WHO Fever Management Guidelines: Challenges in Harnessing the Benefits During Covid-19 Pandemic

Samer Singh, PhD1*; Dhiraj Kishore, MD, FICP2; Rakesh K. Singh, PhD3

1Centre of Experimental Medicine & Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi – 221005, India
2Department of General Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi – 221005, India.
3Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi – 221005, India.

* Address for correspondence: samer.singh10@bhu.ac.in

ABSTRACT:

Fever remains an integral part of the acute clinical diseases management, esp. viral, for which effective therapeutics remains desired. However, the presence of often confusing fever reduction recommendations for COVID-19 in the public domain during the pandemic, as late as 28 April 2021, seems to suggest the reduction of any ‘uncomfortable’ fever ranging from 37.8 - 39°C, as opposed to WHO fever reduction guidelines (≥39°C), urgently need attention. The confusion could percolate down into different agencies who look up to these agencies for guidance in framing their own, denying the benefits of fever to populations, and effectively undo whatever successive WHO’s guidelines have achieved in the last two decades. The existence of conflicting guidelines in public domains which are open to interpretations has consequences to public health and the healthcare infrastructure, on implementation. For controlling acute infectious diseases, esp. viral, the fever remains the most important enabler. Historically, our chief obstacles to harnessing the benefits of fever in acute clinical diseases with limited therapeutics had been: a) widespread myths about ‘fevers’ arising from a general misunderstanding of basic facts; b) presence of confusing guidelines by different agencies which are open to alternate interpretation. The article attempts to briefly indicate the benefits of fever in disease resolution, dispel myths, underline vagueness in illustrative national guidelines and the need to align them with evidence-based WHO guidelines, as it has the potential to perpetuate myths/confusion in masses leading to adverse impact on disease management – more morbidity and mortality from diseases including COVID-19.


1. INTRODUCTION:

Fever is an essential part of our natural defense mechanism against acute clinical infections, esp. for whom effective therapeutic agents are limited, e.g., common cold, measles, influenza, etc. [1-8]. The existence of fever is an evolutionary conserved adaptive response, at least > 400 million years old, not just unique to us that protect hosts from potentially dangerous pathogens causing improved survival and early resolution of infections, while reduction of fever in diseases is associated with increased mortality including those in critical conditions [REFs in 1,2,5,6,9-11]. The role of fever in controlling infectious disease is well recognized and remains part of standard immunology textbooks, clearly enumerating its benefits. For example, Janeway’s Immunobiology states “At higher temperatures, bacterial and viral replication is less efficient, whereas the adaptive immune response operates more efficiently” [12, p. 110]. Kuby Immunology [13] variously describes the benefit of ‘fever’ as “helps to eliminate many temperature-sensitive bacterial strains” [p.223], “a protective response, as elevated body temperature inhibits replication of some pathogens’ [p.323], “decrease microbial viability” [p. 401]. However, its true value remains highly underappreciated in the age of antimicrobials where most of the fatal diseases have been largely controlled using vaccines. There had been a sea change in the practice of antipyretics in the last 50 -60 years [14-22]. Now, antipyresis seems to be recommended for every fever no matter how insignificant it may be in the case of infectious diseases, even as low as 37.8°C – 38°C, unqualified ‘uncomfortable feelings’ or ‘feeling uncomfortable’ [23-24]. Recent publications of information and guidelines for COVID-19 [25-28] in disagreement with the World Health Organization (WHO)’s fever reduction guidelines as well as various national/local guidelines for fever management are a cause of concern [29-33]. These conflicting guidelines would have the potential to promote unnecessary fever reduction which could increase the deaths
from unrelated acute clinical diseases for which we may also not have therapeutic agents yet.

