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 biphase 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 unrelenting 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
Table 1. Summary of the clinical studies describing the effect of temperature on virus.

| Study Type | Intervention | Study Design | Population | Outcome |
|------------|-------------|--------------|------------|---------|
| Randomized Controlled Trial | 19 patients infected with RSV (randomized) | Use of ibuprofen vs. acetaminophen | Decreased mortality (18% vs. 58%) and for seasonal influenza, the estimated increase 6.5% (95% CI 0.2-12.1%) | |
| Retrospective Cohort Study | 201 patients from Wuhan | High fever (≥39°C) was associated with higher likelihood of ARDS development (HR 1.7, 95% CI 1.1-2.84) and lower likelihood of death (HR 0.41, 95% CI 0.2-0.83) | |
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