Benefits and Risks of Antipyretic Therapy[a]

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ABSTRACT: Physicians have used various forms of antipyretic therapy since antiquity to lower the temperature of febrile patients. Nevertheless, it has yet to be determined whether the benefits of antipyretic therapy outweigh its risks. It is not known, for example, if core temperatures encountered during the febrile state ever reach levels that are intrinsically noxious (and therefore merit antipyretic intervention) or when, if ever, fever's metabolic costs exceed its physiologic benefits, or if the benefits of symptomatic relief afforded by antipyretic drugs consistently exceed their toxicologic cost. Whereas preliminary experimental and clinical observations suggest that antipyretic therapy has the potential to increase the duration and/or severity of certain infections, such data are as yet too fragmentary to draw firm conclusions regarding their validity. Finally, although clinicians have long suspected that bacteremia and other severe infections might induce fevers that are less responsive to antipyretic therapy than are those associated with self-limited infections, this concept has not held up under scientific scrutiny. Thus, despite over 2.5 millennia of clinical experience, important questions regarding the risks and benefits of antipyretic therapy remain to be answered.

By the time he reached the age of 32 in 323 BC, Alexander the Great had amassed a larger empire than had any commander in history, with the possible exception of Genghis Khan. His conquests ended in Babylon with the onset of a mysterious, acute febrile illness that, over the course of 8 days, took Alexander's life.[1] It is worthy of note, in view of the subject of the current review, that the Babylonian physicians caring for Alexander treated his illness with physical methods of antipyresis in the form of repeated cool baths. Thus, antipyretic therapy has been used by clinicians since the earliest days of the profession.

Prior to 1899, antipyretic therapy consisted primarily of physical methods of cooling. This changed in 1899 when aspirin appeared as the world's first commercially available antipyretic drug. Since then, numerous other drugs capable of suppressing fever have been introduced into clinical medicine. Their widespread application by primary care physicians,[2] emergency room nurses,[3] pharmacists,[4] and parents and other caregivers[5,6] is consistent with a general belief that fever is inherently noxious. This belief is likewise reflected in surveys reporting that approximately 40% of parents and other caregivers regard temperature elevations encountered during fever as harmful[5,6] and that 12% of physicians believe that fever can cause brain damage.[2] Perhaps most indicative of the medical profession's inherent antipathy towards fever is that an estimated 70% of nurses and 30% of physicians routinely use antipyretic drugs to suppress fever.[2,3]

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RATIONALE

Although clinicians have long had at their disposal effective means of lowering core temperature in febrile patients, the actual benefit of such reductions in temperature is still uncertain. Moreover, it has yet to be shown in man that increases in core temperature encountered during fever are harmful *per se*. Certainly, during heat stroke and other forms of hyperthermia, core temperature can, and frequently does, rise to levels that are inherently harmful.[7] However, such levels are almost never reached during fever's regulated rise in temperature, which rarely exceeds 41°C in man.[8] Nevertheless, whereas healthy volunteers have been reported to withstand core temperatures of 42°C for as long as 4 hours without apparent ill effects,[9] the possibility remains that in certain patients, even the relatively modest increases in core temperature encountered during fever are deleterious and should therefore be suppressed.

One such category of patients includes children, primarily those between the ages of 3 months and 5 years. In such children, seizures have been reported to occur during episodes of fever at a frequency of as high as 14% in selected populations.[10] Although most children with febrile seizures have temperatures of ≥ 39.0°C at the time of their seizure,[11] many tolerate even higher fevers at later dates without convulsing.[12] Unfortunately, as will be discussed, antipyretic therapy has not been shown to protect against recurrences of febrile seizures in the few controlled trials conducted thus far.[13]

It has also been suggested that patients with underlying cardiovascular or pulmonary disorders might be especially susceptible to the adverse effects of fever, because of metabolic demands imposed by the elevated temperature.[14] Such demands are particularly high during the chill phase (that is, shivering) as evidenced by increases in sympathetic tone,[15] oxygen consumption, respiratory minute volume, and respiratory quotient.[16] As a result of the associated increase in metabolic demand, the chill phase of fever may be capable of aggravating cardiac or pulmonary disorders. Although this possibility has been offered as justification for antipyretic therapy in patients with these underlying disorders, the risk/benefit ratio of such therapy has yet to be determined.

