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Guest Editorial

What's missing for evidence-based fever management? Is fever beneficial or harmful to humans?

Fever is a common symptom in patients with infection, injury or various inflammatory-related diseases. Since between 29% and 36% of hospitalized patients are estimated to have fever (Bor et al., 1988; McGowan et al., 1987), fever management is an important nursing practice that requires serious study not only because it influences patients' health outcomes but also because providing antipyretic therapy consumes considerable resources and nursing manpower. Physiologically, fever is a complex, coordinated and self-contained response that is induced by a group of pyrogens (Dinarello, 2004). Fever rarely exceeds 41 °C in humans and may be mediated through a natural antipyretic pathway by endogenous antipyretic molecules (Roth et al., 2004). Retrospective clinical studies on patients with the life-threatening illness bacteremia report that patients who were febrile had a higher survival rate than those who were afebrile (Bryant et al., 1971; Mackowiak et al., 1980). However, other studies on different patient populations, with different underlying diseases using various research methods have produced inconsistent results regarding the effects of fever on the host (Gozzoli et al., 2001; Hasday et al., 2011; Kiekkas et al., 2010). Due to ethical considerations, few randomized clinical trials have been conducted on patients, especially those with critical illnesses, to examine outcomes in fever patients with or without antipyretic therapy. There appear to be pros and cons to lowering the body temperature in patients with fever. Studies have reported that nurses hold different perceptions about fever, and practice various fever management protocols (Sarrell et al., 2002; Thomas et al., 1994). The UK National Institute for Health and Clinical Excellence (NICE) has published a guideline for the management of feverish illness in children younger than five years (NCCW and CH, 2007), but few other guidelines are available. There is continuing debate about the accuracy of different devices to measure body temperature (Rubia-Rubia et al., 2011) and consistent evidence from human studies to support clinical guidelines for fever management is lacking.

1. Is less intervention in fever the best intervention?

Studies on patients with non-life-threatening illnesses, e.g., rhinovirus infection, have found that treatment with antipyretics increased and prolonged the symptoms of illness (Doran et al., 1989; Graham et al., 1990). Schulman et al. (2005) conducted a randomized clinical trial on 82 trauma ICU patients. Forty-four patients received an aggressive antipyretic therapy (650 mg of acetaminophen every 6 h for a core temperature >38.5 °C, and a cooling blanket for a temperature >39.5 °C). Thirty-two patients in the control group received no treatment for fever unless the temperature exceeded 40 °C, then acetaminophen and a cooling blanket was used until the temperature was reduced to lower than 40 °C. There were seven deaths in the aggressive treatment group and 1 death in the control group ($P = 0.06$, Fisher's exact test). Therefore, some authors believe that fever is beneficial to a host's defenses and it is unnecessary to give antipyretic therapy unless a patient has neurological damage or cannot tolerate the metabolic burden caused by fever (Barone, 2009; Holtzclaw, 2002; Outzen, 2009). Few authors specify the optimal threshold of body temperature at which antipyretic therapy should be initiated. However, it has been suggested that antipyretics should be given when temperature reaches 39 °C, and external cooling should be provided when body temperature is higher than 39.5 °C (Henker and Carlson, 2007). No physical cooling measures should be used before antipyretics are given to lower the set-point of the thermoregulatory center (Carey, 2010).

2. Is there an optimal temperature for initiation of antipyretic therapy?

Despite the research findings stated above, some scholars continue to argue that the evidence from human studies is inadequate and hesitate to adopt a permissive approach to the treatment of fever. Mackowiak et al. (1980) found that when body temperature exceeds 39.4 °C survival rate decreased in septic patients, and animal

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studies have shown that fever above a certain temperature may cause cell injury in the lungs and be harmful to the host (Rice et al., 2005). In a prospective observational study of 239 ICU patients where febrile patients were divided by peak body temperature into four groups of <38.3 °C, 38.3–39.2 °C, 39.3–40.2 °C and >40.2 °C, mortality rates were 16.7%, 20%, 44.4% and 100% respectively. A higher peak body temperature is thus associated with higher mortality rates (Kiekkas et al., 2010). The authors of this study speculate that there may be an optimal febrile range in which fever may be beneficial. In other words, fever may become harmful and cause cell damage or impaired-oxygen release in tissues when body temperature exceeds a certain level. However, it is uncertain whether suppression of body temperature during high or extreme fever improves a patient's prognosis.

