# Hyperpyrexia in a Patient with COVID-19

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## Abstract

**The COVID- 19 pandemic has been a significant burden on global health care systems leading to over 5 million deaths worldwide and notable increase in morbidity. The second wave of the pandemic in India posed new challenges in the form of increased cases of severe disease, high case loads, younger patients and atypical presentations. It is critical to keep an eye on these unusual cases in order to increase the awareness about varied presentation of this relatively new disease.**

**Keywords:** Hyperpyrexia, COVID 19, hypothalamus

## Introduction

The body temperature is regulated by the thermoregulatory centre located in the anterior hypothalamus. At a temperature of 37°C the human body functions optimally. The normothermia is steadily maintained by the hypothalamic thermoregulatory center which balances the excessive heat production with heat dissipation from skin and lungs.[1] Hyperpyrexia is the term used to describe a core body temperature of more than 41.5°C. It is usually found in patients undertaking excessive exercise in high ambient temperatures and those with neurological conditions & severe infections.[2] In COVID-19 patients, extremely high fever can lead to multi-organ failure and is a high predictor of mortality.[3]

Herein, we are presenting a case with hyperpyrexia as a rare and possible complication of COVID-19.

## Case Report

A 32-year-old female was brought to the Emergency Department (ED) with four days history of cough, high-grade fever and shortness of breath. The symptoms had progressively worsened over the last 24–48 hours. On presentation, she had tachycardia and hypoxaemia with oxygen saturations of 67% on room air which improved to 92% on 15 L/min of oxygen by reservoir bag. Her initial body surface temperature was 38°C. Her blood sugar level was 322 mg/dL and point of care blood ketone was negative. She was not a known diabetic and this was the first elevated blood sugar noted. She was hemodynamically stable, conscious and oriented to time place and person. She was in respiratory distress with the use of accessory muscles of respiration. Blood gas was suggestive of type I respiratory failure. Supportive care was initiated and all investigations, including investigations to evaluate for cause of fever, metabolic work-up and inflammatory markers, were sent. Throat and nasal swab for COVID-19 was also sent.

Computed Tomography (CT) of the chest revealed extensive multifocal peripheral as well as centrally located confluent ground-glass opacities with intralobu-

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lar septal thickening in bilateral lung parenchyma with a CT Severity score of 23/25.

She was started on intravenous fluids, subcutaneous low molecular weight heparin and intravenous methyl prednisolone (40 mg) as per the advisory of Ministry of Health and Family Welfare for management of severe COVID pneumonia. Her swab was detected positive for SARS-CoV-2 (COVID-19).

The initial lab work revealed high levels of D dimer, Interleukin-6, LDH and C-Reactive protein. The total leucocyte counts, coagulation and metabolic profile was within normal limits. In view of severe disease convalescent plasma and remdesevir were started. Insulin infusion and strict blood sugar monitoring was instituted. In view of increased work of breathing she was switched to non-invasive ventilation with pressure support settings. During the course of her admission she developed hypotension, central venous access was taken through right internal jugular vein and vasopressors were initiated in addition to ongoing fluid hydration. Foley's catheterisation was done and strict input output charting was done.

On Day 2 owing to persistent shock, raised inflammatory markers and worsening hypoxemia intravenous Tocilizumab 400 mg single dose was given to the patient. Elective Mechanical ventilation was done as a rapid sequence intubation. Standard lung protective ventilator strategies were used along with use of sedation / paralysis to avoid dys-synchrony. Proning was not feasible due to high BMI (42 Kg/m$^2$) of this patient, hence frequent lateral positioning was done.

The next two days, the patient remained hypoxic and had a P/F ratio of less than 100 inspite of above measures and required 100% Fio2 on ventilator. The trend of PaO2 and lactic acidosis are given in Figure 1.

Blood culture grew staphylococcus and antibiotics were started as per sensitivity. The patient had frequent fever spikes, fluctuations in blood sugar and postassium levels, which were managed by insulin and potassium infusions.

On Day 4 of the illness,the inflammatory markers persisted to have a rising trend. The trend of inflammatory markers is shown in Figure 2. Temperature of 41.6°C was noted. In addition to intravenous antipyretics, additional measures like intravenous cold saline gastric lavage, tepid sponging, ice packs in axilla were instituted to bring down the body surface temperature. However, the temperature remained above 41.6°C with highest recording being 42°C. The temperature did not respond to antipyretics which suggested central cause of hyperpyrexia. Continuous core temperature monitoring was done through a rectal probe. Creatinine phosphokinase (CK) was markedly elevated. The patient suffered a cardiac arrest within six hours of developing hyperpyrexia as she entered Day 5 of hospitalisation and return of spontaneous circulation could not be achieved in spite of all measures as per advanced cardiac life support protocol. Cause of Death was declared as Severe acute respiratory distress syndrome, hyperpyrexia and septic shock in a case of COVID-19 Pneumonia with Diabetes.

