What do you do when you get the flu and have a fever? Most of us take an antipyretic such as acetaminophen, ibuprofen, or aspirin. Fever is the body's reaction to infection, and it is not without purpose, and the use of antipyretic medications is not without risk. The use of an antipyretic in patients with viral influenza is associated with a 5% increase in mortality,[1] and in critically ill, septic patients, the use of an antipyretic may also decrease survival.[2]

Fever helps fight infections by activating immune cells and increasing WBC population growth, survival, and migration to the site of infection. An elevated environmental temperature even helps cold-blooded lizards that cannot mount a fever response fight infections more efficiently.[3] A desert iguana was found to have a 75% decrease in survival from infection if prevented from raising its core temperature 2° Celsius through muscular activity.

Fever activates the immune system. White blood cells are more active and efficient at fever temperatures. In warm-blooded mammals, white blood cells have increased activity at fever temperatures of 39.5° C. The poliovirus replication rate in cells is 200 times lower with a fever of 40 to 41° C than at normal body temperature.[4]

Thus, fever is a physiologic function that helps fight viral and bacterial infection. Fever increases the susceptibility of infected cells by bacteria and viruses to pyroptosis. Fever actually helps kill infected cells.

Exposure to mild hyperthermia, 40° C (104° F), a level that normally does not cause injury, creates stress that that actually induces thermotolerance and protects the cell from endoplasmic reticulum (ER) stress-induced apoptosis.[5] These moderate, fever level temperatures appear to spare normal cells from damage. Fever, by design, promotes apoptosis of cells containing aberrant proteins, RNA, and DNA from viruses and bacteria, while sparing normal cells.

Between 42° C (107.6° F) and 43° C (109.4° F) cells die orderly, programmed cell deaths.[6] Thus these temperatures can kill compromised cells with severe oxidative damage or DNA damage that has halted cell reproduction. At 45° C (113° F), cells die a necrotic death. They die from a lethal systemic collapse of functions. This is not a programmed death, and it kills all cells, not just cancer cells. Thus, during infection, the temperature should not be allowed to rise above kept below 42° C (107.6° F), and better should be kept below 40.5° C (104.9° F) especially in the elderly and those with chronic disease. These people are likely to have cells in vital organs susceptible to programmed cell death at these temperatures.

While fever can help fight infection, it needs to be recognized that fevers cause in increase in metabolic demands and may worsen ischemia to stressed organs, such as the heart and brain. For every 1° C increase in body temperature, the cells increase their metabolism by 10 to 12%.[7]

This means that for every 1° C increase in temperature, the bodies demand for oxygen also increases by by 10 to 12 percent. A rise in temperature from a normal 37° C to a fever of 40° C can therefore increase oxygen demand by a third! Thus, fever can add to the risk of hypoxia during pneumonia. During pneumonia, myocardial ischemia, stroke, or other ischemic condition, fever should be treated. Fever also increases the requirements for fluids and caloric energy needs, so these needs also need to be accommodated.

Caution:

A recently published letter in Lancet Respiratory Medicine[8] points out that ibuprofen (Motrin, Advil) increases the expression of ACE2, the protein that SARS-CoV-2 binds to; thus, use of this or similar medications (NSAIDs) may increase the risk of lung damage in COVID-19. Other NSAIDs likely to act by this mechanism include: sulindac sulfide> diclofenac > indomethacin > ibuprofen, as a result of their activation of PPARγ.[9] Acetaminophen does not pose this risk.

Acetaminophen (Tylenol, paracetamol) is not an NSAID and does not increase ACE2 expression. If an NSAID type of medications required, celecobix (Celebrex) does not appear to cause PPARγ activation and may decrease macrophage activity,[10] and thus limit damage caused by cytokine storm, and thus, while not recommended are likely a safer choice during COVID infection.

(Sections of this note were adapted from "Unraveling Cancer" also written by this writer)

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[1] Fever and the thermal regulation of immunity: the immune system feels the heat. Evans SS, Repasky EA, Fisher DT. Nat Rev Immunol. 2015 Jun;15(6):335-49. PMID:25976513

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