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Fever in critically ill patients: monitoring, management, and outcomes

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Fever in critically ill patients: monitoring, management, and outcomes

by

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DISSERTATION

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Acknowledgments & Dedication

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Dedication

This dissertation is dedicated to the critically ill patients and families who participated in the clinical research for this dissertation. I am inspired by and grateful for their generosity during their time of uncertainty, crisis, and/or grief. I would also like to dedicate this to the nurses, pharmacists, respiratory therapists, and physicians in the adult ICUs at UCSF Medical Center who supported and facilitated the research for this dissertation as well as other important clinical trials that impact the care and outcomes of critically ill patients.

Abstract

Fever in critically ill adults: monitoring, management, and outcomes

Fever is a common occurrence in intensive care unit (ICU) patients and is routinely treated with antipyretic therapies. Evidence to inform guidelines for fever management in ICUs is limited due to the low level of evaluable data. The introduction (Chapter 1) provides the background and significance of fever management in ICU patients. The question of whether fever should be suppressed based on its impact on outcomes in all ICU patients or in specific subpopulations, such as sepsis, neurological injury, and acute respiratory distress syndrome (ARDS), remains unanswered. To describe the impact of fever on outcomes of ICU patients with ARDS, a secondary analysis was completed and found that early in the ARDS trajectory, fever is associated with improved survival rates (Chapter 2).

A common limitation of studies investigating body temperature alterations in ICU patients is the lack of standard measurement of core body temperature. To address this limitation for the primary clinical trial of this dissertation and to evaluate a prospective continuous core temperature monitoring device for use in ICU patients, a method-comparison study was completed (Chapter 3). This method-comparison study tested the agreement and precision of a novel technology for continuous thermometry with standard thermometry methods in febrile ICU patients.

Fever suppression remains widespread and acetaminophen is the most common first line therapy used by ICU clinicians. There is a lack of high-grade evidence about the antipyretic efficacy and the acute hemodynamic effects of the more recently available intravenous (IV) formulation of acetaminophen in ICU patients. To better understand the therapy response and potential acute adverse effects of this commonly administered medication in febrile critically ill

patients, a randomized, double blind, placebo-controlled trial to evaluate the effect of IV acetaminophen on body temperature and hemodynamic responses was conducted (Chapter 4).

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Chapter 1

Introduction

The relationship between body temperature alterations (both hypothermia and fever) in critically ill patients and outcomes is not well understood despite the fact that clinicians frequently intervene to achieve normothermia in their patients (1-7). Body temperature is routinely monitored in intensive care unit (ICU) patients and the presence of fever often triggers fever suppression interventions. Fever is common in critically ill patients and occurs as an adaptive response to inflammation that results from injury, infection, or drug or immune-mediated reactions (5, 7-11).

Fever is defined as a controlled or regulated rise in body temperature above the normal thermal set point in response to inflammation (12, 13). Although there are many temperature thresholds used to define fever in the critical care literature, the American College of Critical Care Medicine and the Infectious Disease Society of America define fever as a core body temperature greater than or equal to 38.3°C and recommend identification and evaluation of febrile patients in the ICU using this criterion (14). Fever management can be defined to include identification of fever from body temperature monitoring, application of fever suppression interventions, and evaluation of body temperature and clinical response of patients receiving antipyretic interventions. Fever suppression interventions include administration of antipyretic medications and physical cooling measures. This dissertation explores 3 areas of inquiry related to fever management and the impact of fever on outcomes of critically ill patients. The main aim is to contribute to the body of scientific knowledge that informs evidence-based management of fever in critically ill patients.

Theoretical Framework

Thermoregulation in humans is the ability of the body to maintain a core body temperature within a hypothalamic-determined range for optimal physiological functioning, regardless of the variable environmental temperatures. Thermoregulation is a result of the integrated and coordinated work of the nervous, endocrine, circulatory, and pulmonary systems along with behavioral responses to generate heat, conserve heat, reduce heat production, and lose heat. The mechanisms of thermoregulation including the afferent thermo-sensory, central hypothalamic regulatory, and thermo-effector responses are presented in **Figure 1**.

Fever is an adaptive neuro-immunologic response to inflammation secondary to severe injury and/or infection. It is a complex physiological response including thermal, immunologic, metabolic, and neuro-endocrinologic effects. Preservation of the species over the individual is a basic principle of evolution. The strongest evidence that the fever response, including the associated inflammatory response, is adaptive in mammals is the argument that fever would not have been preserved over time with its "metabolically expensive" impact on body systems if there was no survival benefit (15). The mechanisms of fever are presented in **Figure 2**. Models for clinical assessment and management of fever response are presented in **Figure 3** and **Figure 4**, respectively. The 2 physiological models and the 2 clinical care models presented provide the theoretical framework used to guide the study of body temperature and fever in critically ill adults in this dissertation.

Significance

Fever is a common occurrence in ICU patients, with reported incidence rates ranging from 26% to 70% (5, 11, 16). Fever is a complex physiologic response and is associated with increases in oxygen consumption, heart rate, blood pressure, and respiratory rate (17-21).

Although fever is typically a beneficial adaptive response to infection and injury, the associated cardiopulmonary and metabolic stress is a concern of clinicians caring for patients with critical illness. Despite the limited evidence relating adverse outcomes to cardiopulmonary or metabolic stress from fever in critically ill patients, clinicians routinely administer antipyretic interventions.

Studies that have examined the relationship between fever and outcomes in critically ill patients have yielded disparate results of increased and decreased mortality as well as no association with mortality (5, 16, 22-24). Fever has been associated with improved outcomes in subpopulations of critically ill patients with infection, sepsis, trauma, and acute respiratory distress syndrome (ARDS) (16, 22, 24, 25). Fever in the subpopulation of neurologically injured critically ill patients has been associated with worse outcomes including extension of neurologic injury, longer ICU length of stay, poor functional outcomes, and increased mortality, yet a direct cause has not been established (25). Prolonged fever and intracranial hypertension plus fever are significant prognostic indicators for poor outcomes in traumatic brain injury patients (26). Although the American Heart Association and American Stroke Association recommend treatment of fever with antipyretic medications in patients with acute ischemic stroke, the recent guidelines for management of spontaneous hemorrhagic stroke only recommend that treatment of fever be considered (27, 28). The recently published European Stroke Organization guidelines for management of temperature in patients with ischemic stroke could not make a recommendation for treating fever due to the low level of evidence relating fever suppression to improved outcomes (29). Despite the disparate evidence relating fever to poor outcomes in the different subpopulations of critically ill patients, antipyretic interventions are commonplace in ICUs (16, 25, 30-33).

Fever suppression interventions are widespread in hospitals with reports that up to 70% of ICU patients receive antipyretic interventions (1, 16, 33, 34). Routine management of fever in ICU patients includes administration of antipyretic medications and/or physical cooling interventions to reduce body temperature (1, 10, 16, 34-36). Acetaminophen is the most common antipyretic medication ordered for ICU and hospitalized patients (10, 37, 38). Survey responses from critical care physicians and nurses consistently report that acetaminophen is the first line antipyretic intervention chosen for febrile patients and physical cooling methods as second line interventions when fevers persist (31, 34). Although acetaminophen is routinely administered for fever suppression in ICUs, there are limited prospective data on the antipyretic efficacy of acetaminophen in adult critically ill patients.

The recently published multicenter randomized trial that evaluated the impact of IV acetaminophen compared to placebo on outcomes in febrile ICU patients with infection found no significant differences in ICU-free days and 90-day mortality (39). It will be interesting to see if fever management practices change in the large subpopulation of ICU patients with infection based on this finding of a neutral impact of acetaminophen on outcome.

The gaps in research to support evidence-based guidelines for fever management in critically ill patients include: 1) indications for fever suppression that are related to improved patient outcomes; 2) selection of effective antipyretic methods; and 3) safe administration of fever suppression interventions including monitoring for effectiveness and side effects. Despite the lack of evidence-based guidelines for fever management in critically ill patients, thermometry methods vary and fever suppression interventions are ubiquitous in ICU care. The current state of fever management practice in ICUs has clinical significance related to the

unknown impact of that fever suppression, per se, or the side effects of antipyretic interventions on patient outcomes in this vulnerable population.

Nurses routinely monitor body temperature and have a major role in administration of temperature management interventions. The lack of high-level evidence has been implicated as a potential rationale for the variability in nursing practice for fever management (1, 31). Thompson and Kagan (1) conducted a qualitative study of ICU nurses to explore and describe fever management decision-making by ICU nurses. They found that most nurses chose fever suppression interventions based on their personal and past experiences with "what works" or trial and error. Studies evaluating the administration of antipyretic interventions have reported variations in practice and have concluded that nurses are the primary decision makers for implementation of these interventions (1, 2, 40). Further research evaluating the effectiveness of fever management interventions and their impact on outcomes is significant for nursing science as body temperature maintenance is one of the fundamentals of core nursing care (41).

