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EDITORIAL

Role of fever and ambient temperature in COVID-19

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Fever is one of the most preserved evolutionary response over 600 million years to infections in invertebrates, amphibians, reptiles, fish, and mammals [1]. It is a complex cytokine-mediated physiological response that stimulates both the innate and adaptive arms of immunity involving adrenergic stimulation pathways [2]. Guan et al. reported fever in 42.8% at the time of admission and 88.7% of the COVID-19 patients at the time of hospitalization [3]. This suggests although fever is the most common symptom in COVID-19 patients, the absence of fever at the time of initial screening does not exclude COVID-19. Chen et al. reported the median duration of fever in COVID-19 patients; 10 days (95 confidential intervals [CIs]: 8–11 days. Resolution of fever coincided with PCR negativity of upper respiratory sample; 11 days (95 CIs: 10–12 days), radiological and clinical recovery. Those who received intensive critical care (ICU) services were more likely to have a longer duration of fever than the COVID-19 patients who did not receive ICU care (31 days vs. 9 days after onset of symptoms, respectively, $P < 0.0001$) [4]. Although the median duration of fever in SARS-CoV-1 patients was comparable to fever duration in COVID-19 (11.4 ± 6.8 days) [5], the biphasic pattern of fever – characterized by the recurrence of fever in the second week – was only noted in SARS-CoV-1 pneumonia, in contrast to the COVID-19 [4,6]. The duration of fever noted in MERS and other corona viruses was shorter; MERS median duration 8 days (range, 0–54 days) [7,8].

Bats are known to have a vast reservoir of corona-viruses, and COVID-19 is likely to have its origin in bats [9]. During the flight, the bats increase the metabolic rate by 15–16 fold, which is accompanied by high fevers. Daily high temperatures, in the setting of high metabolic rates, attained during the flight activates the immunity and has been proposed as a mechanism through which the bats can harbor pathogenic viruses [10]. The effect of fever or the ambient temperature has been studied previously on other viruses. In the experimental mammalian models, the higher ambient temperature has been shown to enhance resistance against the herpes simplex virus [11]), poliovirus [12], Coxsackie B virus [13], rabies virus [14], influenza virus [15], and gastroenteritis virus [16](Table 1). A population-based study estimated that the use of antipyretic drugs to suppress fever would increase the cases and mortality in influenza [17]. In a randomized controlled trial on 56 volunteers infected with the Rhinovirus, the use of aspirin and acetaminophen was associated with increased nasal symptoms and decreased neutralizing antibody response [18]. In another randomized clinical trial on 72 children, the use of acetaminophen was associated with an increased duration of scabbing in childhood varicella infection [19].

The role of fever in COVID-19 has not been studied in large studies. In our review of the literature, only two studies have related the ambient temperature or fever to the outcomes of the COVID-19 patients. In a non-peer-reviewed observational study, the high ambient temperature was correlated with decreased mortality in COVID-19 patients in Wuhan and Hubei provinces; however, no data on the patient's temperature was available in the study which limits the derivation of any conclusion from the study [20]. Regular high fever in COVID-19 is considered to be an indicator of severe infection. In a study of 201 patients in Wuhan, high fever (>39°C) was associated with a higher likelihood of acute respiratory distress syndrome (HR, 1.77; 95% CI, 1.11–2.84), and lower risk of mortality (HR, 0.41; 95% CI, 0.21–0.82) [21]. The preliminary results may point toward an association of improved prognosis in terms of mortality in severe COVID-19 patients with fever. The study was not geared toward identifying the impact of fever or antipyretics in COVID-19 patients, however, it provides a glimpse into the possible impact of fever on COVID-19 prognosis.

The initial presentation of the fever in COVID-19 in the first week, during the viral phase of the illness, is likely a manifestation of the body's immune response to the viral replication to augment immunity. However, if the viral infection does not resolve in due course, the disease process is complicated by the viral triggered state of dysregulated inflammation described as cytokine storm or secondary hemophagolymphocytosis, heralded by unremitting fever [22]. In such cases where extreme inflammation sets in, fever can be counterproductive. Fever may promote further inflammation and further immune activation may not be beneficial at this stage. The role of immunity in COVID-19 in the early and later phase of the illness can be gauged from the recent trial [23]. Immunosuppression using dexamethasone improved mortality in the mechanically

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Table 1. Summary of the clinical studies describing the effect of temperature on viruses.