3. Does the optimal febrile range vary depend on site of infection?

To examine the survival effects of optimal febrile range in mice with infection at various sites, a model of febrile-range hyperthermia (FRH) was developed and a series of studies were conducted. Mice were inoculated with *Klebsiella pneumoniae* into the peritoneum (Jiang et al., 2000), or lipopolysaccharide (LPS, a bacterial toxin) was injected into the trachea (Rice et al., 2005). To induce FRH mice were housed at 35 °C rather than the regular 23 °C. The core temperature of FRH mice was elevated by around 2 °C from 36.5–37.5 °C to 39.2–40 °C. Mice exposed to 35 °C were referred to as "febrile mice" and control mice exposed to 23 °C were referred to as "afebrile mice".

The level of plasma pyrogens in mouse plasma, e.g., TNFX, IL-6, IFN-V and bacterial growth at infection site were measured and associations between pyrogens, bacterial growth and host survival (Jiang et al., 2000; Rice et al., 2005) were examined. The peritonitis study reported that the level of plasma cytokines varies at different phases of infection. There was less peritoneal pathogen growth in febrile mice than in afebrile mice. The febrile mice showed a 50% increase in survival rate that investigators concluded may be due to reduced bacterial growth resulting from enhanced host defense rather than the elevated temperature killing bacteria directly (Jiang et al., 2000).

In the study of intratracheal LPS-challenged mice, FRH increased pulmonary vascular endothelial injury, loss of bronchiolar epithelial barrier function, and pulmonary neutrophil accumulation (Rice et al., 2005). These changes are similar to the pathophysiologic changes seen in human adult respiratory disease syndrome. This pneumonia study showed that FRH resulted in lower survival and excessive lung injury (Rice et al., 2005). The findings of these FRH-mice studies indicate that the effects of physiologic response of fever on the host vary according to the site of infection and core body temperature. The researchers concluded that the different survival outcomes are a result of the net effect of enhanced bacteria clearance and collateral injury to tissue of infected organs. In other words, the lung is more susceptible and vulnerable to the injury due to immune-mediated inflammation than the peritoneum (Hasday et al., 2011).

To conclude, the findings of clinical studies and animal studies have not yet established whether fever is a harmful byproduct or a beneficial host-defense response. Fever management may need to be disease-specific, determined by pathogen of infection, site of infection or injury, peak temperature of fever response, and period of fever response. More rigorous clinical trials are needed to address the following questions

1. What is the safe range of core body temperature in fever?
2. If fever is beneficial only within a certain range of temperature, what is the temperature at which fever starts to do more harm than good to cells and tissues in humans?
3. Will antipyretic therapy be beneficial to patients who have fever exceeding the upper limit of optimal febrile range?
4. If suppressing high fever is good for health outcomes, what is the best protocol to lower patient's body temperature?

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References

Barone, J.E., 2009. Fever: fact and fiction. Journal of Trauma-Injury Infection & Critical Care 67 (2), 406–409.

Bor, D.H., Makadon, H.J., Friedland, G., Dasse, P., Komaroff, A.L., Aronson, M.D., 1988. Fever in hospitalized medical patients: characteristics and significance. Journal of General Internal Medicine 3 (2), 119–125.

Bryant, R.E., Hood, A.F., Hood, C.E., Koenig, M.G., 1971. Factors affecting mortality of gram-negative rod bacteremia. Archives of Internal Medicine 127 (1), 120–128.

Carey, J.V., 2010. Literature review: should antipyretic therapies routinely be administered to patients with [corrected] fever? Journal of Clinical Nursing 19 (17–18), 2377–2393.

Dinarello, C., 2004. Review: infection, fever, and exogenous and endogenous pyrogens: some concepts have changed. Journal of Endotoxin Research 10 (4), 201–222.