This dissertation explores 3 areas of research related to fever management of critically ill patients and contributes to the scientific body of evidence intended to inform practice guidelines that optimize safe and effective care of critically ill patients who often experience fever. The dissertation chapters are in the format of manuscripts prepared for publication in peer-reviewed journals.

Chapter 2: Fever would be an expected clinical sign of ARDS since inflammation is the main pathophysiological mechanism. Yet, until recently, little was known about the incidence of fever in the ARDS subpopulation of critically ill patients and whether there was an association between fever and outcomes. This chapter presents the completed and published study that examined the relationship between body temperature in early ARDS and mortality. This was a

secondary analysis of body temperature and mortality using data from the ARDS Network Fluid and Catheter Treatment Trial (24). Body temperature, primary cause of ARDS, severity of illness, and 90-day mortality were analyzed using multiple logistic regression.

Chapter 3: A common limitation of studies investigating body temperature alterations in ICU patients is the lack of standard core body thermometry methods. To address this limitation for the primary clinical trial of this dissertation, the 3M™ SpotOn™ temperature monitoring system (3M™, Eden Prairie, MN) was used to measure core body temperature during the study period. A method-comparison study in eligible patients enrolled in the primary clinical trial was completed to test the agreement and precision of this novel technology (SpotOn™ Temperature Monitoring System) with standard thermometry methods in febrile ICU patients. One objective of this study was to prospectively evaluate the SpotOn™ monitoring device for potential use in ICU patients requiring continuous core temperature monitoring. This study included 38 of the 41 patients enrolled in the aforementioned primary clinical trial who had standard urinary bladder or rectal thermometry during the study period. The standard thermometry method was compared to the SpotOn™ temperature monitoring system that was used to measure core body temperature in the primary clinical trial. The Bland and Altman method was used to analyze the thermometry method-comparison data to estimate the direction and extent of agreement and the precision among the measurement methods.

Chapter 4: To better understand the therapy response and potential acute adverse effects of this commonly administered medication in febrile critically ill patients, a randomized, double blind, placebo-controlled trial was conducted to evaluate the effect of IV acetaminophen on body temperature and hemodynamic responses. This trial enrolled 41 patients and was conducted in the adult ICUs at the University of California, San Francisco Medical Center. A t-test or Mann-

Whitney U test was used to analyze the effect of treatment with acetaminophen compared to placebo on body temperature and hemodynamic outcome variables. Analysis of covariance using group as the fixed effect and baseline values as covariates was performed to further explore the differences between the study groups for any important differences in baseline characteristics.

Chapter 5: The concluding chapter of this dissertation will provide a summary of the scientific contributions of the research completed. Discussion of the implications for future research and implications for clinical practice related to fever management will also be presented.

Figure 1: Thermoregulatory Mechanisms: physiological and behavioral responses to maintain body temperature at hypothalamic set point

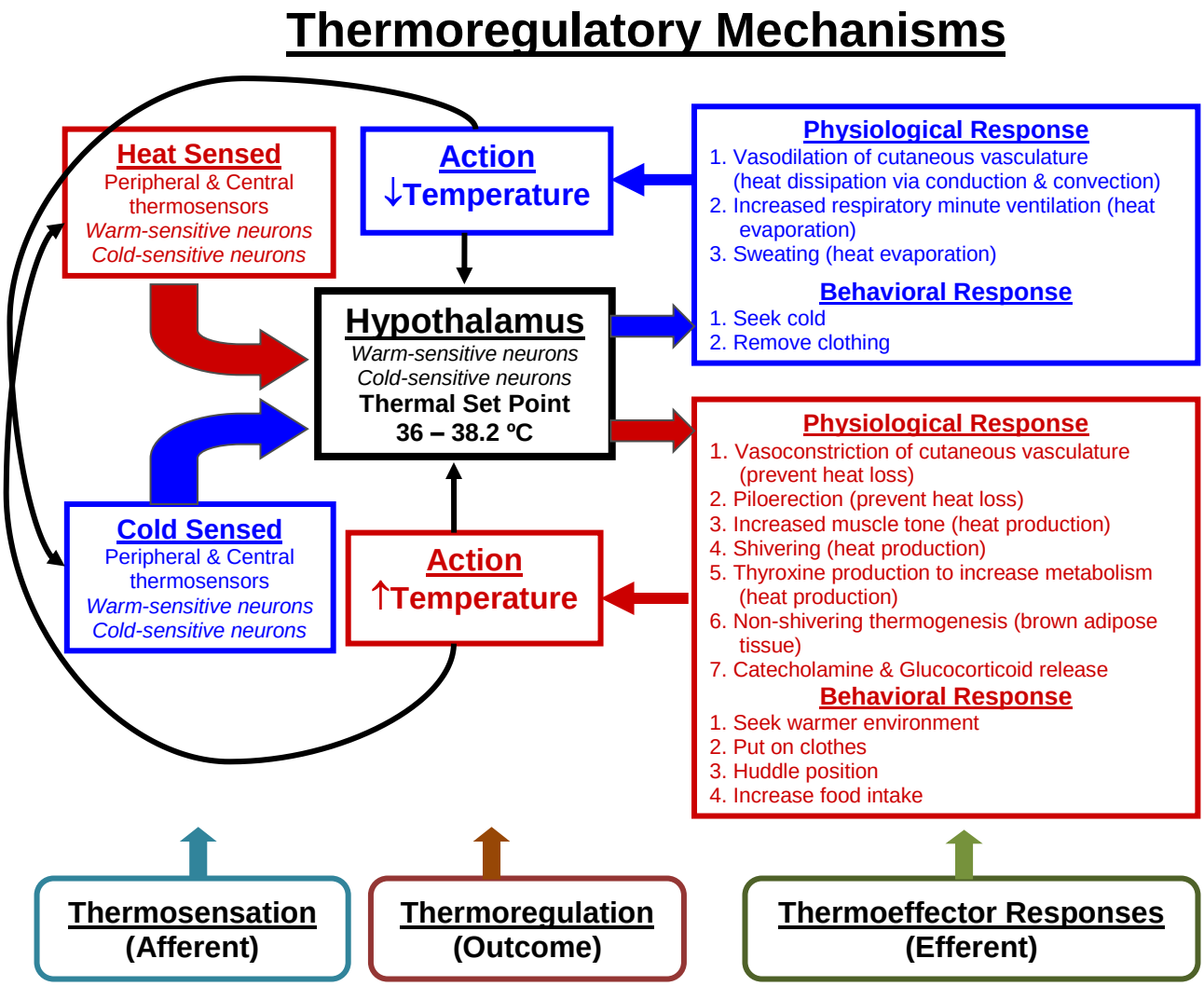
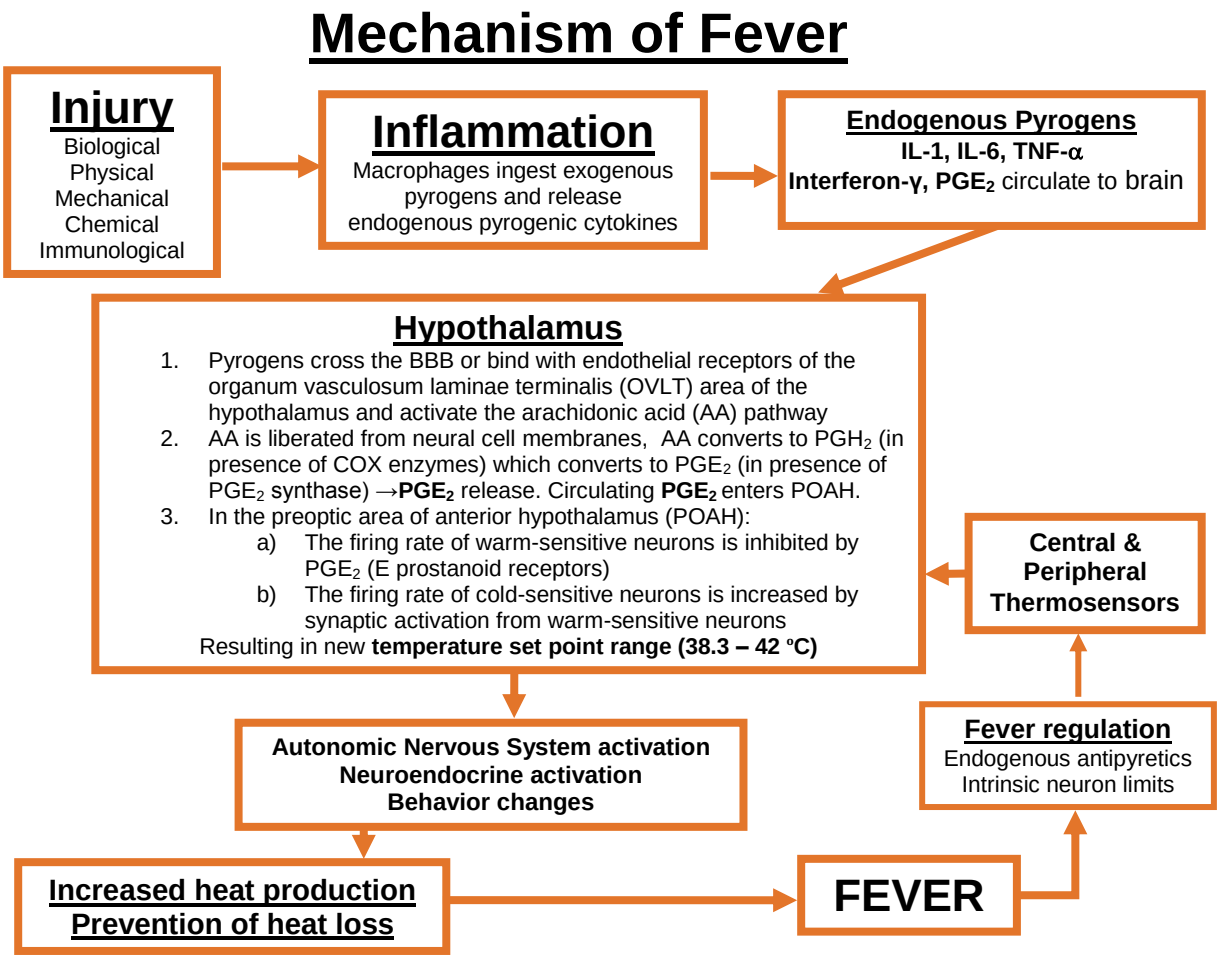
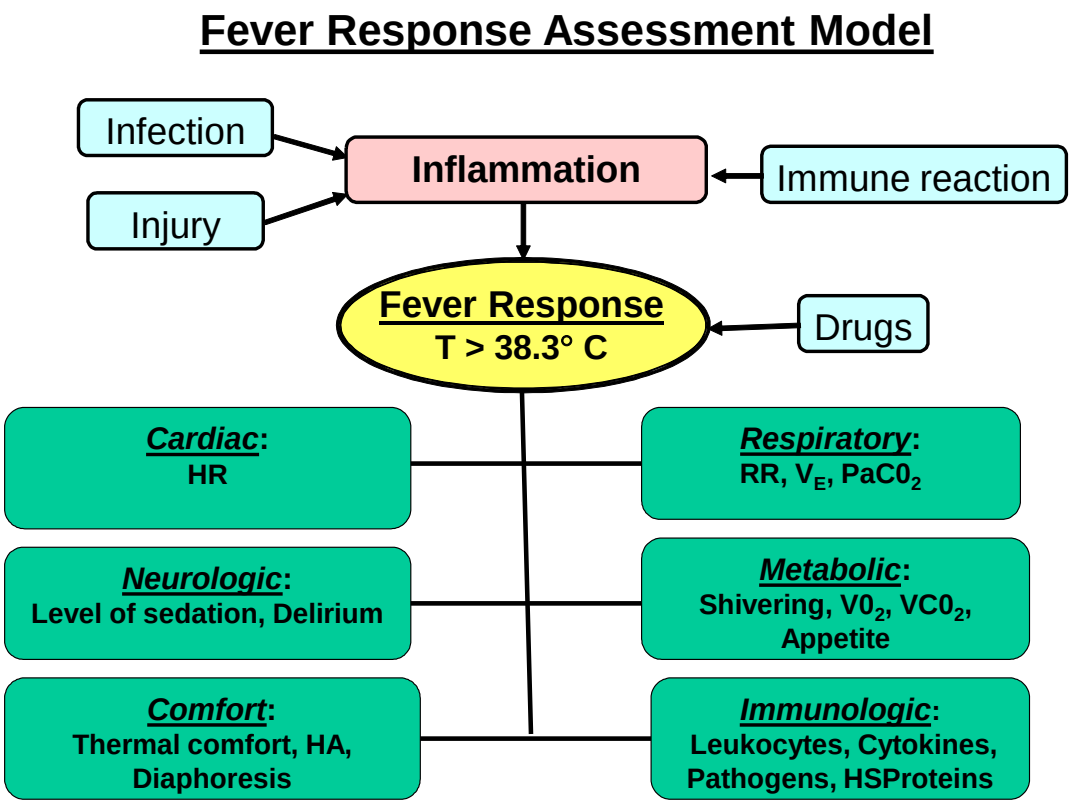


