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THE FEBRILE PATIENT: DIAGNOSTIC, PROGNOSTIC AND THERAPEUTIC CONSIDERATIONS

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1. ABSTRACT

Although clinicians have long pondered the diagnostic and prognostic implications and the treatment of fever, fundamental questions remain unanswered. The value of the height or pattern of a fever in predicting the etiology or course of the illness causing it is a case in point. Whether fever is ever harmful and should, therefore, be suppressed is another. These controversies and others concerning the febrile patient are the subject of this manuscript.

2. INTRODUCTION

Clinicians have long pondered the significance of fever and used whatever means available to treat it. In recent times, highly sophisticated techniques for detecting febrile illnesses and monitoring their course have been developed along with an astonishing array of treatments designed to suppress fever. This article examines current data related to the diagnostic and prognostic significance of fever and its treatment.

Humans have probably always pondered the significance of fever and felt the need to treat it with whatever means seemed to be effective (1). During his terminal illness of 323 BC, Alexander the Great developed a fever his physicians treated with cool baths as they struggled in vain to diagnose its cause. The ancient Assyrians, Egyptians, Romans and Chinese recognized the value of plant products containing salicylic acid (e.g. willow leaves) in reducing fever, as did our own Native Americans. Thus, the history of the diagnosis and treatment of fever is long, so long that one would assume that fundamental questions related to its diagnostic, prognostic and therapeutic implications would long since have been answered. This, however, is far from the case.

3. DIAGNOSTIC CONSIDERATIONS

Although techniques for measuring body temperature have progressed over time from simple palpation to the use of highly sophisticated electronic thermometers, the purpose of such measurements has remained basically unchanged - - to detect febrile illnesses and monitor their course. In the past, considerable energy has been devoted to documenting the pattern of daily temperature fluctuations exhibited by febrile patients in the hope of identifying patterns diagnostic of specific diseases. These efforts have given rise to a vast and frequently arcane terminology, including descriptors such as *remittent, intermittent, hectic, quotidian, picket fine, sustained, quartan,* and *saddleback* (2). Such terms have been used to codify fever patterns into general categories in an attempt to enhance their diagnostic utility. A few, such as the Pel-Ebstein pattern of Hodgkin's disease, the typhus inversus (i.e., reversal of the normal diurnal pattern) of disseminated tuberculosis, the pulse-temperature disassociation of typhoid fever, and the sustained fever of gram-negative bacterial pneumonia and central nervous system damage have been posited as having especially high specificity for particular diseases. Unfortunately, with the possible exception of the tertian and quartan patterns of malaria, these fever patterns are neither sensitive nor specific enough to be considered diagnostic of any disease.

This is not to say, however, that time spent scrutinizing fever patterns is necessarily unproductive or misleading. In the context of other signs and symptoms and laboratory data, distinctive patterns can suggest specific diagnoses to the alert clinician (Figure 1). Likewise, the resolution of fever after the institution of disease-specific therapy is occasionally the most compelling, if not the only, evidence of the cause of a febrile illness.

Why certain infections produce characteristic fever patterns is largely unknown. The distinctive patterns of tertian and quartan malaria develop because of synchronization of parasitic life-cycles, such that after an initial period of chaotic replication, all parasites emerge from infected erythrocytes simultaneously in a synchronized 2- or 3-day life cycle (3). Likewise, the relapsing fever pattern of borelliosis reflects recurrent cycles of replication and suppression as the parasite grows, is destroyed by newly-produced, specific antibodies, and emerges again after altering its surface antigens so that it is no longer recognized by antibodies terminating prior replication cycles (4). Why typhoid fever induces a sustained fever, occasionally accompanied by relative bradycardia, or why endocarditis, in which exogenous pyrogens (bacteria) circulate continuously in the blood, exhibits a remittent rather than a sustained fever, or why