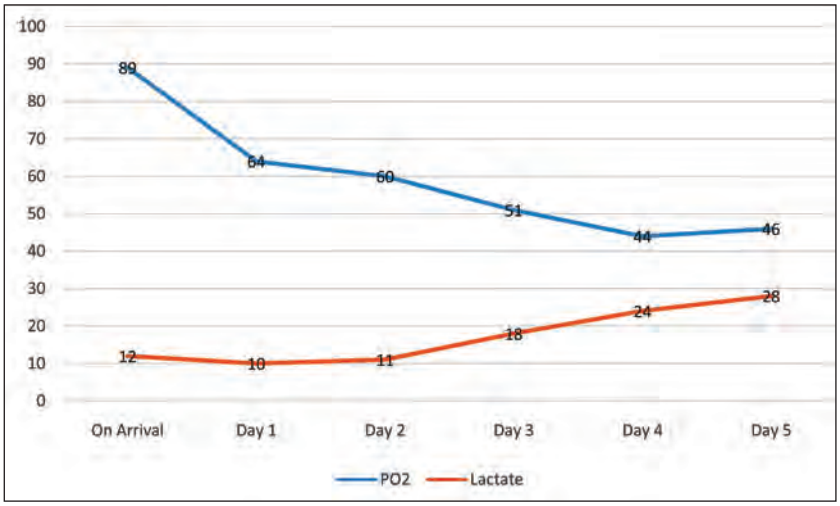


**Figure 1: Trend of hypoxemia and lactic acidosis**

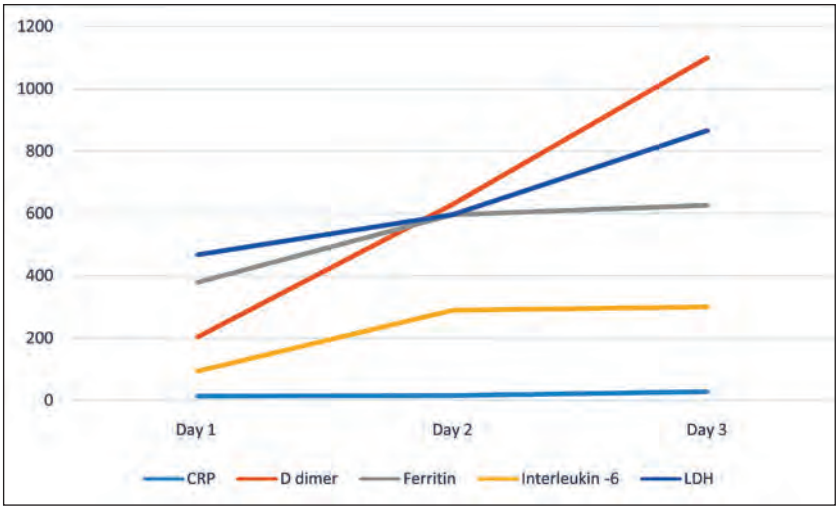


**Figure 2: Trend of inflammatory markers**

The possible causes of hyperpyrexia in this patient could be COVID-19 or gram positive sepsis. However, as the patient failed to respond to sensitive antibiotics with no improvement in fever and had no response to antipyretics, suggestive of a central cause, possibility of COVID-19 causing hyperpyrexia is highly considered.

## Discussion

The pathology of hyperpyrexia is centrally regulated, resulting in a hypothalamic reset to a higher level. Extremely high body temperature may lead to extensive cellular damage and eventual death, making it a medical emergency mandating immediate implementation of active and passive cooling methods.[3,4] Effective techniques for reducing core temperature include cold-water immersion or evaporative techniques. The evoparative techniques are more widely available.[5]

Our patient had hyperpyrexia and increased acute inflammatory markers, especially IL-6 which is a pro-inflammatory cytokine.[6,7] In severe COVID-19 cases, greater serum level of proinflammatory cytokines (TNF-$\alpha$, IL-1, and IL-6) and chemokines have been observed.[7,8] Raised IL6 has also been noted in malaria patients with hyperpyrexia.[9] This may suggest role of IL-6 in COVID 19 related hyperpyrexia as well. Suwanwongse *et al*[10] proposed three possible pathophysiologies of hyperpyrexia in COVID-19 patients: (i) direct brain injury from SARS-CoV-2, (ii) vascular thrombosis and (iii) persistent immune dysfunction and dysregulation of cytokines. SARS-CoV-2 invasion to the brain can damage the hypothalamic-thermoregulatory pathway and also increase the pro-inflammatory and pyrogenic cytokines.[10,11] In our case, an extreme rise in body temperature and non responsiveness to treatment support the hypothesis that direct brain injury from SARS CoV-2 may have lead to hyperpyrexia in our patient.

All cases of hyperpyrexia described in previous series also succumbed to their illness like our patient suggesting hyperpyrexia in COVID-19 is an indicator of poor prognosis.

There is a need to define the primary cause that leads to hyperpyrexia in COVID-19 patients to decide the definitive line of treatment and improve outcomes in this subset.

## Conclusion

COVID-19 is an evolving pandemic that has had global consequences over last 2 years. Identification of uncommon symptoms is necessary as it can help create awareness and sensitize healthcare providers regarding early identification and management. It will also lead to further research onto the yet unexplored aspects of this disease.

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