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Fever: Could A Cardinal Sign of COVID-19 Infection Reduce Mortality?



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ABSTRACT

With mortality rising from the COVID-19 pandemic, we may be overlooking a key aspect of the immunological response. Fever is a cardinal sign of this rampant infection; however, little attention has been paid towards how a fever may work in our favor in overcoming this disease. Three key aspects of patient care – fever, fluid, and food – can be harmonized to overcome COVID-19 infection. Both animal and human studies have demonstrated that fever suppression during viral infections, either through low ambient temperatures or antipyretic use, may increase morbidity and prolong the illness. As fever rises, so do antidiuretic hormone levels, leading to solute-free water retention – making conservative fluid management essential. Finally, fever inhibits gastrointestinal function as energy is reallocated to the immunological response, underscoring the need to work in concert with these physiological changes. An opportunity awaits to investigate this natural barrier to infection, let us not pass it by.

Key Indexing Terms: COVID-19; Antipyretics; Fever; Fluid management; Nutrition. [[Am J Med Sci 2021;361\(4\):420–426.](#)]

INTRODUCTION

Fever is one of the cardinal signs of COVID-19 illness, yet routinely suppressed as a part of ‘supportive care’ as soon as it appears. Recent COVID-19 treatment guidelines have encouraged use of antipyretics;^{1,2} however, a COVID-19 rapid evidence summary from the National Institute for Health and Care Excellence in the UK stated that “the current evidence does not support routine antipyretic administration to treat fever in acute respiratory infections and COVID-19”.³ It concludes that further investigations are necessary in this disease. Unfortunately, investigations on the safety of antipyretic use in COVID-19 illness are lacking.

At the beginning of a potentially serious infection, should we provide medication that could impair the immune response in the hope that it may improve patient comfort? Maybe for a younger, otherwise healthy patient, this may not make much difference, but what of the elderly patient? Or the patient who has chronic pulmonary or cardiovascular disease? Are we setting them up for failure as the disease progresses? The ancient medical historian, Celsus, once stated with some astonishment “Denique ipsa febris, quod maxime mirum videri potest, saepe praesidio est” or “Finally the fever, the greatest surprise may be that it is frequently a protection”.⁴ Aulus Cornelius Celsus (c. 25 BC–50 AD) was a Roman nobleman known for writing an encyclopedia on many diverse topics such as agriculture, military tactics, and law, who also wrote a few volumes on medicine. Unlike his other volumes, his medical text, *De Medicina*,⁵ still survives today and has a few useful insights on fever management for the current pandemic. The following is a

discussion of his three key ‘F’s’ in the management of acute diseases: fever, fluid and food.

FEVER

Celsus gained renown with his noted description of inflammation: “now the signs of an inflammation are four: redness and swelling with heat and pain”; yet an interesting phrase which follows is long forgotten: “. . .if there is fever, nothing is to be put on it as the fever at once will dissolve the pain”.^{5p.273} Fever is in fact a highly conserved physiological response to infection that occurs in all mammal and bird species. Moreover, cold-blooded animals that cannot internally raise their body temperature, such as reptiles and amphibians,⁶ and yes, even fish⁷ and the lowly insect,⁸ can generate a ‘febrile response’ by exhibiting heat-seeking behavior during an infection. Thus, we see that this febrile response has been conserved across a great diversity of species. One advantage may be that these animals can rapidly initiate this augmented temperature forcing a single cell bacteria or virus into a sudden thermal disadvantage. Studies in mammals have shown that elevated thermal support during an infectious challenge impairs replication of a variety of viral pathogens.^{9–15} Following infection, pyrogens and other conserved molecules from these invading organisms trigger an innate immune response which recognizes these pathogen-associated molecular patterns (PAMPs) via the pattern recognition receptors, which in turn shape the immune response.¹⁶ A fever then ensues following the release of endogenous pyrogenic cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor

necrosis factor- α (TNF- α), and interferon (IFN). For viral infections, recent studies suggest that an effective temperature-dependent response may operate through the IFN- α/β receptor complex.^{9,10}

But one may ask what about the elderly or an otherwise debilitated patient? Isn't a fever too much to bear for a patient in a weakened condition? One thing we do know is that the elderly generally do not produce the robust fevers of their younger counterparts.¹⁷ The chills and shivering that occur at the commencement of a fever do have significant metabolic costs. Febrile thermogenesis may be associated with an increase in the metabolic rate by 13% for every 1°C of rise in temperature, while fever maintenance also requires a continued elevation in the metabolic rate.¹⁸ A study by Florez-Duquet et al.¹⁹ demonstrated that injection of bacterial lipopolysaccharide at room temperature led to a fever in young rats, but a blunted fever, no fever or even hypothermia in old rats. Yet, when they placed the animals in a thermal gradient; the old rats *all* chose significantly warmer positions than their younger counterparts, but were then able to achieve a similar febrile response – yet without the metabolic costs of having to fuel that fever.

