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

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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.

Key Words: *Beneficial Fever, Infections, WHO, Fever Management, Myths, Guidelines, Antipyresis, Mortality, Heat Shock, Inflammation, Respiratory diseases, ARDS, COVID-19, Paracetamol*

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

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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, orchestra 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 concomitant 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 [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.

TABLE 1. MYTHS AND FACTS ABOUT INFECTION CAUSED FEVER (PYREXIA)

S.No.	MYTHS [58]	FACTS [58]	COMMENTS
1.	* "***fever will hurt their child***" *Or them (FEVER PHOBIA)*	*"In fact, fevers are harmless and often helpful."* [*Still, the **Most Pervasive Fear** Among **Pediatricians (65%), Nursing Staff (70%),** and **Adults (95%) for indicating aggressive fever reduction treatment**] **Myth originated from the observations in uncontrolled fever (Thermia)*	**Myth NOT** applicable to brain-controlled harmless fever '*Pyrexia*' – for infection control. **Fevers are most helpful for bacterial & viral infections without therapeutics.**
2.	***"All fevers are bad for children"***	*"Fevers turn on the body's immune system. They help the body fight infection.* ***Normal fevers between 100° and 104° F (37.8° - 40° C) are good for sick children.***"	***Note the 40°C** is more than **39° C** limit currently erroneously suggested by many for COVID-19 and other viral fever patients who are mostly adults.*
3.	**"Fevers above 104° F (40° C) are dangerous. They can cause brain damage."**	***"Fevers with infections don't cause brain damage. Only temperatures above 108° F (42° C) can cause brain damage. It's very rare for the body temperature to climb this high.*** *It only happens if the air temperature is very high. An example is a child left in a closed car during hot weather."*	**Fevers don't cause brain damage.** **Fevers around 108F is a rarity but still harmless** and can be observed in hot weather or cases when infection could not get controlled at lower temperatures observed previously.
4.	*"**Without treatment, fevers will keep going higher**."*	• ***"Wrong**, because the **brain knows when the body is too hot**.* • Most fevers from infection don't go above 103° or 104° F (39.5°- 40°C). • They rarely go to 105° or 106° F (40.6° or 41.1° C). ***While these are "high" fevers, they also are harmless ones**."*	• In infections, the level of fever **(Pyrexia) is actively controlled** by brain, **unlike hyperthermia**. • Generally bacterial and viral. • Mostly viral
5.	"With treatment, fevers should come down to normal."	"With treatment, most fevers come down 2° or 3° F (1° or 1.5° C)"	**Unnecessary dosage or increase in dosage is futile for *Pyrexia* causing hepatotoxicity [3,49,93-96]**. Frequent dosage needed to manage Hyperthermia.
6.	"Anyone can have a seizure triggered by fever."	"Only 4% of children can have a seizure with fever."	Harmless febrile seizures occur in 3-5% of genetically susceptible children [91].
7.	"Seizures with fever are harmful."	"These seizures are scary to watch, but they stop within 5 minutes. **They don't cause any permanent harm.** They don't increase the risk for speech delays, learning problems, or seizures without fever."	**Seizures are harmless** and don't cause any permanent brain damage.
8.	"All fevers need to be treated with fever medicine."	***"Fevers only need to be treated if they cause discomfort*** (makes your child feel bad). Most fevers don't cause discomfort until they go above 102° or 103° F (39° or 39.5° C**)."**	**For adults the threshold for discomfort is generally around 41°C or higher**
9.	"The exact number of the temperature is very important."	"How your child looks and acts is what's important. The exact number of the temperature is not."	It applies to adults as well. If it feels very sick (discomfort), the cause is more likely to be serious & needs medical attention.
10.	"Oral temperatures between 98.7° and 100° F (37.1° to 37.8° C) are low-grade fevers."	"These temperatures are normal. The body's normal temperature changes throughout the day. It peaks in the late afternoon and evening. A true low-grade fever is 100° F to 102° F (37.8° - 39° C)."	Body temperatures vary by age, sex, day time, physical activity etc. Fever ≥39° C may precipitate inconsequential seizures in <5% children.
	"SUMMARY. Keep in mind that fever is fighting off your child's infection. Fever is one of the good guys." [PYREXIA IS ESSENTIALLY A BRAIN-CONTROLLED HARMLESS MECHANISM TO FIGHT OFF INFECTIONS FOR WHICH WE MAY NOT HAVE OTHER THERAPEUTIC OPTIONS AVAILABLE. Incremental increase in fever over days is part of normal immune response and should not be reduced unless causing 'discomfort'. Usually, fever little over 39 ◦C clears most common infections, whereas temperature > 39 ◦C may be needed for other pathogens requiring higher restrictive temperatures including the novel ones, *e.g.*, strains of influenzae, measles, SARS-CoVs]		**Additionally, fevers at** • ~39 °C generates the heat shock response to prepare the host deal with higher temperature later. • .~ 40◦C enhances interferons production if viruses are still around (permissive) and prepares for safer inflammation resolution. **Reduction of fever in diseases** with limited antibiotics/ antivirals availability **increases the chances of complications and mortality**