Antipyretic therapy might also be justified, at least in theory, if fever's metabolic cost exceeded its physiologic benefit, if the treatment provided symptomatic relief without adversely affecting the course of the febrile illness, or if the toxicologic costs (side effects) of the antipyretic regimen were appreciably lower than its beneficial effects. Unfortunately, although clinicians have long argued the validity of each of these propositions as justification for antipyretic therapy, few scientific data exist to support any of these arguments.

ANTIPYRETIC DRUGS

Antipyretic drugs can be grouped into three general categories based on their mechanisms of action. These include corticosteroids, aspirin and other nonsteroidal antiinflammatory agents (NSAIAs), and acetaminophen. Each exerts its effects at different points in the febrile response pathway.

Although not generally used as antipyretics, corticosteroids are currently believed to prevent fever by blocking transcription of interleukin-1 (IL-1) and cyclooxygenase through a process involving inhibition of phospholipase A_2 by lipocortin 1. Aspirin and the other NSAIAs are active inhibitors of both central and peripheral cyclooxygenase. Although acetaminophen inhibits the production of prostaglandin (PG) in the brain,[17] it does not inhibit such production peripherally and it is not active *in vitro* against most preparations of cyclooxygenase.[18] Acetaminophen's lack of activity against peripheral cyclooxygenase most likely accounts for its negligible antiinflammatory property.

PHYSICAL METHODS OF ANTIPYRESIS

A variety of techniques are currently used to cool patients by physical means. These include sponging with various solutions (e.g., tepid water or alcohol), application of ice packs or cooling blankets, and exposure to circulating fans (most often in conjunction with sponging). In contrast to antipyretic drugs, external cooling lowers the temperature of febrile patients by overwhelming effector mechanisms that have been evoked by an elevated thermoregulatory set-point, rather than by lowering that set-point. Therefore, unless concomitant antipyretic agents have lowered the set-point or shivering is inhibited by other pharmacologic means, external cooling is vigorously opposed in the febrile patient by thermoregulatory mechanisms endeavoring to maintain the elevated body temperature.

Physical methods of antipyresis promote heat loss by conduction, convection, and evaporation. Evaporative methods have traditionally been touted as the most effective physical means of promoting heat loss in febrile patients, because such methods are deemed to be least likely to induce shivering.[19] However, carefully designed comparative trials have not yet established any one physical method of antipyresis as superior.

Direct comparisons of pharmacologic and physical methods of antipyresis are likewise all but nonexistent. In the only extant controlled study, Wenzel and Werner[20] reported that salicilates reduced the second phase of endotoxin-induced fever in rabbits, whereas abdominal cooling increased heat production and did not lower core temperature unless animals were simultaneously exposed to environmental hyperthermia. Neither antipyretic modality abolished the initial febrile response.

The few available clinical studies of the efficacy of physical methods of antipyresis differ in their conclusions. Interpretation of the results of these studies is difficult, because pharmacologic agents are almost invariably administered concomitantly with external cooling. Steele *et al.*[21] found acetaminophen and sponging to be equally effective in lowering fever in children admitted to a pediatric hospital because of fever. However, when combined, the two modalities produced more rapid cooling than did either alone. By contrast, Newman[22] found that tepid-water sponging in combination with acetaminophen was no more effective than acetaminophen alone in lowering the temperature of febrile children. O'Donnell *et al.*[19] concluded that while hypothermia blanket therapy adds little to the action of pharmacologic agents in lowering temperature in adults, it induces wider temperature fluctuations and more episodes of rebound hypothermia.