The aversion to high temperature or the notion of ‘fever is obnoxious’ is not very old. Fever has remained an evolutionary conserved important ally in our fight against diseases and its value has remained well recognized in certain diseases and conditions since the time of Hippocrates [34-36]. Extending on to what was indicated in the literature, the well-documented display of fever’s value in disease resolution by Julius Wagner-Jauregg in the early part of the 20th century helped firmly establish and popularize the benefits of fever in treating otherwise untreatable infectious diseases [37]. Its contribution to propel the growth in our understanding of the molecular basis of fever and its role in pathogen clearance is exemplary. Wagner’s work firmly established the role of fever in disease by showing that induction of fever in neurosyphilis by the introduction of the malaria parasite was curative, which effectively changed an essentially non-treatable condition characterized by progressive paralysis, to a treatable one. For his monumental work on establishing the therapeutic value of fever in disease, he was awarded the Nobel prize in the year 1927. Since then, extensive work of many scientists has contributed to the overall understanding of the essential indispensable beneficial role of fever in disease control [REFs in 1-13]. However, the discovery and increasing availability of antibiotics combined with most dreaded diseases controlled by vaccination programs in the latter part of the last century made reliance on fever for the resolution of common pathogen-caused diseases largely redundant for physicians, besides slowly erasing its benefits from the public memory. The manuscript attempts to briefly indicate the role of fever in disease resolution, dispel fever paranoia, why it is important to appropriately manage fever as suggested by WHO’s fever management guidelines esp. for viral diseases, possible health and implementation issues arising from inexact confusing descriptions in different COVID-19 guidelines in public space by various agencies and the possible way forward.

2. WHAT FEVER DOES?

The benefits of fever in controlling infection are many and are beyond the scope of current discussion [REFs 1-22]. During infection brain elevates body temperature in increments effectively increasing its thermotolerance for the next possible higher temperature exposure, after each cycle figuratively speaking, assessing the benefits-driven and preparing for the next round of onslaught on pathogen through a further increase in temperature as needed. The anti-inflammatory benefits from high fever (>39-42°C) remain some lesser-known facts. Permanent ill effects have not been recorded for fevers from the normal course of infections up to 42°C [20]. One of the reasons for prevailing WHO’s guidelines recommendation of suggesting a delay of antipyresis ≥ 39°C is the fact that raising of the body temperature to about 39°C has been known to inhibit the replication of most of the viruses and bacteria (restrictive temperature) infecting humans [38] and the reported beneficial decrease in the minimum inhibitory concentration of antimicrobials for tested pathogens by 4-16 times by 41.5°C as compared to that at 35°C [39]. For pathogens with higher restrictive temperature the benefit of raising the fever remains grossly underappreciated, e.g., at 41-42°C the replication of poliovirus is reduced by ~200 fold [40] while the serum-induced lysis of Gram-negative bacteria is greatly enhanced [41]. It also triggers the accumulation of various Heat shock proteins (HSPs) and metallothioneins within hrs as a part of heat shock response (HSR) to prepare and protect the cells from future higher temperatures exposures (next day) and possible inflammation damage if the situation is warranted [REFs in 42-46]. Temperature elevation (about 40°C) is known to enhance the production of interferons (IFNs) by infected cells that help the surrounding uninfected cells attain viral infection refractory state through induction of a complex web of host genes leading to inhibition of viral infection and replication, and various interleukins that help enhance bacterial clearance and help reduce inflammatory damage [REFs in 1, 46-49]. The IFNs enhance cells’ capacity to inhibit and eliminate viral infection by enhancing innate and intrinsic antiviral responses [50]. This enhancement could be part of a failsafe mechanism for those pathogens or viruses who have escaped lower temperature exposures (mutants) or whose replication could not be inhibited at a lower temperature due to the temperature being permissive for them [REFs, 38-40,51]. The fever-induced HSR further prepares cells to amicably resolve any threatening stressful situations of thermal, oxidative, and metabolic nature that may arise later from an overwhelming inflammatory response to persisting infection [REFs 52-54]. The HSR is known to be enhanced by repeated heat shocks (including recurrent fever), estrogens (E2) as well as cyclopentenone prostaglandins produced in later stages of disease/inflammation. The appearance of fever with an increasing magnitude over time also prepares host cells through HSR to be able to withstand ‘supraphysiological temperatures’ that the host may be exposed to contain the infection in the future which would otherwise be deleterious.

The HSR and IFNs, together, orchestrate a balanced inflammatory response that minimizes host damage
without jeopardizing an aggressive cell-mediated response, e.g., activation of cytotoxic activity of NK cells, K- cells, T-cells, activation of Macrophages cytocidal activity, activation of suppressor T cells, etc, that may be desired to eliminate the pathogen [REFs in 1,12,13,44,46]. It may be of general interest that the generation of robust HSR is also suppressed to various degrees in most of the COVID-19 pertinent comorbid conditions characterized by chronic inflammation (cardiovascular, obesity, frailty, obesity, diabetes, including metabolic syndrome conditions [55].

