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The Effect of Body Temperature Changes and Antipyretics on Infectious and Non-infectious Patient Outcomes

Abstract

Fluctuations and subsequent body temperature management is common in infectious and non-infectious patient cases. Although mostly beneficial, a fever can have adverse effects on patients' outcomes, causing health practitioners to prescribe fever reducers, known as antipyretics. The literature analyzed focused on whether body temperature affects the outcomes of infectious and non-infectious individuals and the effects of fever regulation. It was determined the presence of fever and the earlier a fever is presented positively effects the outcome of infectious individuals. Although, unregulated fevers are unsustainable for infectious and non-infectious individuals, effectively increasing the mortality rate in such cases. A lack of literature focused on the application of antipyretics, nevertheless, the research suggests antipyretics obstruct the body's natural defenses and increase the death rate of infectious patients. As such, antipyretics should only be used in extreme situations with careful consideration. In summary, this extensive review of literature assists in the determining of infectious and non-infectious patients' prognosis due to their body temperature and demonstrates the association of antipyretics and mortality rate.

Key Words: fever, antipyretics, mortality rate, patient outcomes, fever regulation, body temperature

Introduction

The immune system is a complex web composed of millions of cells and proteins whose sole purpose is to defend the body from infections. Symptoms of infections are signs that the body recognized and is defending itself against pathogens, being bacteria, viruses and other substances that are foreign and possibly harmful. The febrile response, otherwise known as a fever, is known to stimulate and enhance the body's natural defenses. It is triggered when the immune system releases chemicals, called pyrogenic cytokines, which causes the hypothalamus — the body's internal thermostat — to increase the body's temperature (Dai et al., 2015). In a healthy body, the hypothalamus maintains an internal body

temperature of approximately 37℃, however, in the event of an infection this temperature is elevated to above 38℃. This immune response is considered an evolutionary advantage and is observed not only in humans, but in most mammalian species (Young et al., 2012). Fever has been preserved throughout the millennia as it effectively terminates the infectious pathogen, which cannot survive under high temperatures. This substantially inhibits the growth of the infection, although an unregulated body temperature can have detrimental effects on the health of a human. A significant and persistent fever can overly exert the body in the form of increased metabolic rate, increased heart rate, and increased oxygen consumption which most studies report increases the chances of mortality (Lee et al, 2012). However, the application of fever reducers is controversial in the medical community. By suppressing fevers through antipyretics, the body's natural defense mechanisms are being restricted. As such, this review will investigate the conflicting research showing the beneficial and harmful effects of antipyretics.

Simultaneously, this literature review will demonstrate how temperature abnormalities can affect infection prognosis and the consequences of antipyretics. Although similar research has been conducted on this topic, the studies have lacked detailed clinical information of the implications of body temperature changes or have been limited by the small number of patients included within the study. A comprehensive review of literature on this topic will provide a tool for determining the prognosis of individuals with or without infections and grant insight into the positive and negative impacts of antipyretics.

Discussion

Deviations in body temperature are evident in various infections, such as viral, bacterial and fungal to name a few. The substantial increase of body temperature is believed to significantly aid the immune system in the fight against an infection, however, it has also been associated with an adverse outcome of patients. Through an extensive examination of various peer-reviewed articles a few relevant discoveries could be made that illustrate the implications of fever in infectious and non-infectious individuals. Research conducted by Rumbus et al. (2017) demonstrated a fever in the presence of sepsis, a severe bacterial infection response, is more effective than no presence of fever, or normothermia. This conclusion came from a meta-analysis of clinical trials providing statistical analysis results indicating patients with a fever had an average mortality rate of 22.2 %, which increased to 31.2 % for patients with normothermia (Rumbus et al., 2017). These results are consistent with the findings of Dai et al. (2015) who directed a prospective observational study in Taipei, Taiwan of 502 patients with hospital-acquired bacteremia with the aim of determining the correlation between body temperature and survival rate. These researchers found "a 1℃ increase in [max body temperature] was associated with a 28% decrease in the risk of death" (Dai et al., 2015, p. 474). These findings elucidate a linear correlation of body temperature

and mortality rate, demonstrating infected individuals who were able to present an effective febrile response had a survival advantage.

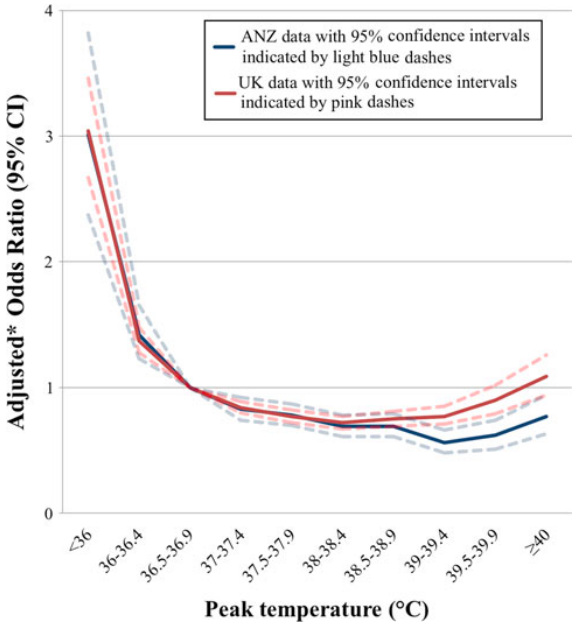
In many studies it became evident that the time in which fever initially presented itself affected the odds of survival. Tharakan et al. (2020) reported a low body temperature at the initial presentation of an infection can be linked to a poor prognosis. This study analyzed body temperature data of COVID-19 patients in the Mount Sinai healthcare system to determine if body temperature correlates with mortality in COVID-19 patients. Dat et al. (2015) also had similar findings, reporting "fever intensity during the early phase of bacteremia were positively associated with survival to discharge" (p. 473). This reveals the earlier the immune system is able to increase the body temperature in the event of an infection, the more effective the febrile response.