DIAGNOSTIC CONSIDERATIONS

Numerous investigators have observed a direct correlation between the height of fever and the rate of serious bacterial infections in children, with the maximal risk of such infections occurring with temperatures in excess of 40°C.[23-26] It has also been suggested that the response of a fever to antipyretic therapy might have diagnostic implications, in that a drop in temperature and/or improvement in the appearance of a febrile child indicates that the fever is not due to a serious illness.[27] This conclusion, however, is not supported by numerous investigations comparing the temperature response of bacteremic and nonbacteremic infections to antipyretic therapy in children.[28-33]

Of six such investigations reported in recent years, only one[33] found a difference in the antipyretic responsiveness of bacteremic and nonbacteremic fever. In that study, bacteremic fevers responded significantly less well to acetaminophen than did nonbacteremic fevers. However, unlike the five other prospective investigations published,

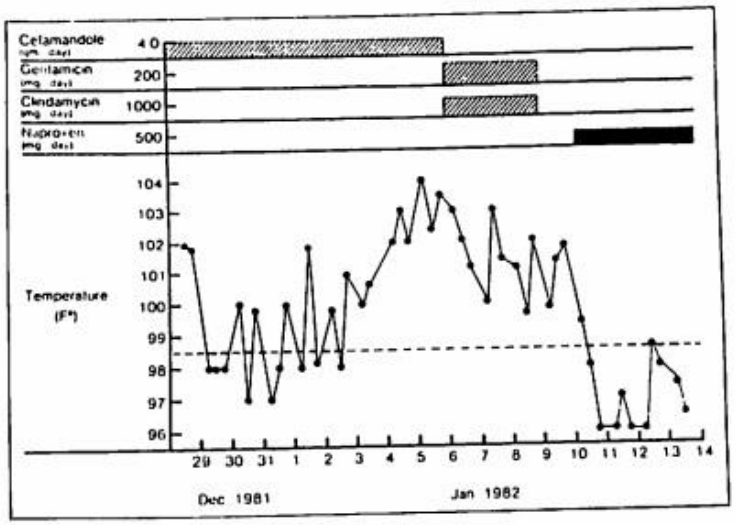

FIGURE 1. Characteristic response of neoplastic fever to a nonsteroidal antiinflammatory agent. Patient had a protracted febrile course for several weeks without significant lysis of fever in response to antibiotics. However, fever disappeared within 12 hours of initiation of therapy with naproxen. (From ref. 34, with permission.)

which found no such difference, this investigation was a retrospective study. Thus, with one retrospective exception, published investigations suggest that in children, fevers due to serious infections (i.e., bacteremic infections) are no less responsive to antipyretic therapy than are less serious infections.

Several studies have suggested that an antipyretic response to nonsteroidal antiinflammatory agents can distinguish fevers of infectious origin from those due to cancer. The classic response of a patient with neoplastic fever to an NSAIA is illustrated in FIGURE 1. Naproxen was the first such agent to be studied in this regard.[34] Subsequent randomized comparisons have shown naproxen, indomethacin, and diclofenac to be equally effective in inhibiting cancer-induced fever.[35] Why nonsteroidal antiinflamatory drugs might be more effective in reducing fever due to cancer than that due to infection is uncertain. Dinarello and Bunn[36] have hypothesized that in contrast to their effect on fevers resulting from infections, nonsteroidal antiinflammatory drugs suppress fevers due to malignant neoplasms by inhibiting cytokine production rather than by altering the responsiveness of the anterior hypothalamus to the pyrogenic effect of such cytokines.

BENEFITS VERSUS RISKS

Two critical assumptions are made when prescribing antipyretic therapy. One is that fever is, at least in part, noxious, and the other is that suppressing fever will reduce, if not eliminate, fever's noxious effects. Neither assumption has been validated experimentally. In fact, considerable evidence indicates that fever is an important defense

mechanism that contributes to the host's ability to resist infection.[37] However, even if fever (or its mediators) does adversely affect the course of disease, as in the case of bacterial sepsis,[38] it does not necessarily follow that inhibiting fever with antipyretic therapy will eliminate this effect, especially if such therapy has intrinsic toxicity of its own.