3. PERVASIVE ‘FEVER’ PARANOIA: PREVALENCE, CAUSE, AND POSSIBLE SOLUTION

Despite obvious established benefits of fever in infectious diseases, the harnessing of its benefits in need remains desirable due to lack of knowledge and education, essentially perpetuating the non-evidence-based management practices [14-22, 56-58]. The unawareness among the masses, nursing staff, and clinicians of the vital beneficial role of fever in infections remain extensive, despite the body of theoretical and practical/experimental evidence to the contrary [14-22,36,56-58]. The decrease in the awareness about fever's beneficial role in infections and the concurrent urge to treat all fevers has been gradual, peaking in the last three decades. Various estimates put rapid increase during 1980s to 2010 among clinicians (12% to 65 %) [3,20], nursing staff (70%) [59,60] and parents (60 % to 90-95%) in countries like USA [REFs in 3,20-22, 59-17]. The situation in other countries may not be drastically different [19,21,22,36]. The WHO and various national agencies/bodies have been making efforts to educate and improve the practice through publications from time to time [29-33], stressing the beneficial role of fever in infections and restricting antipyretics usage to temperatures ≥39°C when defined uncomfortable conditions are present (See section ‘Fever Management Guidelines’). The rational use of antipyresis may have further gone down during COVID-19 with the publication of confusing and contradicting guidelines by different national agencies (e.g., National Health Service (NHS), Scotland, National Institutes of Health (NIH), USA and Indian Council of Medical Research (ICMR), India) which are in conflict with existing WHO guidelines and seem to suggest anything to everything from 37.8°C to 39°C fit for antipyretics treatment [23-28]. Few illustrative examples from different national agencies which may be contributing to the prevailing confusion and hence increased inappropriate usage of antipyretics during the COVID-19 pandemic are discussed later. An increase in unnecessary antipyretics usage could have an upsetting impact on the health of individuals and the health infrastructure. The possibility of the health of masses getting adversely impacted from needless antipyretics usage cannot be ignored given its precedence [3,5,6,10,11,49].

The current notion of treating each and every uncomfortable ‘fever’ despite efforts to educate the masses by agencies like WHO is seemingly contributed by some underlying facts and possible solutions briefly discussed below.

