the physiological abnormalities of sepsis [45,46]. A recent study demonstrated that an inhibitor of pyrogenic cytokines, chimeric CD14 antibody, given to study subjects 2 h prior to the administration of lipopolysaccharide attenuated lipopolysaccharide-induced fever, symptoms, and leukocyte activation and degranulation in the process of suppressing release of tumor necrosis factor-$\alpha$ and interleukins 6 and 10 [47•]. Additional studies are underway to test the safety and efficacy of the CD14 antibody in septic patients [47•]. Although inhibition of pyrogenic cytokines might alleviate the detrimental effects noted above, such interventions have yet to be shown to be effective in reducing mortality in patients with sepsis [33].

## Adverse effects of antipyretic medications

Side-effects of antipyretic medications should be considered whenever such therapy is contemplated. Gastrointestinal toxicity is a common side-effect of non-steroidal antipyretic drug therapy. Such toxic effects can be divided into three categories: mucosal lesions, gastrointestinal discomfort (e.g. dyspepsia), and severe gastrointestinal complications (e.g. perforated ulcer, gastrointestinal bleeding) [48]. Many patients treated with non-steroidal anti-inflammatory drugs (NSAIDs) develop endoscopic lesions, which, fortunately, remain largely asymptomatic [49]. Approximately 10–20% of patients using NSAIDs experience dyspepsia [48]. Interestingly, most patients developing severe gastrointestinal complications report no prior gastrointestinal symptoms [50]. Risk factors for serious NSAID-induced toxicity include high dosages, advanced age, history of peptic ulcer disease or gastrointestinal bleeding, concomitant use of steroids or anticoagulants, and short duration of therapy [51]. Selective cyclooxygenase-2 (COX-2) inhibitors appear to cause fewer gastrointestinal

bleeding episodes than do non-selective NSAIDs [52•]. However, COX-2 inhibitors have been shown to be deficient in the cardioprotective effect shared by aspirin and nonselective NSAIDs [53•]. Hepatotoxicity is the most important form of acetaminophen toxicity. COX-2-induced cholestatic hepatitis is less well appreciated and considerably less common [54]. A single episode of ischemic colitis has recently been reported as a complication of therapy with a COX-2 inhibitor [55].

Renal toxicity is the other important adverse effect of antipyretic drug therapy. It manifests in four different ways: fluid and electrolyte disturbances, acute renal failure, acute interstitial nephritis, and analgesic drug-associated nephropathy [48]. A recent, large, cross-sectional study by Sturmer *et al.* [56•] showed that patients taking recommended doses of NSAIDs had significantly reduced creatinine clearance compared to non-users, especially those using NSAIDs with long half-lives and those receiving concomitant diuretics or angiotensin-converting enzyme inhibitors. The adverse renal effects of COX-2 inhibitors are largely unknown. However, a recent case report of acute tubulointerstitial nephritis believed to be due to rofecoxib suggests that such drugs are potentially nephrotoxic as well [57]. Antipyretic medications can also cause abnormalities of the skin and of the respiratory, blood, and central nervous systems (reviewed in [48]).

## Conclusion

Antipyretic therapy might be justified if the metabolic costs of fever were exceeded by its physiological benefits, if the treatment reduced the metabolic costs or other adverse effects of fever without adversely affecting the course of the febrile illness, or if the side-effects of the antipyretic drug regimen were appreciably fewer than its beneficial effects. Unfortunately, insufficient experimental data are available to validate any of these rationales.

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