Figure 2: Mechanism of fever



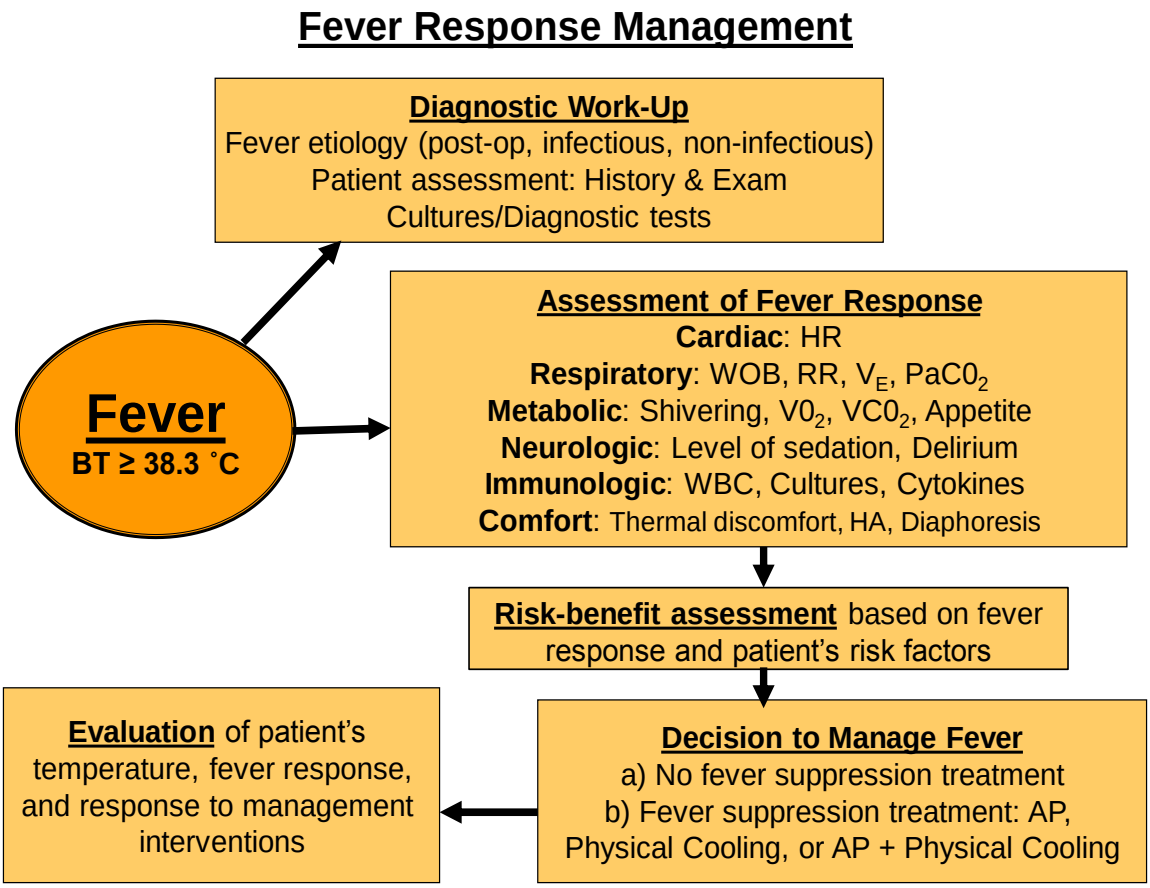
BBB (blood brain barrier), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor necrosis factor-alpha (TNF-α), Interferon-gamma (INF-γ), cyclooxygenase (COX), Prostaglandin H_2 (PGH_2), Prostaglandin E_2 (PGE_2)

Figure 3: Model for Fever Response Assessment



Heart rate (HR), Headache (HA), Respiratory rate (RR), Minute ventilation (V_E), Partial pressure of carbon dioxide ($PaC0_2$), Oxygen consumption ($V0_2$), Carbon dioxide production ($VC0_2$)

Figure 4: Model for Fever Response Management



Body Temperature (BT), Antipyretic medication (AP), Headache (HA), Oxygen consumption (VO_2), Carbon dioxide production (VCO_2), Work of breathing (WOB), Respiratory rate (RR), Minute ventilation (V_E), Partial pressure of carbon dioxide ($PaCO_2$), White blood cell (WBC), Heart rate (HR)

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Chapter 2

Body Temperature and Mortality in Patients with Acute Respiratory Distress Syndrome

ABSTRACT:

***Purpose*:** Little is known about the relationship between body temperature and outcomes in patients with the acute respiratory distress syndrome (ARDS). A better understanding of this relationship may provide evidence for fever suppression or warming interventions, which are commonly applied in practice. The aim of this study was to examine the relationship between body temperature and mortality in patients with ARDS.