One reason commonly given to justify suppressing fever is that the metabolic cost of fever exceeds its clinical benefit. In fact, the metabolic cost of fever is substantial, especially during the chill phase of the response with its shivering-induced increase in metabolic rate, nonepinephrine-mediated peripheral vasoconstriction, and increased arterial blood pressure.[15] Because of the potential adverse consequences of these metabolic effects on cardiovascular and pulmonary function, fever has been attacked with particular vigor in patients with underlying cardiovascular and pulmonary diseases.[39] Although antipyretic therapy has theoretic merit in this regard (if it does not induce shivering[40]), even in patients with underlying cardiovascular and pulmonary diseases, neither the detrimental effects of fever nor the salutary effects of antipyretic therapy has been documented experimentally.

External cooling, which is widely used in such patients to suppress fevers unresponsive to antipyretic drugs, decreases oxygen consumption by as much as 20% in febrile critically ill patients if shivering is prevented by therapeutic paralysis[40] (FIG. 2). If shivering is not inhibited, external cooling causes a rise, rather than a fall, in oxygen consumption.[40] Perhaps more important to febrile patients with underlying cardiovascular disease, (as shown in the middle panel of FIGURE 3), external cooling can cause vasospasm of diseased coronary arteries by inducing a cold pressor response.[41,42] For all these reasons, it has been suggested that a more rational strategy for treating fevers unresponsive to antipyretic drugs is to *warm* rather than to *cool* the skin surface, thereby reducing the vasoconstriction and shivering thresholds dictated by the elevated

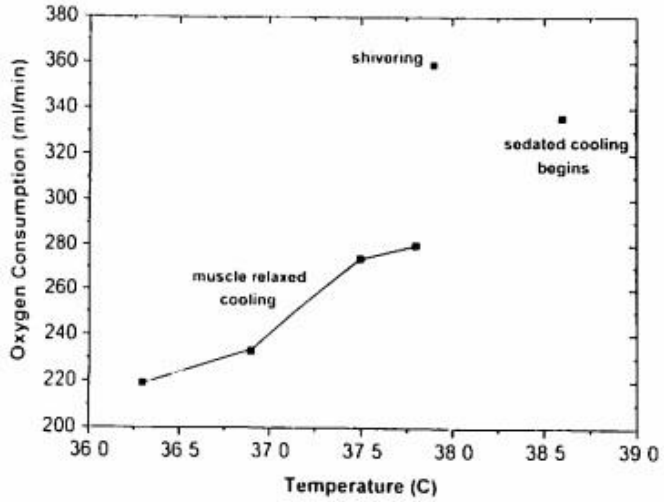

FIGURE 2. Effect of external cooling on oxygen consumption (Vo_2) in a febrile critically ill patient. With cooling from 38.6 to 37.9°C, the patient began to shiver and exhibited an increase in Vo_2 from 336 to 359 ml/min. Once shivering had been inhibited by therapeutic paralysis, subsequent cooling was associated with a progressive fall in Vo_2. (From ref. 40, with permission.)