Intervention/study type	Results
Animal or cell culture Studies	
Herpes Simplex Virus (*Herpesviridae*) inoculation in mice	Mice maintained at 37°C had lower mortality (93% vs. 54%) compared to mice kept at 24°C due to lower virus concentration of virus in the brain
Poliovirus (*Picornaviridae*) development in cell cultures	The yield of the Poliovirus is 250 times smaller than at 37°C
Mice infected with Coxsackievirus (*Picornaviridae*)	Viral replication suppressed and eliminated at 36°C than at 4°C
Intraperitoneal inoculum of Rabies virus (*Rhabdoviridae*) in mice	Decreased mortality (18% vs. 58%) when kept at 35°C ambient temperature than at 21°C
Gastroenteritis virus in newborn piglets	No virus detected in piglets maintained at 35–37.5°C vs. high viral levels detected at 8–12°C
Ferrets infected with influenza virus (*Orthomyxoviridae*)	Correlation reported between increased temperature and number of inflammatory cells and decreased viral titer in nasal washes.
Human Clinical Studies	
Children with chickenpox (*Herpesviridae*); 37 received acetaminophen vs. 31 received placebo	Time to crusting was lesser in placebo vs. acetaminophen group 5.6 days (SD 2.5) versus 6.7 days (SD 2.3), $p < 0.05$
Population study estimation based on published studies on influenza (*Orthomyxoviridae*)	Fever increases the expected number of influenza cases and deaths in the US; for pandemic influenza, the estimated increase is 1% (95% CI: 0.0–2.7%), and for seasonal influenza, the estimated increase is 5% (95% CI 0.2–12.1%)
Randomized Controlled trial of 56 patients infected with Rhinovirus (*Picornaviridae*) randomized to receive acetaminophen, aspirin, ibuprofen or placebo	Use of aspirin and acetaminophen was associated with suppression of serum neutralizing antibody response and increased nasal symptoms vs. placebo ($p < 0.05$)
Non-Peer reviewed observational study in COVID-19 (*Coronaviridae*) patients	High ambient temperature correlated with decreased mortality in COVID-19 patients both in Wuhan ($r = -0.441$, $P = 0.012$) and Hubei ($r = -0.440$, $P = 0.012$)
Retrospective COVID-19 cohort study of 201 patients from Wuhan	High fever (≥39°C) was associated with higher likelihood of ARDS development (HR, 1.77; 95% CI, 1.11–2.84) and lower likelihood of death (HR, 0.41; 95% CI, 0.21–0.82)

ventilated COVID-19 patients (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; $p < 0.001$ and a trend toward increased mortality were observed in patients with mild disease who did not need any respiratory support (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; $p = 0.14$). Likewise, fever may also have a differential impact in relation to the prognosis during the viral and inflammatory stage of the disease, mimicking the relationship of different stages of immunity to the outcomes. This may have led to the variable results in the human clinical trials in septic patients. The human clinical trials elucidating the role of fever in critically ill septic patients with bacterial infection have resulted in clinical equipoise. A randomized clinical trial on 200 patients, attributed the use of external cooling in septic shock patients to the reduction in vasopressor use and decreased early 14-day mortality. The mortality reduction, however, was not significant at ICU or hospital discharge. Furthermore, the trial was not designed or powered to conclude about mortality [24]. In the largest 'HEAT'randomized clinical trial on 700 patients, the early use of acetaminophen for fever in critically ill patients with suspected infections did not affect the number of ICU-free days. The secondary outcomes, which included death and the hospital length of stay, were not significantly different between the two groups [25].

Keeping into perspective the evolutionary, physiological evidence, and in the light of the aforementioned animal and human studies on the viral infection (Table 1), there is a need for further clinical studies to clarify the prognostic significance of fever in the viral and inflammatory phase, and the use of antipyretics in different stages of COVID-19 infection, and determine their impact on viral shedding and the duration of symptoms. The effect of ambient temperature on COVID-19 also needs to be studied further.

Expert opinion

The bats have developed immunity against coronaviruses by raising body temperature in-flight. The prognostic implications of fever and ambient temperature in COVID-19 need to be explored. Since the impact of fever may vary in the viral and inflammatory phases of COVID-19, studies in the future should take this into consideration.

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•• **Characteristics of fever in COVID-19 patients.**

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• **The largest clinical trial concluded that early use of acetaminophen for fever in critically ill septic patients did not change outcomes.**