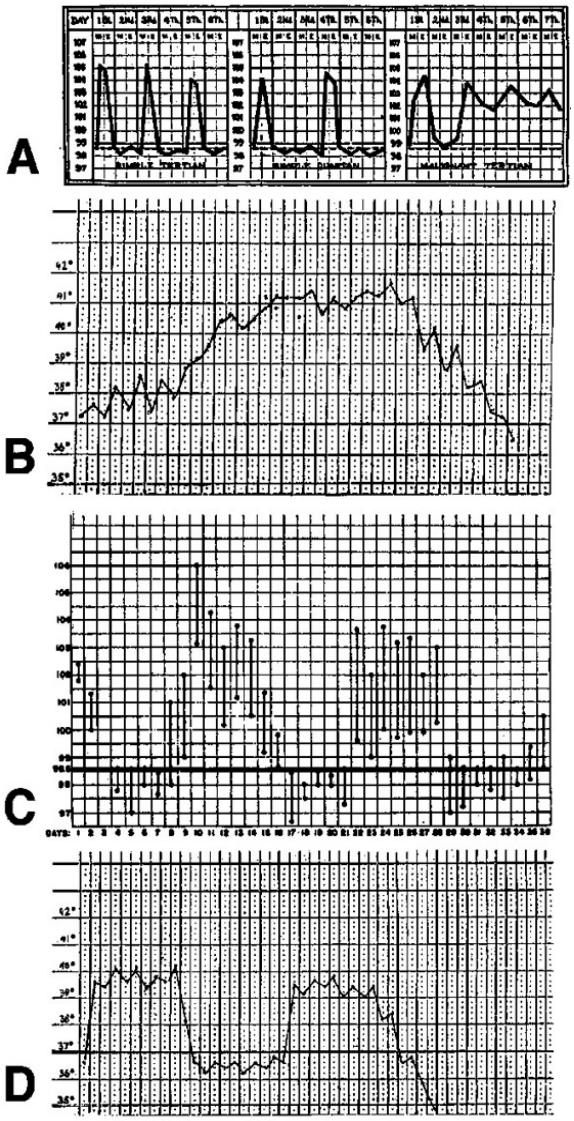

Figure 1. Distinctive fever patterns A. Malaria; B. Typhoid fever (continuous pattern); C. Hodgkin's disease (Pel-Ebstein pattern); D. Borreliosis (relapsing fever pattern) (from Woodward TE, ref. 2).

the other distinctive fever patterns mentioned above develop is not known.

Several studies have suggested that neoplastic fevers are more responsive to NSAIDs than infectious fevers, and that this difference in antipyretic responsiveness can be used to distinguish fevers of infectious origin from those due to cancer (5-7). Unfortunately, because patients with obvious infections were excluded from analysis in these studies, the results may have been biased. Naproxen was one of the first such drugs to be studied in this regard (5). Subsequent randomized comparisons have reported naproxen, indomethacin, and diclofenac to be equally effective in inhibiting cancer-induced fever (7). No satisfactory explanation has been offered to date as to why NSAIDs might be more effective in reducing fever due to cancer than that due to infection.

4. PROGNOSTIC CONSIDERATIONS

The prognosis of a fever is dictated by the disease that causes it. It has been speculated, nevertheless, that in the absence of a specific diagnosis, the height of a fever or its response to antipyretic therapy might have prognostic relevance. In pediatric populations, for example, the height of a fever correlates roughly with the likelihood of bacteremia. McCarthy has reported that in young children with febrile illnesses, the likelihood of bacteremia is 7% in children with temperatures of 40°C or less, 13% with temperatures of 40.5°C to 41°C, and 26% with temperatures of 41.1°C or greater (8, 9). Although there is a general perception that a similar relationship exists between the height of a fever and the likelihood of bacteremia in adults, this belief has not been substantiated through clinical investigation. Unfortunately, the relationship is at best a relatively loose one even in children, with numerous examples of bacteremia in which there is little or no fever and nonbacteremic conditions, such as drug-induced fever, thrombophlebitis, and recurrent pulmonary emboli, in which extremely high fevers are encountered. Thus, although the height of fever might be useful in predicting bacteremia in febrile populations, the relationship should be invoked with caution in individual patients.