Numerous animal studies have shown that lower ambient temperatures during viral infections enhance viral replication while increasing morbidity and mortality.^{20,21} Similarly, animal studies where antipyretics were administered during an infectious challenge have consistently shown a survival disadvantage when fever was suppressed.^{6,22} In a study analogous to intensive care, Su et al.²³ developed an ewe septic shock model induced by acute peritonitis. Following the surgically provoked peritonitis, animals were then divided into a fever group, or groups kept at normal or hypothermic temperatures, through the use of acetaminophen and external cooling. While all animals eventually succumbed to the infection, animals that were allowed to develop a fever had significantly higher oxygen delivery (DO₂), lower lactate concentration, superior gas exchange, and a longer survival time. In an example more relevant to our current viral pandemic, Husseini et al.²⁴ carried out experiments in a ferret model of influenza. In the first experiment, animals were infected and then divided equally into a fur-shaved group (to mimic a lack of thermal support) or unshaved. Temperatures and viral titers in nasal washings were then measured every 10 hours. The unshaved animals were all able to mount a robust fever to the infection and had the lowest viral titers. Of the shaved animals, some were still able to mount a fever and had lower viral levels than those who had a blunted fever, but the unshaved animals had the lowest titers. In a second experiment,²⁴ ferrets were infected and then half were given an antipyretic. Similar to the previous experiment, those receiving no antipyretic mounted a vigorous fever and had the lowest viral levels, but some given an antipyretic were still able to mount a fever. Again, this latter group had lower viral levels, though generally not a low as in the

non-antipyretic group; those that had a suppressed fever had the highest viral titers.

Human studies are much fewer in number, but randomized trials in viral infections, either spontaneous (measles,²⁵ varicella²⁶) or induced (rhinovirus,^{27,28} influenza A²⁹), have shown prolonged disease, reduced immune responses or greater viral shedding. Ahmady and Samadi²⁵ conducted a study in Afghanistan in 200 children with measles, where half received aspirin and half phenobarbitone (they stated for sedation and preventing convulsions due to high fever). The study was initiated to test “the popular belief in Afghanistan that fever facilitates eruption of the skin rash and reduces the duration and severity of the disease”. Patients in the antipyretic arm were found to have a significantly increased duration of illness. In addition, respiratory complications (pneumonia, bronchopneumonia, bronchitis and laryngitis) were higher in children who received aspirin – a finding particularly notable in underweight children. In a study by Doran et al.,²⁶ 72 children with varicella (chickenpox) were randomized to acetaminophen or placebo. Time to total scabbing was reduced in the placebo group (5.6 days vs 6.7 days) and itching on day 4 was also less in the placebo group. In contrast to the spontaneous infections, several randomized studies were conducted where viral infections were induced. Stanley et al.²⁷ carried out two randomized studies using two types of rhinovirus. In the first trial, participants received RV21 and the second study RV25, then participants were randomized to receive aspirin or placebo. Data were examined on 24 infected participants who developed a mild illness (all but one were afebrile). Viral shedding in nasal washes was examined. On the first day, an excess frequency of viral shedding was observed which continued up to and including the seventh postchallenge day in the antipyretic group relative to placebo. In a subsequent study by Graham et al.,²⁸ 60 volunteers were challenged with rhinovirus type 2 (RV2) and then randomized to aspirin, acetaminophen, ibuprofen, or placebo. Again, most subjects developed a mild illness and only five had a rise in temperature over 37.4°C. Those on placebo showed a trend towards less prolonged viral shedding (<9 days) and it was observed that all antipyretic groups had significantly higher nasal obstruction and nasal turbinate swelling relative to placebo. Antibody titers were lower in subjects on antipyretics. There was also a trend towards greater cervical adenitis in the placebo group and cervical adenitis was associated with a significantly greater rise in antibody titer. Finally, Plaisance et al.²⁹ examined outcomes from subjects who received an intranasal challenge of influenza A who were then treated with acetaminophen, aspirin or no antipyretic. The infection in participants treated with antipyretics lasted significantly longer than those not receiving antipyretics (8.8 vs 5.3 days). Moreover, they observed a statistically significant positive correlation between the number of doses of acetaminophen/aspirin received and duration of illness. Thus, the limited number of randomized human studies