Objective: To examine the relationship between body temperature and mortality in patients with ARDS.

***Methods*:** Secondary analysis of body temperature and mortality using data from the ARDS Network Fluid and Catheter Treatment Trial (n = 969). Body temperature at baseline and on study day two, primary cause of ARDS, severity of illness, and 90-day mortality were analyzed using multiple logistic regression.

***Results*:** Mean baseline temperature was 37.5 ± 1.1°C (range 27.2 to 40.7 °C). At baseline, fever (≥ 38.3 ºC) was present in 23% and hypothermia (< 36 ºC) in 5% of the patients. Body temperature was a significant predictor of 90-day mortality after adjusting for primary cause of ARDS and APACHE III score. Higher temperature was associated with decreased mortality: for every 1°C increase in baseline temperature, the odds of death decreased by 15% (OR 0.85, 95% CI 0.73 - 0.98, p = 0.03). When patients were divided into five temperature groups, there was lower mortality with higher temperature (p for trend = 0.02).

***Conclusions*:** Early in ARDS, fever is associated with improved survival rates. Fever in the acute phase response to lung injury and its relationship to recovery may be an important factor in determining patients' outcome and warrants further study.

Summary of key points

Little is known about the relationship between body temperature and outcomes in patients with ARDS. A better understanding of this relationship may provide evidence to guide future research and clinical practice related to fever suppression or warming interventions, which are commonly applied in clinical practice.

- In a large cohort of ARDS patients, baseline body temperature alterations were present in 28% of the sample (fever in 23% and hypothermia in 5%).
- Body temperature at baseline and study day two were significant predictors of 90-day mortality after controlling for the etiology of ARDS and APACHE III score.
- Higher baseline temperature was associated with decreased mortality: for every 1°C increase in temperature, the odds of death decreased by 15% (OR 0.85, 95% CI 0.73 - 0.98, $p = 0.03$).

INTRODUCTION

The relationship between body temperature alterations (both hypothermia and fever) in critically ill patients and outcomes is not well understood, despite the fact that clinicians often intervene to achieve normothermia in these patients (1-6). Fever is common in critically ill patients and occurs as an adaptive response to inflammation that results from injury or infection (7-9). Fever is defined as a regulated rise in body temperature above the normal thermal set point in response to injury and inflammation (10). Studies that have examined the relationship between fever and mortality in critically ill patients have yielded disparate results (1, 7, 9, 11-13). High fever, typically defined as 39.5 °C or greater, has been associated with increased mortality in critically ill patients (7-9, 12).

A large multinational observational study evaluating the relationship between temperature and mortality in critically ill patients with and without infection found a reduced risk of in-hospital mortality with fever relative to normothermia in critically ill patients with infection (11). The non-infection group from this study also had reduced risk of mortality with elevated temperatures up to 39 ºC, after which mortality increased. Hypothermia was associated with increased mortality in both infection and non-infection groups. In another recent multi-site observational study, the presence of fever on admission to the intensive care unit (ICU) had no significant association with ICU case-fatality in medical and surgical ICU patients (9).

In a large randomized double-blind, placebo-controlled trial evaluating the effects of ibuprofen on outcomes in critically ill septic patients, temperature was significantly reduced in the febrile group that received ibuprofen (14). However, despite finding significant reductions in fever, heart rate, lactate levels, and oxygen consumption values in the treatment group, there were no differences in oxygen delivery, organ failure free days, or mortality. A recent

observational trial investigated the association of fever and antipyretic interventions with mortality in both septic and non-septic critically ill patients (1). In the septic cohort they found that fever was an independent predictor of decreased mortality and that use of acetaminophen and ibuprofen was an independent predictor of increased mortality. In the non-septic cohort, only high fever (≥ 39.5 °C) was found to be independently associated with increased mortality and no associations were found with antipyretic medication use and mortality. Thus, there is lack of robust evidence to guide management of fever in critically ill patients. Nonetheless, the use of antipyretic medications and physical cooling interventions to treat fever is widespread in clinical practice (1-4).

Acute respiratory distress syndrome (ARDS) is one of several forms of critical illness characterized by the presence of the acute phase response, a series of complex neuro-immunologic reactions that include stimulation of fever and the release of cytokines and other immunologically activated proteins in response to injury or infection in an attempt to re-establish homeostasis (15-16). The acute phase response stimulates leukocytosis, complement activation, coagulation activation, opsonization, cytotoxicity, vascular permeability, and chemotaxis of monocytes, neutrophils, and T-cells (17). Since fever is a hallmark sign of the acute phase response to infectious and non-infectious sources of tissue injury, we would expect fever to be common in patients with ARDS. However, little is known about the incidence of fever in patients with ARDS and whether body temperature has an association with the trajectory of illness and recovery.

Thus, a better understanding of the impact of body temperature on ARDS patient outcomes can inform future research. Specifically, because the relationship between temperature and patient outcomes is unknown, it is unclear whether temperature altering interventions are

beneficial, detrimental or neutral in patients with ARDS. The purpose of this study was to examine the relationship between body temperature in early ARDS and mortality.

METHODS

We conducted a secondary analysis of temperature using data from the National Heart, Lung and Blood Institute (NHLBI) ARDS Network Fluid and Catheter Treatment Trial (18, 19). This multicenter factorial study randomized patients with acute lung injury for 48 hours or less to receive a central venous catheter or a pulmonary artery catheter (PAC) and to receive either liberal or conservative fluid management strategies per protocol (19-21). The institutional review boards of participating centers and the NHLBI approved the original study. Written consent was obtained from the patient participants or their legal surrogates in the original study. Certification from the investigators' center IRB was obtained for this secondary analysis.

Adult patients who met the American-European Consensus criteria for acute lung injury for 48 hours or less were eligible for study enrollment. With the exception of 0.2% of this study's sample, patients met the recently published criteria for the Berlin definition of ARDS (16). Exclusion criteria included presence of ARDS for more than 48 hours; presence of a PAC prior to study enrollment; presence of chronic conditions that could influence compliance with the study protocol or ventilator weaning; and terminal conditions with estimated six-month mortality of greater than 50%. Due to missing temperature and APACHE III score data, 31 patients were excluded from the original sample of 1,000 patients.

MEASUREMENT OF VARIABLES

The source of baseline temperature measurement in the original study included rectal, tympanic, or axillary sites. Baseline temperature was obtained from the 4-hour period preceding randomization which occurred immediately after consent was obtained. Daily temperature

measurements from the same time each day from rectal, tympanic, axillary, or PAC sites were recorded for up to seven days. Temperature ranges used to create five groups were selected based on definitions of deep hypothermia (< 34 ºC), mild-moderate hypothermia (34 to 35.9 ºC), normothermia (36 to 38.2 ºC), fever (38.3 to 39.4 ºC), and high fever (≥ 39.5 ºC) (9, 20-22).

Patients were followed for 90 days from study enrollment or until death, whichever occurred first. The Acute Physiology, Age, Chronic Health Evaluation (APACHE) III score was calculated using baseline patient data (23). A primary lung injury etiology category of trauma, sepsis, multiple transfusions, pneumonia, aspiration, or other causes was selected for each patient.

STATISTICAL ANALYSIS

An independent samples t-test was conducted to compare baseline temperatures for survivors and non-survivors. In order to control for potential confounding variables, multiple logistic regression was performed to assess the impact of three factors on the likelihood of mortality at 90 days in patients with ARDS. The three factors in the model were baseline temperature, primary cause of ARDS, and severity of illness, measured by the APACHE III score. These variables were included due to their potential physiological and clinical significance as well as their significant association with mortality in univariate analyses. In addition, a sensitivity analysis to explore whether hypothermia influenced the results of the study, the multiple logistic regression was repeated with exclusion of patients with temperatures less than 36 °C. Multiple logistic regression was also repeated using temperature from day 2 of the study in place of baseline temperature to determine whether the relationship was sustained at another time point early in the ARDS trajectory.

To better understand the relationship between body temperature and mortality, we used five categories of baseline temperature (moderate to deep hypothermia, mild hypothermia, normothermia, fever, and high fever) and used logistic regression to test for a trend in the mortality amongst the temperature groups. Baseline comparisons of characteristics amongst the five temperature groups were performed using one-way analysis of variance for continuous variables and chi-square analysis for categorical variables.

Because temperature is a part of the APACHE III score calculation, correlation analyses and collinearity diagnostics of the independent variables were completed and low correlations ruled out concern of multicollinearity issues. The Hosmer-Lemeshow test was used to assess the goodness of fit of the model (24). Odds ratios (OR) and 95% confidence intervals were calculated. Statistical tests were two-sided and assumed significance at $p<0.05$. Data analyses were performed using SPSS® computer software, version 21 (SPSS®, Inc., Chicago, IL).