Among the studies collected, there is a lack of knowledge of the effects of a substantial increase in body temperature in patients with or without infections. Research conducted by Dai et al. (2015) and Lee et al. (2012) found no significant difference in mortality rate for infectious and septic patients with max temperatures above 39.4°C. However, Lee et al. (2012) did report patients without sepsis who demonstrated a high fever, being 39.5℃ or above, is correlated with a decreased odd of survival. This multi-centered prospective study in Japan and Korea focused on identifying the association of maximum body temperature of critically ill patients with or without sepsis with mortality.

Young et al. (2012) evaluated databases consisting of critically ill patients admitted in ICUs in Australia, New Zealand and the United Kingdom with the hypothesis that early peak temperature is associated with reduced mortality in infectious patients and increased mortality in non-infectious patients. As demonstrated in Figure 1, these researchers determined in infected patients an increase of body temperature causes the odds ratio of mortality drastically decreases. However, a slight upward curve begins at a temperature of 39-39.4℃, indicating the beginning of slightly increased mortality at these temperatures. Although this slight increase is barely significant, it provides visual evidence of the impacts of increased body temperature.

Figure 1.

Adjusted odds ratios for in-hospital mortality versus peak temperature in the first 24 hours for infectious patients.



From "Early peak temperature and mortality in critically ill patients with or without infection," by Paul, J. Young, M. Sexena, R. Beasley, R. Bellomo, M. Bailey, D. Pilcher, S. Finfer, D. Harrison, J. Myburgh, K. Rowan, 2012, *Intensive Care Medicine,* 38, p. 437- 444 (https://doi-org.ezproxy.tru.ca/10.1007/s00134-012-2478-3).

Further, Laupland et al. (2008) conducted a study on 20,466 ICU admitted patients and concluded a high body temperature was associated with a significant increase for death. The analysis yielded patients with a max temperature above 39.5°C had a higher mortality rate than patients below 39.5°C, mortality rates being 20.3% and 12% respectively (Laupland et al., 2008). However, in this study only 31 % of patients with high fever had bacteremia confirmed blood cultures. The lack of infected patients limits the relevance of the study to this literature review, however the results of Laupland et al. (2008) are still valuable in many regards. Additionally, Tharakan et al. (2020) presented an analysis of 7614 positively confirmed patients with the SARS-CoV-2 virus, with results that are similar to Choron et al. (2021). Tharakan et al. (2008) confirmed the mortality rate "was as high as 42% in those with maximum [body temperature] > 40.0°C" (p. 2). Choron et al. (2021) also focused on positively tested Covid-19 patients and found peak temperature in the ICU was significantly higher among deceased individuals compared to the survivors. Similar findings were observed for non-infectious individuals. These results associating a

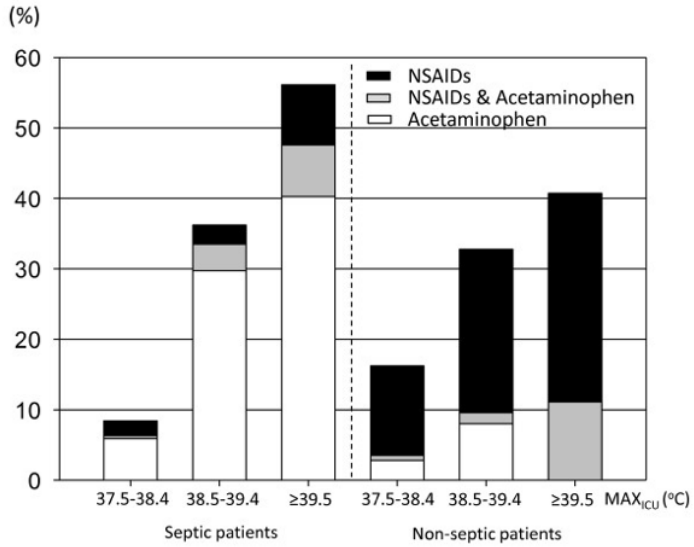
higher body temperature with an increased mortality rate confirm a significant and persistent fever can have detrimental impacts on the prognosis for individuals with or without infections. It can be inferred for infectious and non-infectious patients that a body temperature above 39.5 °C is a cause for concern, as it excessively stresses the body.