Doran, T.F, De Angelis, C., Baumgardner, R.A., Mellits, E.D., 1989. Acetaminophen: more harm than good for chickenpox? Journal of Pediatrics 114 (6), 1045–1048.

Gozzoli, V., Schottker, P., Suter, P.M., Ricou, B., 2001. Is it worth treating fever in intensive care unit patients? Preliminary results from a randomized trial of the effect of external cooling. Archives of Internal Medicine 161 (1), 121–123.

Graham, N.M., Burrell, C.J., Douglas, R.M., Debelle, P., Davies, L., 1990. Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers. Journal of Infectious Diseases 162 (6), 1277–1282.

Hasday, J.D, Shah, N., Mackowiak, P.A., Tulapurkar, M., Nagarsekar, A., Singh, I., 2011. Fever, hyperthermia, and the lung: it's all about context and timing. Transactions of the American Clinical and Climatological Association 122, 34–44.

Henker, R., Carlson, K.K., 2007. Fever: applying research to bedside practice. AACN Advanced Critical Care 18 (1), 76–87.

Holtzclaw, B.J., 2002. Use of thermoregulatory principles in patient care: fever management. Online Journal Clinical Innovations 5 (5), 1–23.

Jiang, Q., Cross, A.S., Singh, I.S., Chen, T.T., Viscardi, R.M., Hasday, J.D., 2000. Febrile core temperature is essential for optimal host defense in bacterial peritonitis. Infection & Immunity 68 (3), 1265–1270.

Kiekkas, P., Velissaris, D., Karanikolas, M., Aretha, D., Samios, A., Skartsani, C., Baltopoulos, G.I., Filos, K.S., 2010. Peak body temperature predicts mortality in critically ill patients without cerebral damage. Heart & Lung 39 (3), 208–216.

Mackowiak, P.A., Browne, R.H., Southern Jr., P.M., Smith, J.W., 1980. Polymicrobial sepsis: an analysis of 184 cases using log linear models. American Journal of the Medical Sciences 280 (2), 73–80.

McGowan Jr., J.E., Rose, R.C., Jacobs, N.F., Schaberg, D.R., Haley, R.W., 1987. Fever in hospitalized patients. With special reference to the medical service. American Journal of Medicine 82, 580–586.
National Collaborating Centre for Women's and Children's Health, 2007. Feverish Illness in Children: Assessment and Initial Management in Children Younger than Five. NICE, London, UK.
Outzen, M., 2009. Management of fever in older adults. Journal of Gerontological Nursing 35 (5), 17–23.
Rice, P., Martin, E., He, J.-R., Frank, M., DeTolla, L., Hester, L., O'Neill, T., Manka, C., Benjamin, I., Nagarsekar, A., Singh, I., Hasday, J.D., 2005. Febrile-range hyperthermia augments neutrophil accumulation and enhances lung injury in experimental gram-negative bacterial pneumonia. Journal of Immunology 174 (6), 3676–3685.
Roth, J., Zeisberger, E., Vybiral, S., Jansky, L., 2004. Endogenous antipyretics: neuropeptides and glucocorticoids. Frontiers in Bioscience 9, 816–826.
Rubia-Rubia, J., Arias, A., Sierra, A., Aguirre-Jaime, A., 2011. Measurement of body temperature in adult patients: comparative study of accuracy, realiablility and validity of different devices. International Journal of Nursing Studies 48 (7), 872–880.
Sarrell, M., Cohen, H.A., Kahan, E., 2002. Physicians', nurses', and parents' attitudes to and knowledge about fever in early childhood. Patient Education & Counseling 46 (1), 61–65.
Schulman, C.I., Namias, N., Doherty, J., Manning, R.J., Li, P., Elhaddad, A., Lasko, D., Amortegui, J., Dy, C.J., Dlugasch, L., Baracco, G., Cohn, S.M., 2005. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. Surgical Infections 6 (4), 369–375.
Thomas, V., Riegel, B., Andrea, J., Murray, P., Gerhart, A., Gocka, I., 1994. National survey of pediatric fever management practices among emergency department nurses. Journal of Emergency Nursing 20 (6), 505–510.

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