RESULTS

Characteristics of the 969 participants with baseline temperature data available are presented by temperature group in **Table 1**. Mean body temperature at baseline was 37.5 ± 1.1 °C (range 27.2 to 40.7 °C). Mean body temperature on day 2 was 37.4 ± 0.9 °C (range 34.5 to 40.6 °C). At baseline, fever was present in 227/969 (23%) and hypothermia in 48/969 (5%) of the patients. The overall 90-day mortality rate of the sample was 267/969 (28%). Baseline temperatures were compared between survivors (n=702) and non-survivors (n=267). There was a modest but statistically significant difference in mean temperature between survivors and non-survivors (37.6 ± 1°C vs. 37.3 ± 1.2 °C, $p <0.001$).

As shown in **Table 2**, multiple logistic regression showed that baseline temperature and APACHE III score made significant contributions to the model. Baseline temperature was a

significant predictor of mortality when controlling for the etiology of ARDS and APACHE III score. Remarkably, for every 1°C increase in temperature, the odds of death at 90 days decreased by 15% (OR 0.85 per 1°C increase in temperature, 95%, CI 0.73-0.98, p = 0.03).

To test whether the hypothermic patients significantly influenced our finding, we performed a sensitivity analysis excluding these patients from the logistic regression. When patients with hypothermia (≤ 36°C, n = 48) were excluded from the analysis, baseline temperature remained a significant predictor of mortality after controlling for the etiology of ARDS and APACHE III score, with higher baseline temperature being associated with decreased mortality (OR 0.82 per 1°C increase in temperature, 95% CI 0.69-0.98, p= 0.03). Similarly, our findings were unchanged when the data were analyzed without the single subject with an extremely low temperature (27.2 ºC).

To test whether the relationship between body temperature and mortality was significant at another early time point in the ARDS trajectory, we repeated the multiple logistic regression analysis using temperature from the second study day (see **Table 3**). Temperature on study day 2 was also a significant predictor of mortality, controlling for APACHE III score and etiology of ARDS (OR 0.82 per 1°C increase in temperature, 95%CI 0.69-0.98, p=0.03).

As shown in **Figure 1**, there was a significant trend in lower mortality in the fever and high fever groups (23% and 19%, respectively) compared to in the normothermia (29%) and mild-moderate- and deep-hypothermia (36% and 67%, respectively) groups (p for trend = 0.02). Although patients in the deep hypothermia group were older and had higher APACHE III scores, there were no statistical differences in baseline characteristics found amongst the five temperature groups as shown in **Table 1**.

DISCUSSION

The presentation of body temperature alterations, both fever and hypothermia, and the impact on physiologic and recovery outcomes in patients with ARDS are not well understood. This study adds to the literature on temperature abnormalities in critically ill patients with ARDS and is one of two new studies to investigate the association between temperature and mortality in this subgroup of critically ill patients. Netzer et al (25) recently published findings from their secondary analysis of 450 patients from the Improving Care of Acute Lung Injury Patients (ICAP) study cohort. The frequency of temperature alterations in their study was higher than in our sample. They found at least one febrile day (≥38.0 °C) in the first three days of ARDS onset in 65% of their sample and 46% of their sample had at least one hypothermic day (< 36 °C). Febrile days in early ARDS in their study were not associated with increased in-hospital mortality in their multivariable model, yet two or more hypothermia days were found to be associated with increased risk of in-hospital mortality. The incidence of body temperature alterations in our sample is more similar to those found in an observational study of 493 medical and surgical critical care patients in whom 28% had fever and 9% had hypothermia using the same temperature thresholds as our study (8). However, similar to our findings, in this study, hypothermia, rather than fever, was associated with an increased risk of death.

Laupland et al (9) prospectively studied temperature on admission and outcomes in 10,962 patients (75% medical and 25% surgical admission types) from French ICUs over 10 years. Body temperatures at presentation were hypothermia (16%), normothermia (55%), fever (26%), and mixed hypothermia and fever (3%). Although it is unclear whether ARDS was present, in the sample requiring mechanical ventilation (n=5019), 27% presented with fever and 23% with hypothermia. After controlling for severity of illness and other confounders, fever was

not associated with increased ICU mortality. Indeed, hypothermia was found to be a significant independent predictor of ICU mortality in the medical subgroup. These findings are consistent with the increased odds of mortality as body temperature decreased that we found in our study. Similar to our study, their study also lacked evaluation of temperature-altering interventions (antipyretics and warming), limiting interpretation of their potential confounding effects.

In a study by Bernard et al (14), ibuprofen administration did not significantly alter the rates of organ failure and mortality in a large sample (n = 455) of septic patients, of whom 29% had ARDS. They evaluated whether this cyclo-oxygenase inhibitor impacted fever and the increased metabolic demands of sepsis. This study included febrile and hypothermic patients and excluded those with normothermia. A significant reduction in body temperature was achieved in the ibuprofen group compared to the placebo group. However, the use of acetaminophen and physical cooling methods for fever reduction were not controlled for, and patients in both placebo and treatment groups received acetaminophen before and during the study.

Using data presented in their original study, we calculated mortality rates in the subgroup of febrile patients in the two arms; mortality in the ibuprofen and placebo groups was the same at 35%. Although the study intervention was not targeted to fever suppression, these results suggest that at a minimum there is no mortality benefit to fever suppression. Furthermore, the 54% mortality rate of the ibuprofen-treated hypothermic subgroup was significantly lower than the 90% mortality in the placebo hypothermic subgroup ($p = 0.02$), while both mortality rates were higher than that of the febrile patients. The finding that mortality rates were lower in patients who presented with fever rather than hypothermia is consistent with our results, where mortality was lowest in the febrile group. In our study, this association remained significant, even after adjusting for severity of illness and primary etiology of ARDS.

In a large (n=1,425), multi-site observational study, there were different findings for fever and mortality and for antipyretic intervention use and mortality between the septic and non-septic cohorts (1). They found that fever is an independent predictor of decreased mortality in septic patients, but not a predictor in non-septic patients. This result suggests that future investigations evaluate the risk and use of antipyretic interventions based on etiology of the fever in future studies. Although ARDS was not a specified patient characteristic in this study, a large number of patients were mechanically ventilated (67%) and had respiratory/thoracic disease as the reason for admission (38%). In our study, 71% of the sample had sepsis (n=228) or pneumonia (n=458) as the primary etiology of their ARDS. Therefore, the importance of fever in the acute phase response to infection, which is often associated with acute lung injury, and its relationship to recovery may be underestimated.

Researchers who have examined the relationship between fever and outcomes including mortality in critically ill patients have reported mixed results (7-9, 14, 26). However, experimental animal studies suggest that febrile-range hyperthermia in lung injury models worsens lung function and increases mortality, yet the mechanisms are not well understood (27-29). Induced hypothermia has been used as a therapeutic strategy in critically ill patients post cardiac arrest and with acute liver failure to optimize outcomes (30, 31). A recent randomized controlled trial compared the effect of fever suppression using external cooling to no cooling for 48 hours on vasopressor dose reduction in febrile patients with septic shock (32). In this study in which 70% had pneumonia as the primary source of infection, there was a significantly higher occurrence of a 50% reduction in vasopressor dose from baseline to 12 hours in the cooling group, but significance was not sustained to their primary endpoint of 48 hours. Although the study was not powered to detect significant differences in mortality, they reported a lower 14-

day mortality rate in the cooling group which did not sustain significance at ICU or hospital discharge.

Earlier, in the first known study examining the relationship of mortality and body temperature in ARDS patients, Villar and Slutsky (33) found an association between induced hypothermia and survival. They conducted a case-controlled prospective trial to evaluate whether induced hypothermia impacted clinical outcomes in 19 patients with moribund sepsis and ARDS. In contrast to our results, they found a significant increase in survival in the hypothermia intervention group as well as reductions in intrapulmonary shunt, heart rate, and oxygen tension-based indices. Interestingly, they found no difference in oxygen consumption between the groups, and whether induced hypothermia initiated a protective mechanism is unclear.

In spite of the positive results, their study had several limitations, including small sample size, the moribund condition of the sample, the potential for historical bias, and the lack of a standard severity of illness evaluation. Furthermore, it is important to distinguish between induced hypothermia and spontaneous hypothermia as well as induced normothermia when reviewing literature on thermoregulation. Mechanisms of spontaneous hypothermia include impaired heat production, excessive heat loss, and/or impaired thermoregulation and may be the result of exposure or metabolic/endocrine, neurologic, or toxic disease states. It is unclear whether the presentation of hypothermia in early ARDS is a sign of disease severity or of discordant thermoregulatory response to severe inflammation, and/or if the hypothermia adversely affects lung recovery and patients' survival.

A prospective clinical trial comparing infection and mortality rates in 85 critically ill trauma patients randomized to permissive fever or aggressive fever suppression groups was stopped after an interim analysis because there were more deaths in the aggressive fever

suppression group (26). Although the target sample size was not achieved, this raises the question of whether clinicians should routinely intervene to suppress fever in critically ill patients. Along the same lines, our study, which shows an association of lower mortality with higher baseline and day 2 body temperatures, supports the rationale for a randomized clinical trial that compares the effectiveness of permissive fever to the common practice of fever suppression on the recovery and outcomes of critically ill patients including those with ARDS.