Note: ***Unless indicated otherwise 'fever' refers to temperature increase caused by acute infection or 'Pyrexia'.*** The information in quotes " ..." is taken verbatim from Seattle Children's hospital web page (updated as on 13 May 2021) [58]. Other information is provided to further clarify the meaning. The temperatures are indicative not absolute and are closest approximate. It may be little different for each individual as everyone is unique.

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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 a 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

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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

TABLE 2a: FEVER REDUCTION GUIDELINES: WHO (2013)

FEVER MANAGEMENT GUIDELINE	COMMENTS
WHO GUIDELINES, 2013 (in "quotes") [29] "***10.3 Management of fever*** The temperatures given in these guidelines are rectal temperatures, unless otherwise stated. Oral and axillary temperatures are lower by approximately 0.5 °C and 0.8 °C, respectively. **FEVER** is **NOT** ***an indication for antibiotic treatment*** and **MAY HELP THE IMMUNE DEFENCE AGAINST INFECTION**. High fever (> 39 °C or > 102.2 °F) can have harmful effects, such as: • reducing the appetite • making the child irritable • precipitating convulsions in some children aged 6 months to 5 years • increasing oxygen consumption (e.g. in a child with very severe pneumonia, heart failure or meningitis). All children with fever should be examined for signs and symptoms that indicate the **underlying cause of the fever, and should be treated accordingly** (see Chapter 6, p. 149). ***Antipyretic treatment*** ***Paracetamol*** Treatment with oral paracetamol should be restricted to children aged ≥ 2 months who have a fever of ≥ 39 °C (≥ 102.2 °F) **AND** are uncomfortable or distressed because of the high fever. **CHILDREN WHO ARE ALERT AND ACTIVE ARE UNLIKELY TO BENEFIT** from paracetamol."	• The section deals with both *pyrexia* **(brain-regulated during infections)** and *thermia* (unregulated, e.g., heat shock) • In pyrexia, the body temperature is increased in response to pathogen **to prepare fight off an infection - including incapacitating the pathogen at restrictive temperature**. Temperatures can rarely increase upto 42°C if risk remains. • **FEVER IS GOOD FOR IMMUNE SYSTEM.** • **Unregulated increase in temperature (thermia) > 39 °C** (103-105F) when body is not prepared for the shock, **can be lethal** and **subject to emergency fever reduction,** WHEREAS ***Hyperpyrexia upto 108F*** *can be* ***well tolerated*** *and* ***remains important mechanism for pathogen control*** (SEE TABLE 1. for facts and myths about pyrexia) • *Convulsions* occur in *genetically predisposed* children (<5%) but has not *harmed a kid in any way* [91]. • ***Asks for the treatment of the 'cause'. Chapter 6, p. 149 deals with antibiotics choice*** making the guidelines more aligned to bacterial diseases. ***At higher temperature antibiotics efficiency increase, so antibiotics administration without antipyretics would be more efficient.*** • The fever of ≥ 39 °C treatment should be only considered when the defined 'uncomfortable or distressed' conditions are present. • Antibiotics coadministration with antipyretics for most of the common bacterial diseases would not affect disease resolution. However, **REDUCING FEVER in VIRAL DISEASES with causative agents having ≥39°C restrictive temperature**, e.g., strains of Influenzae, Measles, SARS-CoVs, **the effects can vary from inconsequential to severe (death)** depending upon the presence of preexisting immunity, previous heat shock response/temperature and ability to handle cytokine storm

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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 metanalysis 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)