Firstly, inability to differentiate fever by type, i.e., ‘Hyperpyrexia’, the brain-controlled incremental increase in temperature observed over a period during infection, from ‘Hyperthermia’, the uncontrolled temperature elevation as from heat shock or failure of the thermoregulatory mechanism. The blame also partly lies in the oversight of preferential use of generalized term ‘fever’ and ‘Hyperthermia’ in literature for any temperature elevation above 37°C, where the use of the term ‘Hyperpyrexia’ or some more widely agreed precise terminology (e.g., ‘pathogen-hyperpyrexia’) would have been more accurate for the uninitiated. Equal blame could be placed on its liberal use to a range of temperatures, making the situation chaotic where any elevation of the body temperature could be construed as ‘hyperthermia’ so naturally ‘dangerous’ and ‘fit for treatment’ in the eyes of the general population. In literature, the term ‘hyperpyrexia’ has been also used for anesthesia-driven uncontrolled temperature elevation above 37°C [61]. It should be clarified that while for uncontrolled hyperthermia the temperatures around 40°C or higher could be lethal, the case for controlled-hyperthermia or more appropriately the ‘hyperpyrexia’ (or infection driven hyperpyrexia or ‘pathogen-hyperpyrexia’) temperature up to 42°C (108 F) are considered within safety limits [See Table 1; 58]. There is an urgent need to clarify the terminology in the literature and arrive at a consensus to remove the currently chaotic perception among a large majority of clinicians and the normal populace alike. Additionally, in clinical practice, many a time it is difficult for physicians and healthcare staff to know the origin of fever, so the alleviation of symptoms takes precedence. Naturally, it makes the scenario conducive for clinicians and individuals to act upon the logical ‘well-intentioned’ step of ‘why take chances’ when antimicrobials and antipyretics are readily available [62,63]. However, the prescription of antipyretics for diseases without antibiotics or antivirals available for use makes it a risky proposition.
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<thead>
<tr>
<th>S. No.</th>
<th>FACTS</th>
<th>MYTHS</th>
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<tbody>
<tr>
<td>1</td>
<td><em>Fever</em> will hurt their child.  <em>Fever</em> is a BAD sign.</td>
<td>In fact, <em>fever</em> is a common sign of infection and helps the body fight the infection. <em>Fever</em> is actually a good sign.</td>
<td>HEALTHY TIPS: <em>Fever</em> is a normal response to infection and helps the body fight the infection. <em>Fever</em> should not be suppressed except in cases of high fever (39°C or above) in young children.</td>
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<td>2</td>
<td>Most people are born with a fever.</td>
<td>Most people do not have a fever at birth. <em>Fever</em> is a sign of illness and is not normal.</td>
<td>INFANT CARE: <em>Fever</em> in infants is a common sign of illness and should be managed appropriately.</td>
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<td>3</td>
<td><em>Fever</em> is caused by the body's defenses against infection.</td>
<td><em>Fever</em> is caused by a rise in body temperature, not by the body's defenses against infection.</td>
<td>IMMUNE SYSTEM: <em>Fever</em> is a result of the body's inflammatory response and is not caused by the immune system directly.</td>
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<td>4</td>
<td><em>Fever</em> <strong>alone</strong> does not cause brain damage.</td>
<td><em>Fever</em> alone does not cause brain damage. However, in some cases, <em>fever</em> can be a sign of an underlying medical condition that requires treatment.</td>
<td>NEUROLOGY: <em>Fever</em> alone is not harmful to the brain, but other medical conditions may cause brain damage.</td>
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<td>5</td>
<td><em>Fever</em> is dangerous if it lasts for more than 2 weeks.</td>
<td><em>Fever</em> lasting for more than 2 weeks is cause for concern. If <em>fever</em> persists, consult a doctor.</td>
<td>PRIMARY CARE: <em>Fever</em> lasting for more than 2 weeks requires medical attention.</td>
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<td>6</td>
<td><em>Fever</em> is a sign that the body is fighting an infection.</td>
<td><em>Fever</em> is a sign that the body is trying to fight off an infection.</td>
<td>IMMUNE RESPONSE: <em>Fever</em> is a part of the body's immune response to fight off infection.</td>
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<td>7</td>
<td><em>Fever</em> is always a bad sign.</td>
<td><em>Fever</em> can be a sign of infection, but it can also be a sign of other medical conditions.</td>
<td>GENERAL MEDICINE: <em>Fever</em> can be a sign of many different medical conditions, not just infection.</td>
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<td>8</td>
<td><em>Fever</em> is a sign of infection.</td>
<td><em>Fever</em> can be a sign of infection, but it can also be a sign of other medical conditions.</td>
<td>PRIMARY CARE: <em>Fever</em> can indicate infection, but it may also be caused by other conditions.</td>
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<td>9</td>
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<td>GENERAL MEDICINE: <em>Fever</em> can be caused by many different conditions, not just infection.</td>
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<td>PRIMARY CARE: <em>Fever</em> can indicate infection, but it may also be caused by other conditions.</td>
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Note: Unless otherwise noted, *fever* refers to temperatures over 38°C (100.4°F). Other information provided is based on general medical guidelines and should be confirmed with a healthcare provider.
Secondly, fear of brain damage from high fever. The assumption is valid for hyperthermia but invalid for hyperpyrexia. The widely ingrained fear of brain damage in populations including the physicians perceptibly originates from the experience of seizures and writhing observed in 2-5% children <5 years of age around 39°C of pyrexia, largely ignoring the hard evidence that no one died or had brain damage as a result of normal course of pyrexia in almost last one century except an often-quoted anecdotal report from the 1950s [64]. One study estimated that up to 65% of physicians indicated that fever was harmful and 90% believed that febrile convulsions could cause brain damage [18,20].

Thirdly, in the clinical practice of a physician that currently largely relies on antibiotics, there appears to be "no evidence of ill effects" of fever reduction. Since the 1950s, progressively, most acute diseases got controlled by vaccines, availability and heavy reliance on the use of antibiotics/antivirals has made the dependence on fever for the resolution of common diseases largely redundant.

Fourthly, most of the dangerous pathogens with the potential to cause heavy mortality affecting humans to have a restrictive temperature around 39°C, so antipyresis ≥39°C had been mostly inconsequential in clinical practice possibly leading to progressive abandonment and loss from public memory. However, when caring for a disease whose causative pathogen has a restrictive temperature above 39°C, the effect of unnecessarily keeping the temperature down would range from inconsequential to disastrous to patients depending upon their genetic makeup, the virulence of the pathogen, prevailing protective immunity/ previous exposure, health status, age, comorbidities (see the section below), etc.