Our analyses had some limitations. The lack of standardized body temperature measurement methods could have resulted in patients being incorrectly categorized into the temperature groups used in our analysis of the five temperature groups. Although 51% of the sample had temperature measured by a pulmonary artery catheter for the study day 2 analysis, the rectal, tympanic, or axillary methods of measurement have varying levels of agreement with pulmonary artery catheter measured core temperature. Temperature altering interventions such as antipyretic medications, external cooling, and warming measures were not collected. We also did not have information regarding unit-based protocols or unit routines for managing hypothermia and fever, which can be variable. These limit the interpretation of whether the study results are related to spontaneous body temperatures or temperatures altered by fever suppression or warming interventions. Nonetheless, the results suggest that, despite frequent use of antipyretic interventions in critically ill patients, there may be equipoise in support of a randomized clinical trial of such interventions to determine if they have any benefit.

Although not specific to the ARDS population, studies of the impact of fever and fever suppression interventions on outcomes in critically ill patients are underway. In effort to evaluate the safety and feasibility of studying aggressive versus permissive temperature control and its impact on mortality and inflammatory biomarkers in non-neurologically injured critically ill

patients, a pilot randomized clinical trial was recently conducted in Canada (34). Although the pilot study reported no difference in mortality or safety outcomes between the aggressive and permissive treatment groups, they concluded the study with less than 50% of their targeted sample size due to enrollment challenges which informed their feasibility aim. The HEAT trial (permissive HypertherEmiaA Through avoidance of paracetamol in known or suspected infection in ICU trial) is a multi-site, randomized clinical trial to compare the effect of intravenous acetaminophen and placebo on survival, body temperature reduction, and organ injury in febrile critically ill patients with infection is currently enrolling subjects in Australia and New Zealand (35).

Finally, since fever is a biomarker of the acute phase response, it is difficult to determine whether the favorable outcome of patients with fever is due to their ability to mount an appropriate acute phase response or related to the fever response itself. Furthermore, it is unclear whether there is an ideal target temperature range that is optimal for lung recovery or that is protective against further lung injury in patients with ARDS. Therefore, the design of future studies evaluating temperature and outcomes should include measurement of temperature-altering interventions and biologic markers of the acute phase response such as cytokines and acute phase proteins, to optimize interpretation and testing of our results.

This study had the largest cohort of patients with ARDS ever used to evaluate alterations in body temperature. Fever was present in 23% of the sample at baseline and a smaller proportion of patients had hypothermia early in their ARDS trajectory. Although fever was associated with improved survival even after accounting for severity of illness and etiology of ARDS, we cannot conclude that permissive fever or aggressive fever suppression influences mortality due to the aforementioned limitations of our study. The routine practice of fever

suppression in patients with ARDS requires further research to test whether fever suppression has a harmful, helpful, or neutral impact on patient outcomes. Well-designed randomized controlled trials are warranted to test the therapeutic value of treating or not treating fever in patients with ARDS.

Table 1 - Baseline Patient Characteristics by Body Temperature Group

Baseline Patient Characteristics by Body Temperature Group

Characteristic	Moderate-Severe Hypothermia	Mild Hypothermia	Normothermia	Fever	High Fever	P Value
	n = 3	n = 45	n = 694	n = 200	n = 27	
Age (years)	59 ± 19	48 ± 15	50 ± 16	47 ± 15	47 ± 15	.06
Male Gender (%)	67	49	52	60	63	.26
Ethnicity (%)						.22
Caucasian	33	60	64	62	70	
Black	0	29	22	20	19	
Other	67	11	14	18	11	
Etiology of ARDS (%)						.48
Trauma	0	2	7	10	4	
Sepsis	33	29	23	21	33	
Multiple Transfusion	0	0	1	2	0	
Pneumonia	33	51	47	48	52	
Aspiration	33	11	17	10	4	
Other	0	7	5	9	7	
APACHE III Score (mean ± SD)	123 ± 28	103 ± 30	94 ± 31	91 ± 28	96 ± 27	.09

Moderate-Severe Hypothermia < 34 ºC; Mild Hypothermia 34 – 35.9 ºC; Normothermia 36 – 38.2 ºC; Fever 38.3 – 39.4 ºC; High Fever ≥ 39.5 ºC

APACHE = Acute Physiology, Age, Chronic Health Evaluation.
Continuous variables reported as mean ± SD. $p < 0.05$ for statistical significance.

Figure 1. Observed mortality according to five baseline body temperature groups in 969 patients with ARDS. Body temperature groups: Moderate-Deep Hypothermia < 34ºC; Mild Hypothermia 34 – 35.9ºC; Normothermia 36 – 38.2ºC; Fever 38.3 – 39.4ºC; High Fever ≥ 39.5ºC.

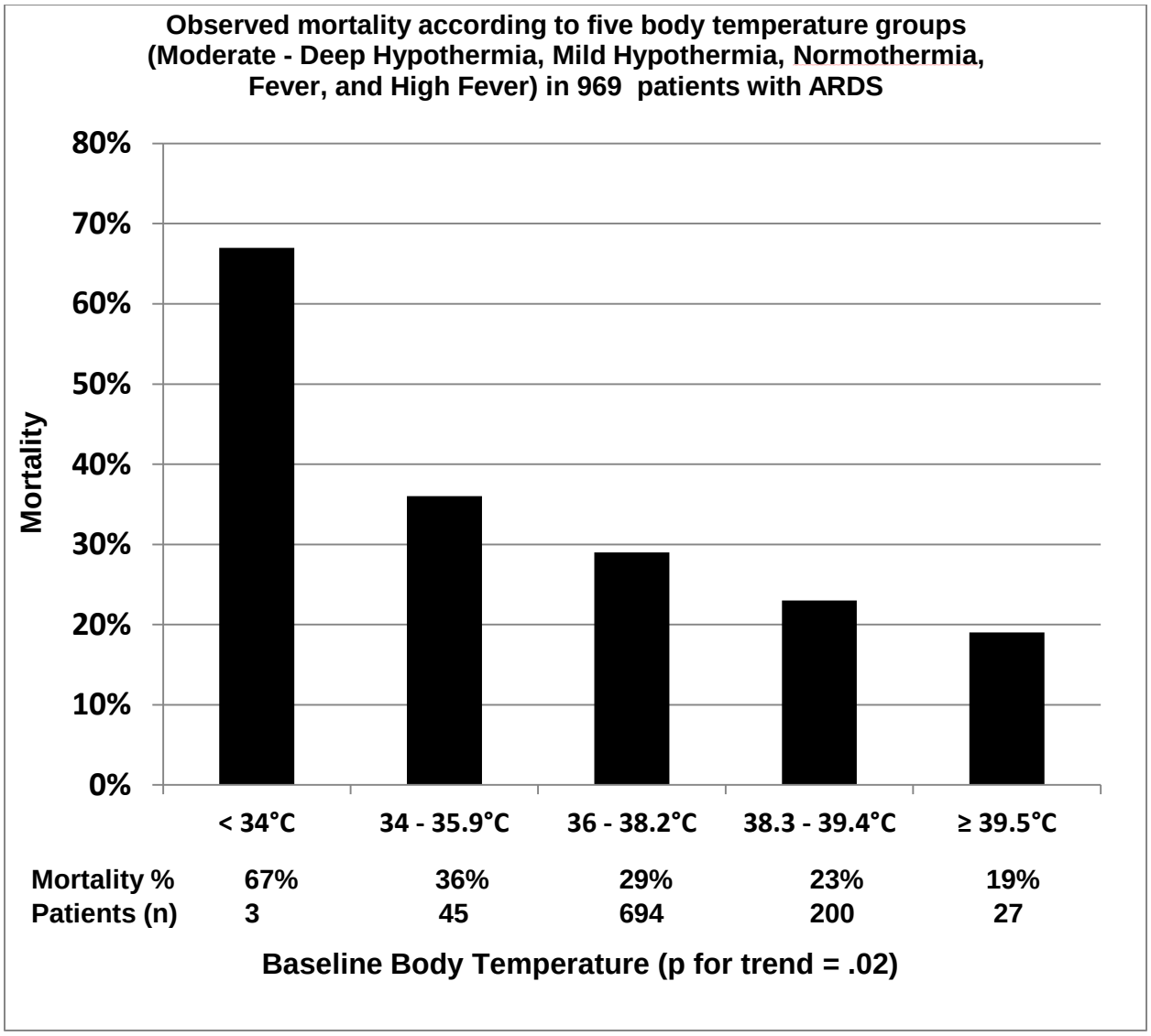

Table 2 - Baseline Body Temperature, Etiology of ARDS & APACHE III score as Predictors of 90-day Mortality