Table 1. Fever support vs fever suppression: advantages and disadvantages

Factors for comparison	Supported fever(thermal support)	Suppressed fever(antipyretics/physical cooling)
Hyperthermia (excessive rise in body temperature)	Fever may continue to rise to thermally injurious temperatures, though rare	Fever height can be controlled through targeted temperature management
Thermal challenge	Many viruses are vulnerable to fever range temperatures, though the thermal sensitivity of COVID-19 has not been established	Suppression of fever could lead to more rapid replication and dissemination of the virus, although this remains to be determined
Hypotension	Maintenance of more consistent mean arterial pressure with reduced need for interventional methods	Acetaminophen may lead to clinically significant hypotension, necessitating intervention with fluids and/or vasopressor support
Metabolism	While an unsupported fever will lead to a significant rise in oxygen consumption and cardiac output, thermal support would greatly reduce this increase in metabolism	Suppressing the fever could save a patient's energy that could be expended on other aspects of the immunological response
Antidiuretic hormone (ADH) levels	ADH levels will rise in parallel with fever, necessitating conservative fluid management and correction of hyponatremia to maintain adequate blood pressure	Possibly may lead to lower ADH levels, though generally the same principles of conservative fluid management apply
Gastrointestinal function	Fever suppresses gastric acid secretion and GI motility, which could complicate nutritional support	Reduced temperature may improve appetite, but could also shift energy resources away from the immune response
Patient comfort	Thermal support can reduce the discomfort of chills/rigors	Restraining fever can counter discomfort that may occur from chills/rigors
Costs	While fever is a free gift of the immune system, effective management requires monitoring to ensure thermal support matches the hypothalamic temperature setpoint	Costs include antipyretics, methods for physical cooling, but may also include sedatives, neuromuscular blocking agents, and blood pressure support (fluids, vasopressors)
Febrile response to infection	A 'febrile response' to infection occurs in mammals, birds, reptiles, amphibians, fish, and insects	Humans are the only known species that will intentionally suppress a fever during an infection

support data in animal studies demonstrating that antipyretics may have a negative impact on the course of a viral infections.^{20,21} While these studies provide some interesting insights, there is much more to fever management than whether one does or does not use antipyretics (Table 1).

Often concerns are raised about the significant increase in metabolic demand and oxygen consumption associated with fever. While there is a notable increase in the metabolic rate as the fever rises, this is very much dependent on ambient temperature. Ambient temperature will determine the thermoregulatory mechanisms by which fever is achieved. At high ambient temperatures, the major route is heat storage: cutaneous vasoconstriction and reduced respiratory evaporative heat loss; whereas at low ambient temperatures there is still minimization of heat loss, but temperature is also augmented through shivering and non-shivering thermogenesis, as well as, symptoms such as chills, which encourage heat-seeking behavior.³⁰ Thus, Celsus advised, in anticipation of rigors, that the patient "is to be covered up quite soon with a quantity of bed-clothes".^{5p.275}

What if the fever goes too high? Generally, a higher fever is associated with a more serious infection, as has been borne out with the current SARS-CoV-2 virus in comparison to the other coronaviruses that usually circulate during the winter season (i.e. HCoV-OC43, HCoV-HKU1, HCoV-229E, HCoV-NL63), but similar to SARS-CoV and MERS-CoV viruses, which are also associated

with more severe disease;^{31–33} however, one must keep in mind that it is the central nervous system working in concert with immune system's regulatory mechanisms that controls what is the appropriate height of fever necessary to overcome each particular infection. One can conserve the patient's energy for other aspects of this immunological response, if one provides the appropriate thermal support. This is achieved by matching the hypothalamic temperature setpoint by keeping the patient's skin warm and dry during the rise and maintenance of the fever, then allowing them to cool down comfortably as the fever declines. If a patient develops a high fever, then clearly that is what is deemed immunologically necessary to fight the virus and thus it seems counterproductive to suppress a fever at the height of battle against a disease. Yet, even without intervention, fever will not just continue to rise unabated.^{34,35} DuBois in reviewing 1,761 fevers over 39°C (Fig. 1), during an era before the introduction sulfanilamides, penicillin and streptomycin, noted that only 4.3% were over 41.1°C (106°F) and none were over 42°C.³⁶ He concluded "thus it is evident that in fevers the great majority of readings are lower than 106° F which is safely below the point at which temperature itself is dangerous".³⁶