Fifthly, many times physicians tend to make the oversight of equating 'no evidence of harm' with 'evidence of no harm', in prescriptions though largely understandable in their practice and scope, these are fatal flaws in epidemic situations or when dealing with a new disease where nature of the pathogen is unknown and the therapeutic options available are of limited use. Under these circumstances, unnecessary fever reduction could help wider dissemination of unrelated pathogens/diseases as modeled for influenza [65] besides the obvious potential to increase the severity and mortality from pathogens for which suitable therapeutic agents (antibiotics, antivirals) are unavailable.

Sixthly, the underappreciation of the role of fever in disease resolution and perpetuation of myths among medical students and future practitioners are partially contributed by widely used medical textbooks' unqualified remarks without clarifying the context to students, e.g., Harrison’s Principles of Internal Medicine, [66, p.104] under “The Decision To Treat Fever” states “treatment of fever and its symptoms does no harm and does not slow the resolution of common viral and bacterial infections”. Many health care providers seem to err to equate ‘common’ with ‘all’ infections in their practice where effective therapeutics are “commonly” available. They also fail to miss the immediate context in which text would be applicable, i.e., “Most fevers are associated with self-limited infections, such as common viral diseases”. Generalization of something applicable to ‘common’ and ‘self-limiting diseases’ to ‘all diseases and conditions would have no consequences for ‘common diseases’ but their non-applicability to the treatment of those rare or novel diseases which do not have effective therapeutics available or the therapeutics is not being co-administered with antipyretics need to be always remembered or highlighted by the internal medicine textbooks as the fever has an unquestionable essential role in the resolution of diseases of undetermined origin for which therapeutics are limited [8].

4. WHY THE FEVER REDUCTION MAY BE MORE PROBLEMATIC TO SOME THAN OTHERS?

Suppression of initial low-grade fever that prepares host to minimize damage from a future surge of cytokines besides keeping the infection down, would logically increase the risk of being exposed to sudden overwhelming cytokine storm and experience adverse complications due to host bodies' non-preparedness, i.e., reduced capacity to resolve the ensuing damaging inflammation [4-6, 12, 13]. The induced normothermia by antipyretics or non-steroidal anti-inflammatory drugs (NSAID) has the capacity to blunt the HSR and essentially the capacity of the host to suitably respond to resolve inflammation triggered in the future to clear an infection. Fever-induced HSR response through HSF1 also controls the expression of proinflammatory cytokines including IL-6 which had been purported to be one of the culprits behind cytokine storm and increased mortality in diseases precipitating acute respiratory distress syndromes [1, 52, 53, 67-69].

The intact HSR circuitry along with HSF-1 that may be variously deficient in different backgrounds is required for generating appropriate cytokine responses, protection from inflammation [52-54] as well as IgG response [70]. It would be noteworthy that most conditions currently identified to be associated with higher mortality including COVID-19 as well as other respiratory tract viral infections are
also characterized by increased prevalence of reduced and/or defective HSR, e.g., aging [71], diabetes (both types 1 and 2) [72-73], acute respiratory distress syndrome [74], sepsis [75-76], renal failure [77], cigarette smoking [78], and chronic obstructive lung disease [79].

The induced normothermia by antipyretics usage has been shown to increase viral shedding and prolonging recovery [80-81] while associated with increased mortality from pneumonia [82-85] and reduced activity of antibiotics towards all tested pathogens to date [38,39]. The individuals unable to generate appropriate HSR would be logically more prone to adverse outcomes from unnecessary antipyresis during infections. Metanalysis of animal studies using animal models of influenza has indicated an increased pooled odds ratio of 1.34 for mortality with the antipyretics use [86]. Interestingly, hyperthermia preconditioning had been demonstrated to decrease mortality in models of various relevant conditions like sepsis [87], stroke [88], myocardial infarction [89], and hepatic ischemia [90]. It may be pertinent here to remind that before the discovery of antibiotics and their availability became widespread, the fever had remained a known beneficial ally for infectious disease resolution.