Baseline Body Temperature, Etiology of ARDS & APACHE III score as Predictors of 90-day Mortality [a]				
		95% C.I. (Odds Ratio)		
Predictor variable	**OR**	**Lower**	**Upper**	**P value**
Baseline Body Temperature [b]	.85	.73	.98	.03
Apache III Score	1.03	1.02	1.03	<.001
Primary etiology of lung injury [c]				.31
Trauma vs. Aspiration	.51	.20	1.26	.14
Sepsis vs. Aspiration	1.27	.76	2.13	.37
Multiple Transfusion vs. Aspiration	1.89	.44	8.07	.39
Pneumonia vs. Aspiration	1.16	.72	1.86	.55
Other causes vs. Aspiration	.84	.38	1.83	.65

a. Hosmer-Lemeshow goodness of fit p= 0.55

b. Per 1 °C increase in body temperature

c. Reference category for analysis was the Aspiration group

APACHE = Acute Physiology, Age, Chronic Health Evaluation

Table 3 - Body Temperature Day 2, Etiology of ARDS & APACHE III Score as Predictors of 90-day Mortality

Body Temperature Day 2, Etiology of ARDS & APACHE III Score as Predictors of 90-day Mortality

		95% C.I. (Odds Ratio)		
Predictor variable	**OR**	**Lower**	**Upper**	**P value**
Body Temperature Day 2	.82	.69	.98	.03
Apache III Score	1.03	1.02	1.03	<.001
Primary etiology of lung injury				.31
Trauma vs. Aspiration	.46	.18	1.19	.11
Sepsis vs. Aspiration	1.20	.71	2.01	.50
Multiple Transfusion vs. Aspiration	1.85	.43	7.93	.41
Pneumonia vs. Aspiration	1.16	.72	1.87	.54
Other causes vs. Aspiration	.83	.37	1.85	.64

APACHE = Acute Physiology, Age, Chronic Health Evaluation.

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Chapter 3

Comparison of non-invasive core body temperature monitoring using zero-heat-flux technology to rectal and urinary bladder thermometry in critically ill adults

Abstract

Objective: To evaluate the agreement and precision between a zero-heat-flux thermometry system (SpotOn™) and continuous rectal and urinary bladder thermometry methods during fever and defervescence in critically ill adults.

Design: Prospective method-comparison study

Setting: A 32-bed medical-surgical ICU and a 29-bed neuroscience ICU at a large academic medical center.

Patients: Adults (18 years and older) with fever (≥38.3˚C) and either rectal or urinary bladder thermometry who were enrolled in a randomized clinical trial testing the effect of acetaminophen on core body temperature and hemodynamics (ClinicalTrials.gov NCT01869699).

Interventions: Body temperature monitoring with SpotOn™ device.

Measurements and Main Results: A total of 748 paired temperature measurements from 38 patients that had both SpotOn™ and either continuous rectal (n=29) or bladder (n=9) thermometry were included in this study. Temperatures during the study period ranged from 36.9 to 39.7°C (rectal), 36.9 to 39.9°C (bladder) and 36.6 to 39.4°C (forehead core SpotOn™). The bias for SpotOn™- bladder was -0.07 ± 0.24°C with 95% LOA of ± 0.47°C (-0.54, 0.40°C). The bias for SpotOn™- rectal was -0.24 ± 0.29°C with 95% LOA of ± 0.57 °C (-0.81, 0.33°C). A majority of method difference temperatures were within ± 0.5˚C in both method comparison groups (96% and 85% for bladder and rectal groups, respectively).

Conclusion: The SpotOn™ thermometry system has excellent agreement and good precision and is an accurate, non-invasive, and comfortable alternative for continuous temperature monitoring in ICU patients, especially when alternative methods are contraindicated or not available.

Introduction

Body temperature alterations in critically ill patients are common and may be related to the patient's clinical diagnosis, the therapies administered, and/or exposure in the intensive care unit (ICU) environment (such as during bathing and procedures). Frequent monitoring of body temperature facilitates early detection of changes in clinical condition and patient responses to therapies. For example, the early detection of a fever due to an infection or drug reaction and/or hypothermia related to continuous renal replacement therapy or massive blood transfusion can prompt for further assessments and interventions. However, body temperature monitoring in ICUs is highly variable with regard to the site of measurement, thermometry technology used, and the frequency of measurement (1-3).

The ideal monitoring system would provide a continuous, non-invasive accurate measure of core body temperature that is feasible, comfortable for patients, and compatible with care interventions and activities of patients in the ICU environment. Unfortunately, the standard thermometry methods used in ICUs for continuous monitoring are invasive and have barriers to use. The pulmonary artery (PA) catheter provides the gold standard measure for core body temperature, yet it is invasive, associated with potential risks, not used broadly across ICUs today, and is typically in place for a short duration (4-7). Although there is strong agreement between temperatures obtained from urinary catheter and PA catheter thermometry, urinary catheter thermometry is also invasive. Current practice standards include efforts to reduce urinary catheter days due to device-related urinary tract infection risk (8-10). Esophageal probe thermometry also provides accurate measures of core body temperature, yet it is challenging to maintain probe position beyond short time frames, and use is typically limited to intubated patients (11). Rectal thermometry was a common method of continuous monitoring, yet it is

used less frequently in ICUs today for various reasons: recent focus on prevention of device-related pressure injury to skin and mucosa; introduction of new fecal management devices; and concerns about patient dignity and discomfort (2, 12). Thus, obtaining continuous core body temperature data remains a challenge in ICUs today.

A recently available continuous, non-invasive temperature monitoring system that uses zero-heat-flux (ZHF) technology to measure core body temperature is the 3M™ SpotOn™ system (Arizant Health Care Inc., a 3M™ Company). This system consists of a control unit, cable, and small disposable sensor applied to the lateral forehead. The ZHF system uses the thermal insulator and resistive warming circuit to eliminate flow of skin surface heat to the environment, establishing conditions where the temperature gradient should be zero between the thermistor on the skin surface and deep tissue. The ZHF system is designed to measure core body temperature (1 to 2 centimeters below the surface) via the isothermal tunnel created under the skin sensor as shown in **Figure 1**.

A manufacturer-sponsored clinical trial to evaluate device accuracy reported good agreement between forehead core SpotOn™ system and PA temperatures with a mean difference between methods (bias) of -0.23 ± 0.42˚C in perioperative cardiac surgery patients (13). The manufacturer's stated accuracy for the SpotOn™ system is ± 0.2˚C for temperatures between 25˚C and 43˚C (Arizant Healthcare Inc., a 3M™ Company, Eden Prairie, MN, 2012).

Method-comparison studies designed to evaluate the accuracy of earlier thermometry systems that used ZHF technology compared to standard core body thermometry methods (pulmonary artery, esophageal, nasopharyngeal, urinary bladder) used in perioperative and ICU settings have found the ZHF technology to be a sufficiently accurate measure of core body temperature in surgical patients (13,14). However, there is a need for method-comparison

studies of the recently available SpotOn™ system that uses ZHF technology in diverse critically ill populations across a range of body temperatures to determine the utility of this thermometry method in ICUs before widespread adoption into clinical practice. Thus, the purpose of this study was to evaluate the agreement and precision between the SpotOn™ temperature monitoring system and established rectal and urinary bladder continuous thermometry methods during fever and defervescence in critically ill adults with medical, surgical, and neurological conditions.

Materials and Methods

Patients from a randomized clinical trial to test the effects of intravenous acetaminophen on core body temperature and hemodynamic responses in febrile critically ill patients (ClinicalTrials.gov NCT01869699) were eligible for this study. A method-comparison study design was used to compare simultaneous body temperature measurements obtained from the continuous, non-invasive SpotOn™ temperature monitoring system with measurements from established continuous, invasive rectal or urinary temperature monitoring systems in critically ill adults. The method-comparison design comparing the SpotOn™ system to both rectal and urinary bladder thermometry methods was selected since it was not feasible to obtain the gold standard core temperature due to the limited use of PA catheters in the research site's ICUs. We hypothesized that the non-invasive SpotOn™ system using ZHF technology is sufficiently comparable to invasive continuous rectal and urinary bladder thermometry methods to within a value of ± 0.5˚C for agreement and precision.

Enrolled patients from the adult medical-surgical and neuroscience ICUs at the University of California, San Francisco were randomized to receive study intervention of either intravenous acetaminophen (1 gram) or normal saline placebo and were monitored for a 4-hour post study intervention period. Patients were eligible for study enrollment if they were 18 years

of age or older, weighed at least 50 kilograms, had a temperature of greater than or equal to 38.3°C and did not meet exclusion criteria of hyperthermia, acute liver failure, therapeutic temperature management, or extracorporeal blood circuit therapy. Patients who did not have continuous rectal or urinary bladder thermometry were excluded from this study. Approval was obtained from the Committee on Human Research at the University of California, San Francisco and signed written informed consent was obtained from patients or surrogates prior to data collection.