Some potentially harmful effects of fever should be weighed against possible benefits. While it is quite rare for a fever to go above 41–42°C, there are reports of much higher fevers where patients survived.^{36,37} One of the highest fevers recorded without a fatality involved a

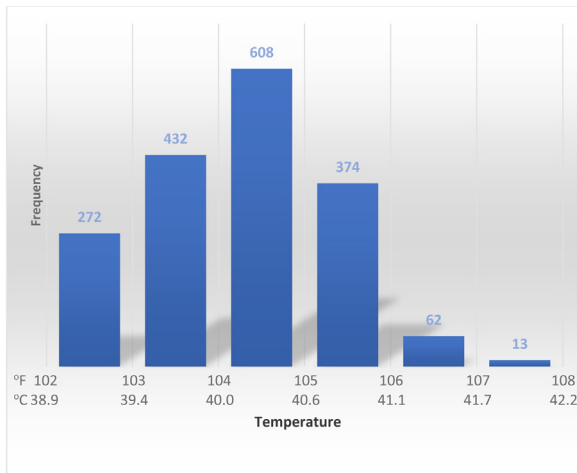


FIGURE 1. Summary of 1,761 fever readings above 39°C from 357 patients admitted to New York Hospital before 1932. Redrawn from DuBois.³⁶

56 year-old female patient with recurrent ovarian carcinoma.³⁷ She was receiving intravenous treatment with a bacterial immunotherapy vaccine and following her 12th infusion, she developed a fever that rose to 114°F (45.6°C). Salicylates and physical cooling were employed to reduce her temperature. She was later discharged and well 2 months later at the time of follow-up. As mentioned previously, as the metabolism rises to fuel the fever, this means that oxygen consumption increases, and could seriously compromise a patient's metabolic reserves if adequate thermal support is not provided. In addition, fever occurring following traumatic brain injury, cardiac arrest, and stroke is often associated with a worse prognosis relative to those patients without fever;^{38,39} however, these fevers are not always due to an infectious cause, but may relate to impaired control of thermoregulation. Another point to consider is that the fever could also merely be a marker for more severe injury, but this remains to be conclusively determined. A final concern relates to febrile convulsions – the most common form of seizures seen in children, with 3–5% of children experiencing a febrile seizure in the first 6 years of life.³⁰ In general, febrile seizures are benign, with a low probability that these children will later develop epilepsy.³⁰ Due to the temporal association noted between fevers and seizure activity, a number of studies have been carried out to examine whether antipyretics can prevent febrile seizures; however, no study to date has demonstrated a benefit for antipyretic use (i.e. acetaminophen, diclofenac, or ibuprofen) in decreasing the incidence or recurrence of febrile seizures.^{30,40}

Where does this lead us? A trial comparing antipyretic treatment vs placebo would be meaningless if the placebo arm did not include thermal support to follow the patient's hypothalamic setpoint as it rises and falls over the course of a febrile illness. The typically cool hospital environment is not conducive for an interventional study of this nature without the added thermal support.⁴¹

Similarly, for animal studies, research is needed where one compares an infectious challenge between animals fixed at a thermoneutral temperature vs a thermal gradient where an animal can select the optimal temperature. Past studies have had animals confined to fixed temperatures: below, at, and above room temperature,^{20,21} but a thermal gradient, as used in studies of cold-blooded animals,⁶ would provide a more real-world scenario as animals during a fever normally seek a thermally supportive environment.²²

FLUID

One might think that during the early stages of a respiratory infection it would be advantageous to provide patients with useful advice that could prevent worsening of the illness; yet, regrettably public health bodies are advising patients with COVID-19 illness to drink “a lot of fluids”⁴² or “plenty of fluids”.^{43,44} Although we live in a generally well-hydrated society, apparently when we get a cold even that is not enough. Does such superfluous fluid intake during health really need to be augmented during a respiratory infection? In summarizing the views of ancient physicians on this matter, Celsus stated that “There is sufficient agreement that for all who are feverish an excess of fluid is unsuitable”.^{5p.253} Only after many decades of research are we beginning to come to the same conclusion.⁴⁵