It has also been suggested that the response of a fever to antipyretic therapy might be important prognostically, in that a drop in temperature and/or improvement in the general appearance of a febrile child indicate that the fever is not due to a serious illness (10). This conclusion, however, is not supported by several investigations comparing the response of children to antipyretics (primarily oral acetaminophen) during bacteremic and nonbacteremic infections (11-16) (Table 1). Of 6 such published investigations, only one (16) found a difference in the antipyretic responsiveness of bacteremic and nonbacteremic fever. In that study, bacteremic fevers responded substantially less well to acetaminophen than nonbacteremic fevers. However, unlike 5 other prospective investigations that showed no such difference, this investigation was a retrospective study. Thus, with 1 retrospective exception, published investigations suggest that in children, fevers due to serious infections (i.e., bacteremias) are as responsive to antipyretic therapy as less serious infections.

5. THERAPEUTIC CONSIDERATIONS

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, there is considerable evidence that in some but not necessarily all situations (17) fever is an important defense mechanism that contributes to the host's ability to resist infection (18). However, even if fever (or its mediators) does adversely affect the course of certain disorders, as for

Table 1. Studies in Children of the Oral Temperature Response of Bacteremic vs Nonbacteremic Infections to Antipyretic Agents

				Temperature Response, °C						
				Bacteremic			Nonbacteremic			
Ref. No.	**Study Design**	**Antipyretic Agent**	**Age of Subjects (year)**	**No.***	**T_I†**	**↓T‡**	**No.***	**T_I†**	**↓T‡**	**P§**
11	Prospective/observational	Acetaminophen/ aspirin	≤ 2	16	40.1	1.3	239	39.9	1.05	.14
12	Prospective/observational	Acetaminophen	≤ 6	10	40.1	1.5	225	39.6	1.0	NGII
13	Prospective/observational	Acetaminophen	≤ 2	17	40.5	1.6	216	40.4	1.6	.85
14	Prospective/observational	Acetaminophen	≤ 17	11	NGII	1.4	16	NGII	1.2	.37
15	Prospective/observational	Acetaminophen	≤ 2	19	40.1	1.7	135	40.0	1.6	> .05
16	Retrospective/case control	Acetaminophen	≤ 6	34	39.8	1.0	68	39.8	1.5	<.001

* Number of subjects studied, † Mean initial temperature (T) (i.e. T just prior to administration of antipyretic agent), ‡ Mean decrease in T 60 to 120 minutes following treatment with antipyretic agent, NG indicates not given, § Comparison of ↓T in "bacteremic" vs "nonbacteremic" subjects by t test

example bacterial sepsis (19), it does not necessarily follow that inhibiting fever using current modes of antipyretic therapy will obviate this effect, especially if such therapy has intrinsic toxicity of its own.

One of the reasons commonly given for 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 (20). 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 (21). Although antipyretic therapy has theoretical merit in this regard [if it does not induce shivering (22)], the relative importance of the detrimental effects of fever versus the salutary effects of antipyretic therapy has yet to be critically evaluated.

External cooling, which is widely used in critically ill patients to suppress fevers unresponsive to antipyretic drugs, has been shown to decrease oxygen consumption by as much as 20% if shivering is prevented by therapeutic paralysis (22). If shivering is not inhibited, external cooling causes a rise, rather than a fall, in oxygen consumption. (21). Perhaps more important to febrile patients with underlying cardiovascular disease, external cooling has the capacity to cause vasospasm of diseased coronary arteries by inducing a cold pressor response (23, 24). 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 selected skin surfaces (e.g., the forehead), thereby reducing the vasoconstriction and shivering thresholds dictated by the elevated hypothalamic thermal setpoint, and, in turn, effecting a decrease in the core temperature (25).