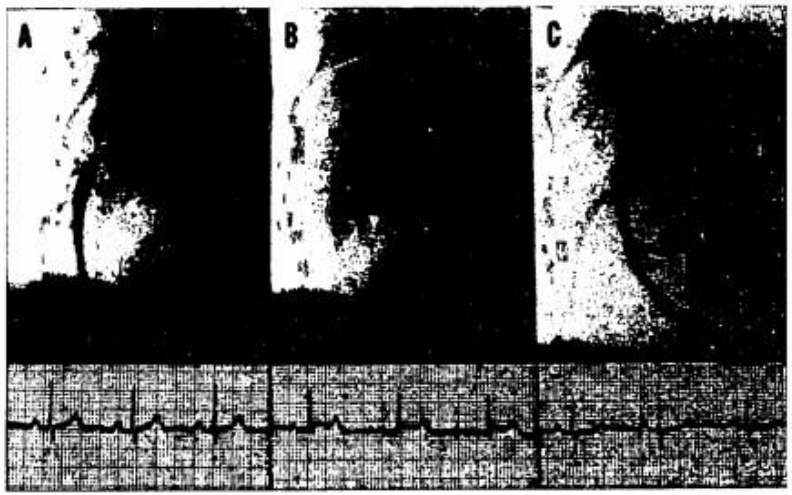

FIGURE 3. Coronary arteriogram and electrocardiographic lead III exhibiting a cold pressor response in the right coronary artery of a patient with coronary atherosclerosis. **(A)** Baseline arteriogram shows 90% stenosis of the middle segment, with good distal runoff. **(B)** During cold pressor stimulation, the artery is almost totally stenosed at the site of the lesion and only faint flow can be seen beyond the stenosis. Mild ST-segment elevation has occurred, but the patient did not experience chest pain. **(C)** After nitroglycerin, the lesion is less stenosed and distal runoff is good. The ST segment has returned to normal. (From ref. 41, with permission.)

hypothalamic thermal set-point and, in turn, effecting a decrease in core temperature.[43]

Antipyretic therapy is also commonly administered to enhance patient comfort.[39] General experience with antipyretic drugs, which are for the most part also analgesic agents, seems to support this contention. However, carefully controlled efficacy studies have not yet established the validity of this contention. Moreover, the relative cost of such symptomatic relief, in terms of drug toxicity and adverse effects of antipyretic agents on the course of the illness responsible for the fever, has never been determined. The importance of such information is underscored by reports that acetaminophen prolongs the time to crusting of lesions in children with chicken pox[44] and that both acetaminophen and aspirin increase viral shedding and nasal signs and symptoms while suppressing the serum neutralizing antibody response in adults with rhinovirus infections.[45,46]

Antipyretic therapy is also occasionally given to prevent febrile seizures in children and to prevent or to reverse fever-induced mental dysfunction in frail elderly patients. As illustrated in FIGURE 4, Beisel *et al.*[47] showed that aspirin (in combination with propoxyphene) ameliorates fever-induced decrements in mental work performance in young volunteers infected with sandfly fever virus, even in the presence of only partial relief of either the fever or the other symptoms of the illness. In view of these observations, antipyretic therapy might be expected to have a beneficial effect on fever-induced mental dysfunction in frail elderly patients. However, studies designed to test this hypothesis have not yet been conducted.