Although some fluid may be lost during a respiratory infection through rhinorrhea, expectoration, or occasionally vomiting/diarrhea, these are not the fluid losses that one might encounter during cholera or dysentery. Inappropriate fluid management at the outset of an infection puts the patient at a critical survival disadvantage. Why encourage patients to present to the hospital with hyponatremia – a poor prognostic factor for almost every illness, including respiratory infections? Hyponatremia is commonplace during more severe respiratory infections,⁴⁶ including SARS⁴⁷ and COVID-19.⁴⁸ This is because water conservation (via increased antidiuretic hormone levels) is enhanced during infectious disease.³⁰ Antidiuretic hormone plays a strategic role in hemodynamic stability by controlling both urine output (at low levels) and vasoconstriction (at high levels). Plasma levels of antidiuretic hormone are elevated in a variety of febrile infections, including respiratory infections.³⁰ Often referred to as the syndrome of inappropriate antidiuretic hormone secretion (SIADH), or during viral lung infections, it probably should be referred Syndrome of Inappropriate fluid Management when AD hormone is elevated (one might call it SIP-MAD). If the body is conserving water during an infection, where does all this excess water go? During hyponatremia, the excess fluid is shifted from the bloodstream into the cells, filling tissues, and yes, even the lungs with unnecessary fluid, ultimately impairing respiration.³⁰ The phenomenon of fluid retention during severe respiratory infections was nicely summed up by Balcar et al.⁴⁹ over 100 years ago “Everyone is familiar with the remarkable emptying out of

water via the kidneys and skin which may follow the crisis in a case of pneumonia. Liters of water may thus be liberated in a few hours, giving visible proof of the water retention of the febrile stage.” Why not limit the fluid intake from the start?

Acetaminophen remains the first line antipyretic used to counteract fever in patients with COVID-19 illness, and likely the most widely used and least studied drug during this pandemic. A key mechanism for lowering temperature is by initiation of cutaneous vasodilation,⁵⁰⁻⁵² similar to what occurs during defervescence, which facilitates arterial heat dissipation from the skin. This vasodilation can occur to varying degrees in a febrile patient, but studies in both adults⁵³⁻⁵⁵ and children^{56,57} have shown this often leads to a clinically significant fall in mean arterial pressure. The subsequent acetaminophen-induced hypotension is then countered with fluid and/or vasopressor support to maintain adequate organ perfusion.⁵³⁻⁵⁷ Thus, a vicious cycle ensues as we desperately work against the normal physiology of the body to maintain blood pressure, but as total body water stores increase, oxygenation in the lungs then becomes compromised, inducing unnecessary harm.⁵⁸

The time for an evidence-based approach to fluid management in the febrile patient is long overdue. Ambiguous advice advocating generous fluid intake at the outset of an illness places the patient at risk for further complications. The combination of fever (which can elevate vasopressin levels and augment water conservation) and a fall in sodium, may synergistically impair respiration. Moreover, use of acetaminophen, which can induce hypotension and lead to further fluid administration in an attempt to bolster the blood pressure, only exacerbates an already precarious situation. Clinical studies are needed investigate how conservative fluid management from the outset can work synergistically with febrile thermal support to overcome this disease.

FOOD

“Feed a cold, starve a fever.” A seemingly straightforward phrase that has led to countless interpretations.⁵⁹⁻⁶¹ A common interpretation is that it is providing clear-cut advice, if you have a cold you should, let’s say ‘eat lots of food’ or ‘eat plenty of food’, but if you have the misfortune of developing a fever, your time of feasting has now come to an end and you must begin your fast. Yet, one might think that ‘eating plenty of food’ during a respiratory infection sounds like rather arbitrary advice, sort of like ‘drinking plenty of fluid’ when you get the flu. Celsus provides some useful observations on this topic: “for of the sick who were without doctors, some in the first days of illness, longing for food, took it forthwith; others, owing to distaste, abstained; and the illness was more alleviated in those who abstained. Again, some partook of food whilst actually under the fever, some a little before, others after its remission, and it went best for those who did so after the fever had ended; and similarly

some at the beginning adopted at once a rather full diet, others a scanty one, and those were made worse who ate plentifully”.^{5p.19} Thus, with his insight we can see that a more likely interpretation is “if you feed a cold, you will have to starve a fever later” or eating heavily during a cold aggravates the disease, causing it to evolve into a more serious febrile illness. Why one should ‘starve a fever’ is discussed below.