5. FEVER MANAGEMENT GUIDELINES

The current WHO guidelines for fever management explicitly stipulate that febrile illness from infections with a fever of >39°C and presented with defined acute complications or discomfort could be considered for fever reduction [29]. Furthermore, treatment should focus on the cause of fever rather than the fever itself which is known to have a beneficial role in infection resolution. Refer to Table 2a for an excerpt from guideline (Chapter 10: Management of Fever; p305) that restricts antipyresis to ‘children uncomfortable or distressed because of fever’ and mentions it may not benefit otherwise active and alert children besides compromising the immune defense, for general reflection. Furthermore, it should be noted that fever reduction for children is not part of ‘treatment’ but only part of ‘Supportive Care’ that too under ‘conditions’ explicitly causing distress and discomfort (‘If the child has a high fever (≥ 39 °C or ≥ 102.2 °F) that is causing distress or discomfort’) [29]. It attempts to explicitly underline the fact in uncertain terms that antipyretics do not provide benefit to infectious disease resolution but may be needed for other conditions including hyperthermia. It should be

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<th>TABLE 2a: FEVER REDUCTION GUIDELINES: WHO (2013)</th>
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<tr>
<td><strong>FEVER MANAGEMENT GUIDELINE</strong></td>
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<tr>
<td>FEVER IS NOT AN INDICATION FOR ANTIPYRETIC TREATMENT and MAY HELP THE IMMUNE SYSTEM.</td>
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<tr>
<td>DECREASED IMMUNITY</td>
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<tr>
<td>- Hypothermia within 24 hours of starting antipyretics is rare.</td>
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<tr>
<td>• Antipyretics should only be considered on the underlying cause of the fever and should be treated accordingly (see Chapter 6, p. 149).</td>
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<tr>
<td><strong>Antipyretic treatment</strong></td>
</tr>
<tr>
<td>Paracetamol</td>
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remembered that the guidelines of fever management are for the most vulnerable, i.e., ~5% of children < 5 years of age that are presented with complications and discomfort like neck stiffness, genetically predisposed seizures/convulsions [91], etc. The consideration of fever reduction should weigh the potential benefit being derived, as the most commonly observed seizures/convulsions though scary to watch are inconsequential to children's wellbeing [29, 49, 58, 91].

It may also be time to clearly identify the temperature range that is harmless in infections. Upwards revision of the temperature range for fever reduction consideration may also be undertaken. Soon after the publication of the first guideline by WHO in 2000 [92], a meta-analysis published in the bulletin of WHO [58] under section ‘Policy and Practice’ identified 41°C as “normal febrile range”, highlighted the continued practice of antipyresis as “parents and health professionals routinely treat fever in young children” despite the clear cut realizations of “fever helps survival during infection, and that antipyresis increases mortality” in many diseases and the “potential for hepatotoxicity” and “overdosage” [93-96]. It goes on to indicate “WHO recommendations for the management of fever in children include the use of paracetamol for children with fever of 39°C” despite “insufficient data, however, support this recommendation” and suggests “We recommend that health professionals should not be encouraged to give antipyretics routinely to febrile children. Treatment should only be given to those children in obvious discomfort or those with known painful conditions” [58]. Understandably, these recommendations with revised fever reduction guidelines and discourse were included in the revised guidelines for fever reduction by WHO in 2013 [29] (See Table 2a). However, the paranoia of bad fever still continues.

The thoroughly revised second edition of fever reduction guidelines from WHO published in 2013 [29] has been an excellent comprehensive endeavor to increase the understanding among healthcare providers and parents alike for adherence to appropriate usage and hence maximize the benefits. Despite the clear benefits of fever in infection resolution, WHO’s endeavors to spread awareness, which has become more important during the ongoing COVID-19 pandemic due to potential for abuse and its implication to different diseases including the COVID-19 itself, the confusion seems to be not abating. (See Table 2b for illustrations about the current guidelines from different national agencies around the world)

The existing guidelines for fever management in the public domain including those for COVID-19 [23-28] could be made more clarifying and explicit in stating the dangers of unnecessary fever reduction and underline the essentiality of fever in resolving diseases caused by pathogens for which antimicrobials are of little use. Additionally, the guidelines could consider including explanatory myth dispelling statements suitable for masses as shown by Seattle Children’s Hospital to allay the fear of hyperpyrexia and establish its positive benefits [58]. Previous publications of the guidelines meant to be manual for trained skilled healthcare personnel needs to be aligned with the understanding of the masses that now have greater access to these documents, so explicitness needs to be the cornerstone of these guidelines to drive the benefits without endangering the lives. The guidelines should consider explicitly identifying the small minority of people to seek immediate medical attention who are at a higher risk of complications from temperatures 39°C, e.g., pregnant women (3-4 weeks), frail who may not even attain 39°C, children < 5 years, individuals unable to generate HSR response, etc. (see sections above). In the age of increased access to information, these clarifications or explicitness in the guidelines is more of necessity than desire before placing them for public access by agencies to which people now actively look during the crises. In the current pandemic situation, inappropriate antipyresis could be contributing to the unspecified number of increased complications and mortality from different infectious diseases including the common seasonal viral diseases. Making guidelines immune to misinterpretation will have the potential to remove the fear of fever (pyrexia) from the masses and decrease the chances of complications and deaths in the vulnerable populations arising from inappropriate usage of fever-reducing agents.