6. *WHAT MORE COULD BE DONE?*

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

TABLE 2b: FEVER REDUCTION GUIDELINES: OTHERS DURING COVID-19 PANDEMIC	
FEVER MANAGEMENT GUIDELINES	**COMMENTS**
NATIONAL HEALTH SERVICE. FEVER IN ADULTS. 2020 [23]. The page, includes even reference to COVID-19 management, states "***Fever helps your body fight infections by stimulating your immune system: your body's natural defense. By increasing your body's temperature, a fever makes it harder for the bacteria and viruses that cause infections to survive.***" **BUT** considers "***fever/high temperature (37.8C or greater)***" and goes on to suggest it to be "***fit for treatment***" on the unqualified ***"uncomfortable feelings associated with a fever***". The supposed guidance given latter for adults leaves much to individuals' interpretation whether to take antipyretics or not, i.e., **"Treating a fever** Most fevers will improve of their own accord in a few days. However, there are a number of things you can do to help the **uncomfortable feelings** associated with a fever. 1. Don't over dress.... 2. Drink more fluids, ... 3. **Take a medicine that reduces fever such as paracetamol (unless you're allergic or have been told by a healthcare professional that you can't take it)**." The link provided for 'ibuprofen' use for whom who may like 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), and catching or making coronavirus worse***. Paracetamol or ibuprofen can be used to help with the symptoms of coronavirus if needed, unless your doctor has told you paracetamol or NSAIDs are not suitable for you…" The '**Coronavirus (COVID-19): Self-care advice**' page[25b] goes on to advice as under: **"Treating a fever at home** It's safe to treat most fevers at home. However, you may be at risk of becoming dehydrated. **Do** ✓ wear loose, comfortable clothing .. ✓ drink more fluids … ✓ monitor your pee colour … ✓ **take paracetamol if you have a temperature** – always follow the manufacturer's instructions…"	• **It contradicts who guidelines for fever reduction** in infectious disease, that specifically asks for cause treatment > 39 °C not just any fever in any infection that too just > 37.8 °C. • **The "uncomfortable feeling" in the guidelines alluding to explicit definition of 'uncomfortable' needing treatment in WHO guidelines (2013) for children that is known to physicians could create confusion in general public promoting unnecessary medication.** • **The unqualified 'uncomfortable feelings' is open to conjecture by masses when considering what is fit for treatment.** In the limited access of well qualified practitioners during the pandemic situation antipyretics usage for any fever could essentially contribute to increased hospital visits, admissions, complications and mortality by unspecified numbers. The '**No evidence to show a link**' or the 'Lack of evidence' is **NOT** equivalent to the '**Evidence of no link**' or the 'Evidence of no effect'. The **latter should be relied in practice** not the former. ***Usually in situations of 'Lack of Evidence', the 'theoretical considerations prevail'***. Antipyretics alone are known to prolong recovery and increased transmission of respiratory tract infections esp. for microbes with no therapeutic agent available. (see main text for examples) **STICK TO WHO GUIDELINES, 2013 [29]**
INDIAN COUNCIL OF MEDICAL RESEARCH, INDIA. [31] For acute fever management it states: **"Management of Acute Fever. Chapter 2** **2.1.7 Principles of empiric therapy** a. **Supportive: Acetaminophen 650 mg every 6 hours** round the clock is advisable, accompanied by tepid sponging **for fever >103 F**. Replace fluid and electrolytes as required. b. **No antibiotics are required for the majority of patients** with **acute febrile illness** without an obvious clinical diagnosis." _____ **The FAQ for COVID-19 [28] states**: "**What can I take (for) pain or fever**? ✓ …**Paracetamol** is one of the safest pain killers to use if needed."	It considers 103 F as acute illness and recommends giving antipyretics, even acknowledging antibiotics may be of no use. It defeats the purpose of WHO's recommendations where the cause is to be treated not the fever *per se*. **STICK TO WHO GUIDELINES, 2013 [29]**

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CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC), USA [24] "CDC considers a person to have a fever when he or she has a measured temperature of 100.4° F (38° C) or greater, or feels warm to the touch, or gives a history of feeling feverish"	**CDC at multiple places clarifies that it considers** 100.4° F (38° C) or above a fever for diseases.
NATIONAL INSTITUTES OF HEALTH (NIH), USA [26] COVID-19 treatment guidelines (Last Updated: April 21, 2021) do not specifically elaborates on fever management. However, '**Outpatient Management of Acute COVID-19**' under '**Symptom Management**' p. 41 rather cursorily advises: "Symptomatic treatment includes using **over-the-counter antipyretics, analgesics, and antitussives for fever, headache, myalgias, and cough**."	**May be appropriate for promoting people to seek medical advice but cursory remarks could promote inappropriate intake.** The widespread availability and use of antipyretics can increase complications and mortality from seasonal viral diseases including COVID-19. **Specific recommendation cautioning against antipyresis would have been better as risk of overuse has increased during covid-19 pandemic.** **STICK TO WHO GUIDELINES, 2013 [29]**
Note: The guidelines floating around for COVID-19 are for qualified physicians for their discretion. These guidelines would need to go extra mile to be in the public domain. ***These guidelines need to align with WHO guidelines on fever management. Extra caution is desired when in public domain*** as any unqualified remark open to alternative interpretation may cause more harm than good to the heath of common masses. It would have potential to result in health issues, extra hospital visits, complications and deaths putting pressure on already stretched medical system of most countries during COVID-19 pandemic.	

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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