In an animal that develops an infection, and the corresponding fever, the natural response is to rest in some warm spot, not to go running around expending energy trying to find food and water.⁶² Yet, even when offered food (no foraging required), sick animals often only consume a scant diet. This is because digestive system shuts down during an infection. Pyrogens (from viruses, bacteria, etc) inhibit gastric acid secretion and gastrointestinal motility in a dose dependent manner,^{63,64} where gastrointestinal motility and secretory activity are inversely correlated with febrile body temperature.⁶⁴ To compensate for this self-imposed nutritional deprivation, the body activates a set of mechanisms that allow it to consume itself for brief periods of time while energy is redistributed to support the immune and wound healing response.⁶⁵ This hypermetabolic and hypercatabolic phase is characterized by muscle protein breakdown, and glucose and insulin insensitivity that promotes gluconeogenesis and lipolysis.^{66,67} Thus, with the GI tract in complete stasis, Celsus adds a useful tip that “the rationing of patients’ food is the easier because often the stomach spues it back”.^{5p.251}

Why does the digestive tract shutdown? Digestion has a high upfront cost in terms of metabolic energy expended and would involve a critical diversion of energy away from the immune response. Due to the rapid replication and dissemination of pathogens, any temporary diversion of resources away from the immune response could easily shift the balance in favor of disease-causing agents.^{6,22} It is during this period of infection-associated anorexia, however, that patients can become particularly vulnerable to water and electrolyte imbalances as discussed previously.³⁰

Now to the animal studies, which have shown that feed restriction and fasting can enhance host resistance to infections in a variety of animal models.^{22,68-70} The study by Hunt et al.⁷⁰ highlights this point quite well. Mice were infected with plasmodium malaria and feed restricted as follows: ad libitum – mortality 100%; 1.0–2.0% weight loss – mortality 47%; 2.5–3.5% weight loss – mortality 43%; 4.0–6.5% weight loss – mortality 10%; 7.0–9.5% weight loss – mortality 53%. Thus, we can see that there may be somewhat of a sweet spot in terms of feeding, where one reduces food intake but not too much. Let us conclude with some sage advice from Celsus on this point “The best medicament is food opportunely given . . . food is less corrupted when introduced in a body free from fever”.^{5p.233}

Overfeeding or hyperalimentation in intensive care has been associated with hyperglycemia, fatty liver,

sepsis, and increased inflammation and mortality, although this is more carefully regulated now than in the past.^{71,72} Still, opportunities remain for further exploration of feed restriction and timing of feedings during intervals where the fever has abated in animals models to examine the effect of these modifications in acute viral infections. This should be undertaken in animals studied within their thermoneutral zone. It has been pointed out by various researchers^{73–75} that the vast majority of research in rats and mice is performed on animals well below their thermoneutral zone. While 20–24°C may be a comfortable laboratory temperature for investigators, this would lead to cold stress in rats and mice (with a thermoneutral zone around 28–30°C) and result in their overfeeding to compensate for the excessive heat loss.⁷⁵ Thus, one could see that this would confound any research of this nature in such animal models.

CONCLUSION

“The history of opinion regarding fever is in great part the history of medicine itself, for no feature of the great systems of medicine from Hippocrates and Galen to the present century so characterizes these systems as the views held concerning the nature of fever”⁷⁶ – wise words from the great pathologist and member of the founding faculty of Johns Hopkins Hospital, William Henry Welch. With the substantial energy expenditure required for a febrile immune response (i.e. increased heart rate, oxygen consumption, and metabolism), it seems unlikely that such a response would be conserved over such a widely diverse range of species unless it had considerable adaptive value.

While the advice of Celsus was bereft of animal models, randomized trials and evidence-based medicine – and dating back nearly two millennia – it does offer a unique path to investigate for improved management of febrile diseases. Elevated temperatures put viruses at a thermal disadvantage and one must ask why we should turn off our defensive system at the most crucial stage of infection? Particularly, when animal studies demonstrate evidence of reduced morbidity and mortality when fevers are supported. TC Brackeen stated during the notorious 1918 flu pandemic “In the future we will look back on this epidemic of influenza with wonder and surprise; yes, in spite of our vaunted advancement, we have utterly failed in the recent crisis”.⁷⁷ We might say the same for the current pandemic; however, a solution is within our grasp that does not involve advanced technology and is really quite rudimentary. With the continuing escalation of mortality rates from COVID-19, a renaissance awaits us in the management of fevers – let us not pass up this opportunity to investigate our natural barrier to infectious disease.

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