Unfortunately, certain antipyretic drugs also appear to cause coronary vasoconstriction in patients with coronary artery disease. Friedman and associates observed significant increases in the mean arterial pressure, coronary vascular resistance, and myocardial arteriovenous oxygen difference after intravenous indomethacin (0.5 mg/kg) in such patients (26). Coronary blood flow decreased simultaneously from 181±29 to 111±14 ml/min (p<0.05). Thus, in this investigation, myocardial oxygen demand increased in the face of a fall in coronary blood flow after indomethacin administration. The authors believe that indomethacin's vasoconstrictor effect most likely derives from to its capacity to block the synthesis of vasodilatory prostaglandins. Perhaps even more disturbing are recent reports suggesting that compared to other nonsteroidal antiinflammatory drugs, COX-2 selective, nonsteroidal antiinflammatory drugs seem to increase the risk of cardiovascular thrombotic events in patients not taking aspirin (27).

Antipyretic therapy is also commonly administered to enhance patient comfort. 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 its validity. 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 have never been determined. The importance of such information is underscored by reports that acetaminophen prolongs the time to crusting of lesions in children with chickenpox, (28) both acetaminophen and aspirin increase viral shedding and nasal signs and symptoms while suppressing the serum neutralizing antibody response in adults with rhinovirus infections, (29, 30) and that antipyretic drugs might prolong the course of influenza A infections (31).

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. Beisel and coworkers have shown that aspirin (in combination with propoxyphene) ameliorates fever-induced decrements in mental work performance in young volunteers infected with sand fly fever virus, even in the face of only partial relief of either the fever or other symptoms of the illness (32). 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 testing this hypothesis have not yet been reported.

In selected populations of children between the ages of 3 months and 5 years, seizures have been reported to occur during episodes of fever at a frequency of as high as 14% (33). Although most children with febrile seizures have temperatures of 39°C (102.2F) or more at the time of their seizure (34), many tolerate even higher fevers later without convulsing (35). Unfortunately, antipyretic therapy has not been shown to protect against recurrences of febrile seizures in the few controlled trials conducted thus far (36). Camfield and colleagues conducted a randomized double-blind study comparing single-daily-dose phenobarbital plus antipyretic instruction to placebo plus antipyretic instruction to prevent recurrent seizure after an initial simple febrile seizure (37). 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% suggesting that a single daily 5 mg/kg dose of phenobarbital is more effective than counseling parents about antipyretic therapy in preventing recurrent febrile seizures. More recently, acetaminophen has been given to children with fever as prophylaxis against febrile seizure recurrences. Whether given in moderate dosage (10 mg/kg/dose four times a day) (38) or in relatively high doses (15 to 20 mg/kg/dose every 4 hours) (39), acetaminophen failed to reduce the rate of febrile seizure recurrence.

Finally, there has been mounting interest in the use of certain antipyretic drugs to modulate the activity of pyrogenic cytokines during bacterial sepsis (40). In some animal models of sepsis, antipyretic drugs that inhibit cyclooxygenase confer protection when given soon after bacterial challenge, presumably by blunting the adverse effects of tumor necrosis factor-α (TNF-α) and interleukin-1(IL-1). In a large clinical trial, Bernard and associates observed that 48 hours of intravenous therapy with the cyclooxygenase inhibitor ibuprofen lowered the core temperature, heart rate, oxygen consumption, and lactic acid blood levels but did not decrease the incidence of organ failure or mortality at 30 days (41). In a more recent retrospective analysis of sepsis trials, Eichacker *et al*. (42) could find evidence of a beneficial effect of antipyretic agents only in septic patients with a high risk of death. Thus, in spite of promising results obtained in some experimental models, antipyretic agents have been shown to be of only limited value clinically in the treatment of bacterial sepsis.

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