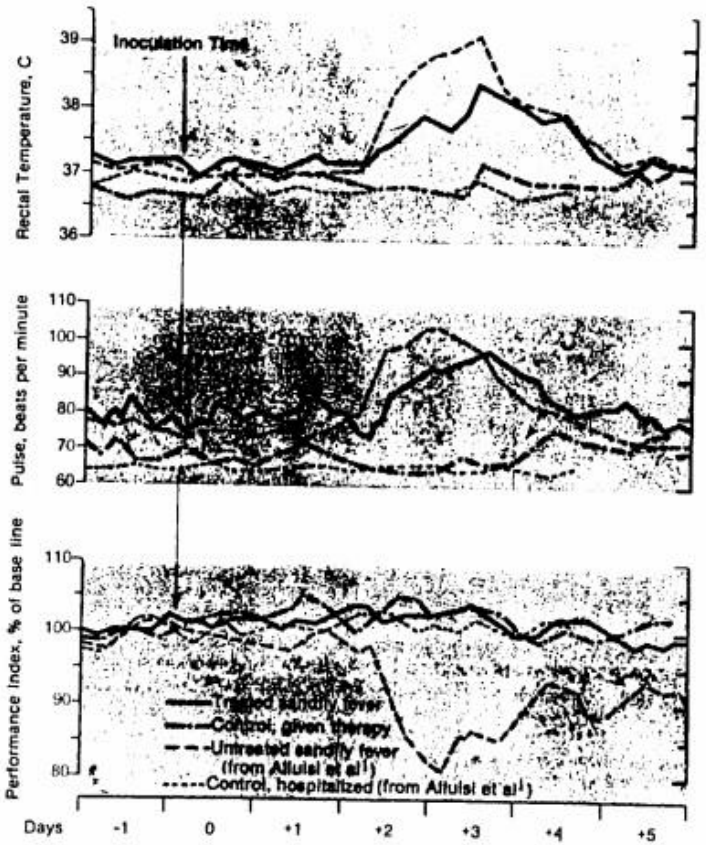

FIGURE 4. Effect of therapy with aspirin and propoxyphene on temperature, pulse rate, and mental work performance during experimentally induced sandfly fever. (From ref. 47, with permission.)

Unfortunately, antipyretic therapy does not appear to be effective in preventing febrile seizures.[13] Camfield *et al.*[48] conducted a randomized double-blind study comparing febrile seizure recurrences in children given daily oral phenobarbital and antipyretics during fever with those given antipyretics and daily oral placebo. In children treated with both phenobarbital and antipyretics, the febrile seizure recurrence rate was 5%, whereas in those given placebo with antipyretics, the rate was 25%. More recently, acetaminophen has been given to children with fever as prophylaxis against febrile seizure recurrences. Whether given in moderate dosage[49] or in relatively high doses,[50] acetaminophen failed to reduce the rate of febrile seizure recurrence.

Recently, there has been considerable interest in the use of certain antipyretic drugs to modulate the activity of pyrogenic cytokines during bacterial sepsis.[51] In animal models of sepsis, antipyretic drugs that inhibit cyclooxygenase confer protection when given soon after bacterial challenge, presumably by blunting the adverse effects of TNF-α and IL-1. In a recent large clinical trial, Bernard *et al.*[52] reported that 48 hours of intravenous therapy with the cyclooxygenase inhibitor ibuprofen lowered temperature, heart rate, oxygen consumption, and lactic acid blood levels, but it did not decrease the incidence of organ failure or mortality at 30 days. Thus, despite promising results in experimental animals, antipyretic agents have not yet been shown to be of value clinically in the treatment of bacterial sepsis.

INDICATIONS

Although clinicians have resorted to various forms of antipyretic therapy since time immemorial, there is a dearth of scientific data on the actual benefits and relative risks of such treatments. Nevertheless, several tentative conclusions regarding antipyretic therapy seem justified in light of the limited data currently available. It is clear, for instance, that short courses of approved doses of standard antipyretic drugs carry a low risk of toxicity. Most of these drugs have analgesic as well as antipyretic properties. Therefore, if not otherwise contraindicated (e.g., aspirin in young children because of the risk of Reye's syndrome), such drugs can be prescribed to provide symptomatic relief in febrile patients in general, to reduce the metabolic demands of fever in patients with underlying cardiovascular and pulmonary disorders, and to prevent or alleviate fever-induced mental dysfunction in the elderly. To minimize antipyretic-induced fluctuations in temperature (as well as the risk of recurrent shivering with its associated increased metabolic demands) antipyretic agents should be administered continuously to febrile patients, rather than as needed for temperatures above some arbitrary level. Whenever prescribing such medication, it should also be recognized that each carries its own risk of toxicity and might prolong the course of the illness responsible for the fever while reducing the intensity of its symptoms.

In view of the capacity of external cooling measures to induce a cold pressor response, it is questionable whether this form of antipyretic therapy should ever be administered to febrile patients (much less to ICU patients for whom it is most commonly prescribed). If external cooling is used to treat fever, care must be taken to prevent shivering, because of its associated increased oxygen consumption. Unfortunately, even if shivering is prevented, there is no guarantee that a cold pressor response will be averted.

The decision to treat fever is an individual one. When making it, the risks and benefits of antipyretic therapy should be carefully weighed against the relative risks (and perhaps benefits) of undisturbed fever in the patient for whom antipyretic therapy is being contemplated.

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