The prescription of antipyretics to treat fevers is a practice that has been surrounded by uncertainties and controversies among the medical community. Although these medicines are used to regulate out of control body temperatures, it can be argued the suppression of the body's natural defense mechanisms can be detrimental in the bodies fight against infections. The literature analyzed within this review concluded various results in the association of mortality and application of antipyretic therapy. Both Dai et al. (2015) and Mohr et al. (2011) concluded similar results of no association found between the use of antipyretics and mortality. The research by Mohr et al. (2011) studied a total of 241 patients that met the criteria for severe sepsis or septic shock. These researchers divided the application of antipyretics into different time periods and determined the use of antipyretics was not associated with increased mortality when compared to those without exposure to antipyretics. Dai et al. determined there was insufficient evidence and as such the researchers could not find a definite association between the use of antipyretics and mortality. By contrast, Lee et al. (2012) found a mild correlation between the usage of antipyretics and mortality rate in septic patients. However, the researchers determined antipyretic treatments were not found to be significantly associated with mortality for non-septic patients. Although as shown in Figure. 2, a limitation of this study is the difference in number of antipyretics administered to the two different categories, being septic and non-septic patients. As demonstrated by the bar graph, in septic patients the use of NSAIDs, nonsteroidal anti-inflammatory drugs, and acetaminophen, also known as Tylenol, is shown to be applied in greater capacity than in non-septic patients, with the exception of the 37.5 – 38.4℃ category. If antipyretic treatment was given in the same quantity between the two groups, it is possible there could have been a different result from this study.

The lack of credible research surrounding the usage of antipyretics is concerning, especially as these medications are frequently and universally used. Although antipyretic treatment is common in the medical community, the literature reviewed suggests the current research cannot support routine antipyretic administration for infectious patients. No correlation was determined for antipyretic therapy and the mortality rate in non-infectious patients, however. With fever phobia continuing to run rampant throughout medical practitioners and patients alike, it is vital to ensure the application of antipyretics is appropriate for the given situation.

Figure 2.

Administration of pharmacological antipyretic treatments (NSAIDS and/or acetaminophen) in each maximum body temperature during ICU stay category.



Note. Data show patients categorized in subgroups according to MAX value range: 37.5°C to 38.4°C, 38.5°C to 39.4°C and ≥ 39.5°C. White bar, patients given NSAIDs; black bar, patients given acetaminophen; gray bar, patients given both NSAIDs and acetaminophen. From "Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multicentered prospective observational study," by B.H Lee, D. Inui, G.Y. Suh, J.Y. Kim, J.Y. Kwon, J. Park, K. Tada, K. Tanaka, K. Letsugu, K. Uehara, K. Dote, K. Tajimi, K. Morita, K. Matsuo, K. Hoshino, K. Hosokawa, K.H. Lee, K.M. Lee, M. Takatori, … Y. Koh, 2012, *Critical Care*, 16(1), (https://doi.org/10.1186/cc11211).

Conclusion

Temperature abnormalities and subsequent medication to regulate such irregularities is common among non-infectious and infectious patient cases. This literature review analyzed various sources to determine the correlation between body temperature and the prognosis of individuals with or without infections as well as determine if antipyretics affect the outcome. It was determined the presentation of the febrile response is advantageous for the fight against infections, with studies exhibiting a linear relationship between mortality and body temperature (Rumbus et al., 2017; Dai et al., 2015; Young et al., 2015). Additionally, an earlier manifestation of fever was shown to successfully boost the immune system and aid in the patient's survival (Tharakan et al., 2020). However, a significant and prolonged fever is dangerous and impedes the immune system's ability to effectively fight the infection (Choron et al., 2021;

Tharakan et al., 2008). The literature suggests a body temperature that is above approximately 39.5°C for infectious and non-infectious individuals is associated with a higher mortality rate, effectively providing health practitioners a standard for determining patients outcomes (Laupland et al., 2008). Prevention measures, such as antipyretics, that give medical professionals the ability to regulate the febrile response, have been shown to hinder the body's natural response to infections (Lee et al., 2020). Although antipyretics are frequently used throughout all healthcare systems, careful thought and consideration is encouraged prior to the use of fever reducers. Altogether, this comprehensive review of literature illustrated that deviations from the normal body temperature and subsequent medicinal regulation can predict the outcome of a non-infectious or infectious patient.

Recommendations

The lack of research found on this topic is concerning, especially due to the commonality of fevers in the event of infections. Future research should focus on the effects of high fevers in individuals with or without infections. Due to the discrepancies found between the articles, and overall lack of research regarding high fevers and their consequences on patients' prognosis, it would be beneficial to have more studies concentrating on the outcomes of infectious individuals with temperatures greater than 39.5°C. Further, although the practice of fever management is widespread, studies specifically focused on their implications is lacking. Continued research is recommended for the beneficial or harmful effects of antipyretics as well as if there could be a standard protocol for administering these medicines in infectious and non-infectious individuals. Lastly, future studies should investigate if fever is beneficial or harmful in other diseases, such as physiological, and to what degree of fever in these cases is harmful and should be reduced.

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