Fever is an essential part of the acute-phase response that besides providing stimulus to the immune system and prepare for ensuing inflammatory response, helps contain the pathogen growth and promotes clearance through increased chemotaxis, phagocytosis, and reactive oxygen radical formation. It gains prominence for the resolution of diseases caused by pathogens with limited therapeutic options. The WHO Guidelines, 2013 had been explicit in identifying the benefits of fever and indicate when fever should be treated. During COVID-19, the presence of various guidelines in the public domain that are seemingly in conflict with WHO guidelines, as well as those of various national agencies may be unknowingly promoting the unnecessary antipyresis endangering public health. It may be in the general benefit of people at large that these conflicting guidelines must be
In the limited access of well qualified practitioners during the pandemic situation anti-inflammatory usage for any could essentially contribute to increased hospital admissions, complications and mortality by unspecified numbers.

The ‘NATIONAL MANAGEMENT GUIDELINES’ for COVID-19 disease in adults [28] states, ‘Fever helps your body fight infections by stimulating your immune system. Your body’s natural defense. By increasing body’s temperature, a fever makes it harder for the backward and viruses that cause infections to survive. Ibid states, ‘fever is a poor indication of the severity of any illness’ and goes on to suggest it to be ‘fit for treatment’ or the unqualified ‘uncomfortable feelings associated with fever never contraindicate treatment’.

The supposed guidance given latter for adults leaves much to individualistic interpretation whether to take anti-inflammatory or not, i.e.,

Most fevers will improve of their own accord in a few days. However, there are a number of things you can do to help:

1.  **Drink more fluids**...
2.  **Don’t over dress...**
3.  **Take a medicine that reduces fever such as paracetamol (unless you’re allergic or have been told by a healthcare professional you can’t take it).**

The link provided for ‘Ibuprofen use for whom who may to use it instead of paracetamol is even more confusing, i.e.,

**Ibuprofen [25]**

There’s no evidence to show a link between Ibuprofen or other non-steroidal anti-inflammatory medications (NSAIDs), anti-inflammatory or paracetamol can used to help with the symptoms of coronavirus if needed, unless your doctor has told you paracetamol or NSAIDs are suitable for you...

**The Coronavirus (COVID-19): Self-care advice** page goes on to advice as under:...
made explicitly for the guidance of general practitioner who clearly understands the meaning of ‘uncomfortable’ ‘fit for treatment’ or ‘fever that needs treatment’ or include their exact meaning/value for common users and state what are the ‘signs’ or ‘dangers’ when they may seek emergency medical attention.

7. CONCLUSION:

Further blurring of the WHO’s fever reduction guidelines reach and their adherence during the pandemic as a result of the appearance of more confusing COVID-19 guidelines from different agencies could negatively impact the health of populations, effectively denying them the benefits of ‘harmless fever’ or ‘pathogen-hyperpyrexia’ in eliminating the pathogens. There is a need to align widely accessible guidelines in line with emerging pathogens and therapy options available to us. The temperature upwards of 40 °C being permissive for certain pathogens, further complicates the situation in the ongoing COVID-19 pandemic. Excessive fever reduction regimens or promotion of such behaviors in masses to not allow the fever to do its job has a more damaging consequence for individuals than imagined for as the restrictive temperature for some strains of Influenzae, Measles and SARS-CoV-2’s is around 40°C. The actual contribution of the unnecessary antipyresis to the increased transmission rate, complications, hospitalization, and deaths from different diseases would only become known in the future through retrospective observational studies. Nevertheless, the existing accumulated evidence and understanding of the beneficial role of fever during infections in the elimination of pathogens without effective therapeutics would favor the timely undertaking of steps by various health agencies to limit the consequences of confusing fever reduction guidelines in public space to effectively alleviate the pressure on overstretched medical infrastructure and possible impact on masses’ health and wellbeing during the current COVID-19 pandemic.

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