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Should we let fever run its course in the early stages of COVID-19?

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Antipyretic drugs are readily available as over-the-counter medication, being taken routinely by most people at the first sign of a fever. But the symptomatic relief achieved with these drugs comes with the price of putting out a host-defence response that has evolved for millions of years to aid the immune system in the clearance of pathogens.[1] While it may be OK to pay this price in unthreatening infections such as a regular cold or a mild flu, the situation may be different when lives are at stake amid the uncertainty of the COVID-19 pandemic.

Fever is considered an early symptom of COVID-19, having been reported in 45%–89% of the adults[2,3] and 42% of the children[4] suffering from mild to moderate forms of the disease. These figures may even be underestimated, considering that it is not uncommon for fever to be masked by the unsupervised use of antipyretic drugs. It is clearly important to understand the connection between COVID-19 and fever. To date, however, this connection has been approached solely from a diagnostic perspective, with no attention being given to the role of fever in immunity or to the question of whether or not antipyretic drugs should be taken by the patients. In an effort to fill this gap, this commentary analyses the cost-value relationship of fever based on the evidence available for related infectious diseases. The pertinent knowledge is then extrapolated to reach a putative recommendation regarding the use of antipyretic drugs in COVID-19, paying special attention to disease stage and severity.

Animal studies provide substantial support for a role of fever in survival, with it being particularly adaptive in the early, less severe stages of an infection, when the benefits of a raised body temperature to immunity far exceed its costs to the host.[5] Albeit less compelling, clinical evidence is also consistent with this notion. In a prospective trial in trauma patients, an aggressive antipyretic protocol strongly tended to increase the risk of acquiring an infection and developing complications, which prompted interruption of the trial after the first interim analysis of the data.[6] Such a robust effect cannot be undermined. Furthermore, two randomised, double-blind, placebo-controlled trials in rhinovirus-infected volunteers have shown that the use of aspirin, acetaminophen or ibuprofen is associated with increased or prolonged viral shedding.[7,8] In one of those trials,[7] aspirin and acetaminophen were further shown to suppress the neutralising antibody response and, paradoxically, worsen nasal symptoms. These drugs are not identical with regard to their effects on local inflammation, but have the suppression of fever as a common denominator. And although fever was thought to be occasional in the rhinovirus-infected volunteers, infrequent measures of body temperature (no more than four times a day) are likely to have underestimated the prevalence of low-grade fever in those trials. Indeed, many of the placebo-treated volunteers reported chilliness,[8] a behaviour known to be linked with development of fever.

Therefore, it is plausible to advise that suppression of fever early in the course of COVID-19 may increase the risk of long-lasting infection and, consequently, the risk of complications. It is also plausible to expect that antipyresis can weaken the development of antibody-dependent herd immunity, which, together with an enhancement in viral shedding, can favour the spread of the disease in the population. These arguments call further attention to the recent warning of avoiding ibuprofen in COVID-19. The warning was based on the effects exerted by the drug at the site of infection, be that the suppression of inflammation[9] or the facilitation of ACE2-dependent targeting of host cells by the SARS-CoV-2 virus.[10] However, it cannot be ignored that the impacts of ibuprofen on COVID-19 may also be related to antipyresis, in which case recommending the use of alternate antipyretic drugs such as

acetaminophen and aspirin may not suit the patients' needs in terms of immunity.

The positive association between age and the risk of complications in COVID-19[11] is another aspect that can be looked upon from the perspective of fever as a host-defence response. Humans and experimental animals are known to mount less pronounced fevers as they age, with fever being completely absent in 20%–30% of elderly patients harbouring a serious infection.[12] While the mechanisms underlying the suppression of fever in the elderly are still poorly understood, an experimental study provides evidence that this phenomenon may be restricted to the autonomic mechanisms of fever, with the behavioural mechanisms being spared to the extent that old rats regain the ability to develop fever if given the chance to move to a warmer environment.[13] If the same thermoeffector pattern occurs in humans, it may open a therapeutic opportunity. More specifically, if an elderly person with respiratory symptoms complains of chilliness, perhaps it would be more adequate to provide him or her with warmth than to seek symptom relief with drugs.

The question then arises as to why so many people are afraid of fever. It has been documented that fever phobia is based on unrealistic concerns and misconceptions that have persisted in our culture despite decades of research on the true nature of fever.[14] The perception that body temperature will reach dangerous levels if fever is not treated is unsubstantiated by scientific evidence. On the contrary, the available evidence indicates that body temperature is precisely regulated during fever, and that endogenous antipyretic mechanisms are at work to prevent excessive rises in body temperature. Accordingly, the body temperature of infected patients usually stays around 38.0–39.5°C, rarely reaching 40–41°C and never exceeding this ceiling. COVID-19 is not an exception in this regard, with fevers of more than 39.0°C being rare in adults[2] and children.[4] Within this physiological range, the temperature rise per se has never been shown to be harmful to neurons or other cellular phenotypes. In young children, febrile seizure is a concern, but it must be considered that only a very small fraction of the children are predisposed to this condition, that febrile seizures are usually self-limiting and benign, and, what is more, that the pre-emptive use of antipyretic drugs may be ineffective at preventing the seizures.[15]

Recognising the value of fever in the fight against infection does not imply that fever has no costs, but the available evidence indicates that the costs of fever outweigh its benefits only at advanced and severe stages of infection,[5] typically when patients are hospitalised because of cardiovascular or respiratory complications.[16,17] In such states of compromised physiological fitness (sepsis), the energetic cost of fever may be too much for the host to bear and, additionally, fever may heighten the maladaptive inflammation underlying the complications. Interestingly, it often happens that fever is replaced with a self-limiting, spontaneous form of hypothermia in severe sepsis,[18] which, at least in experimental animals, appears to be launched by the host as an alternate defence strategy aimed at tolerating the pathogen while preserving vital bodily functions.[5] This dichotomy in the thermal adaptation of critically ill patients may underlie the controversial results obtained in trials regarding the use of antipyresis in this subset of patients.[16,19] More refined strategies of patient stratification, perhaps involving temperature trajectories,[20] may help to solve this matter. But regardless of how complex the situation may be with critically ill patients, the situation is unquestionably less complex when an infection such as COVID-19 is at its inception, and competing demands are not at play to offset the value of fever to immunity.

Taken together, the lines of evidence discussed herein call attention to the value of fever as a host-defence strategy and its possible implications to COVID-19. Prioritising symptom relief over host immunity in the early stages of a potentially life-threatening infection may not be working in our favour in the COVID-19 pandemic. In this moment of uncertainty and crisis, it may be proper to break cultural habits and advise against the use of antipyretic drugs for at least a few days after the onset of symptoms. This recommendation is based on lessons learned from studies on the pathophysiology of other infectious diseases and does not eliminate the need for placebo-controlled studies specifically tailored to COVID-19. These studies are likely to be quite challenging for requiring patient enrolment at the earliest sign of infection, as well as adherence to fever management protocols in an outpatient setting, but those challenges certainly do not undermine the importance of such studies.

Declarations

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