Patient characteristics and therapies administered during the study period were recorded. Ambient temperature of the ICU room was recorded at the start of the study period. Physical cooling and warming interventions were not permitted during the 4-hour study period.

Forehead core body temperature was measured on all patients using the non-invasive SpotOn™ temperature monitoring system (Eden Prairie, MN) during the 4-hour study period. The disposable ZHF sensor (3M™ SpotOn™ Temperature Monitoring Sensor, Model 36000) was connected to the control unit (3M™ SpotOn™ Temperature Monitoring System Control Unit, Model 370). After the skin was cleansed with alcohol, the sensor was placed on the patient's left lateral forehead above the orbital ridge. The system equilibration of temperature from the deeper tissue to the skin surface took 1 to 4 minutes. Simultaneously, temperatures were recorded from the continuous rectal or urinary bladder thermometry system used in the patient's routine care during the study period. Rectal temperature probes (Level-1®, Smiths Medical ASD Inc., Dublin, OH) or urinary bladder temperature-sensing catheters (DeRoyal®, DeRoyal Industries, Inc., Powell, TN) were connected to the Solar® 8000i Bedside Monitor (GE Healthcare, Buckinghamshire, UK). Continuous rectal and urinary bladder thermometry systems use thermally sensitive resistors in the probe and catheter that sense change in the surrounding

environment. Temperatures from both the SpotOn™ system and the rectal or urinary bladder thermometry system were recorded at baseline (within 15 minutes before study drug administration); at the time of study drug administration; every 5 minutes for 15 minutes; and then every 15 minutes for 4 hours.

Statistical Analysis

The Bland and Altman method was used to analyze the thermometry method-comparison data to estimate the direction and extent of agreement and the precision among the measurement methods (15). Graphical plots of the method temperature differences were examined for patterns, and calculated estimates for agreement and precision were analyzed. The mean of differences between temperatures represents the agreement between methods and the bias of the SpotOn™ system relative to the two established thermometry methods. Agreement is presented as the mean difference (bias) and the 95% confidence interval (CI). Precision refers to the repeatability of measurements and the distribution of measurement difference values around the bias (mean of differences) and is calculated using the standard deviation (SD) of the bias. Specifically, precision is presented as the 95% limits of agreement (LOA), either a single value [± (SD x 1.96)] or as upper and lower LOA values [bias ± (SD x 1.96)] surrounding the bias. (Example: if bias = 0.25 ± 0.15, then the LOA would be 0.15 x 1.96 = ± 0.29 or 0.25 ± 0.29 = -0.04, 0.54). An *a priori* defined acceptable limit of ± 0.5˚C for agreement (bias) and precision (95% LOA) was chosen. This value was selected since differences within these limits across the range of body temperatures have little relevance in clinical practice and may be related to circadian rhythm (16). Many thermometry method-comparison studies in critically ill populations have also used ± 0.5˚C as the clinically acceptable limit (9, 11, 13, 14, 17).

The proportion of temperature differences within ± 0.5˚C from SpotOn™ and corresponding rectal and urinary bladder temperature comparisons and the 95% CI were also computed for both groups. Large proportions of temperature differences beyond ± 0.5˚C were interpreted as clinically relevant. Data were analyzed with SPSS computer software, version 23 (SPSS, Inc).

Although the Bland Altman procedure is not strictly a statistical test, the mean difference in temperature between the two methods was determined and examined. The sample size of 180 paired temperatures in the bladder data is more than adequate to provide adequate power to detect a significant difference between the two measures. The mean difference for the bladder comparison was -0.07˚C and the standard deviation of the differences was 0.24˚C. A matched-pair t-test would have power of 97% to detect the small effect size (d = 0.30) calculated using a 0.05 two-sided significance level and 180 paired observations. However, detecting a significant difference between the two measures is not of primary importance. In the context of this situation, the temperatures of the two measurement techniques would have to differ by more than 0.5˚C to be considered clinically important. The average difference was only 0.07˚C in the bladder comparison group. The sample size of 568 paired observations from the rectal comparison group provides even more power (greater than 99%) to detect significant differences between the two methods.

Results

A total of 748 paired temperature measurements from 38 patients from the clinical trial that had both SpotOn™ and either continuous rectal (n=29) or urinary bladder (n=9) thermometry were included in this study. There were 20 temperature pairs recorded from all patients with the exception of 8 pairs collected from one patient in the rectal thermometry group

who did not complete the primary study protocol. Patient characteristics for the sample are shown in **Table 1**. Temperatures during the study period ranged from 36.9 to 39.7°C (rectal), 36.9 to 39.9°C (urinary bladder) and 36.6 to 39.4°C (forehead core SpotOn™).

Figures 2 and 3 show the Bland Altman plots with graphical presentation of agreement and precision for SpotOn™-bladder temperatures and SpotOn™-rectal temperatures, respectively. Inspection of the data plots revealed no patterns of temperature differences between SpotOn™ and either rectal and bladder thermometry methods across the range of temperature values. The bias for SpotOn™- bladder was -0.07 ± 0.24°C (95% CI -0.04, -0.11) with 95% LOA of ± 0.47°C (-0.54, 0.40°C). The bias for SpotOn™- rectal was -0.24 ± 0.29°C (95% CI -0.21, -0.26°C) with 95% LOA of ± 0.57 °C (-0.81, 0.33°C).

The proportion of method temperature differences within ± 0.5˚C in the urinary bladder comparison group was high at 0.96 (95% CI 0.93, 0.99). In the urinary bladder comparison group, the proportion of differences beyond 0.5˚C came from 2 out 9 patients for a total of 8/180 difference measures. The proportions within ±0.5˚C for these 2 patients were 0.70 and 0.90. The proportion of method temperature differences within ± 0.5˚C for the rectal comparison group was 0.85 (95% CI 0.82, 0.88). For the rectal comparison group, the proportion of differences beyond 0.5˚C came from 11 of the 29 patients for a total of 80/568 difference measures. From this subset, the proportions within ±0.5˚C for individual patients ranged from 0.20 to 0.95 (median 0.60, IQR 0.45, 0.95). A majority of method difference temperatures were within ± 0.5˚C in both method comparison groups.

No signs of skin irritation under the sensor were noted upon removal after 4.5 hours and there were no complaints of discomfort from patients who could self-report. Despite sweating in some patients during febrile periods and defervescence, the forehead sensors maintained their seal

during the study period. Severe diaphoresis related to autonomic dysfunction in one neurologically injured patient did not appear to disrupt the SpotOn™ thermometry system as the sensor seal was maintained and the mean difference between this patient's 20 paired rectal and SpotOn™ temperatures was 0.24 ± 0.11˚C.

Discussion

Monitoring body temperature in critically ill patients, an essential part of daily practice in ICUs, requires the reliable and precise technology with capacity for continuous monitoring. Use of the least invasive technology for temperature monitoring is important for patient comfort and prevention of iatrogenic harm. This is the first study to compare the SpotOn™ system to two invasive thermometry methods commonly used to monitor medical, surgical, and neurologically injured ICU patients. Study results demonstrated that the SpotOn™ system demonstrated excellent agreement with the established clinical thermometry systems and was within the *a priori* defined acceptable bias limit of ± 0.5˚C for both bladder (-0.07˚C) and rectal (-0.24˚C) methods in ICU patients. This bias represents the systemic error in the SpotOn™ method relative to the other methods and the negative bias results indicate that the SpotOn™ system slightly underestimates both rectal and bladder temperatures. The SpotOn™ system also demonstrated good precision in both comparison groups despite the 95% LOA for the rectal group barely exceeding our *a priori* defined acceptable LOA of ± 0.5˚C (95% LOA: rectal ± 0.57˚C and bladder ± 0.47˚C).

Eshraghi and colleagues (13) evaluated the accuracy of the prototype SpotOn™ system comparing the forehead core (SpotOn Prototype™) to PA temperatures in 105 cardiac surgical patients during intraoperative and postoperative ICU study periods. They found the level of agreement and precision to be sufficiently accurate for use in intraoperative and postoperative

clinical practice (bias -0.23 ± 0.42˚C; 95% LOA (± 0.82˚C) -1.06, 0.60˚C). The levels of agreement and precision for the temperature comparisons in the postoperative ICU subset were similar to the combined intraoperative and postoperative estimates (bias -0.32 ± 0.38˚C; 95% LOA (± 0.74˚C) -1.06, 0.42˚C). Although their comparison was made to the gold standard PA core temperature, the proportion of temperature differences that were within 0.5˚C in their ICU subset (84%) was similar to our findings that compared rectal (85%) and urinary bladder (96%) to forehead core temperatures.

Studies of other thermometry systems using ZHF technology, mostly prototypes, have been compared to temperatures from PA, esophageal, and urinary bladder sources (13, 14, 18). A method comparison study of esophageal and forehead core temperatures that used a ZHF thermometry prototype in post-arrest patients during targeted hypothermia therapy and rewarming found good level of agreement and precision with a bias –0.12˚C and 95% LOA (± 0.48˚C) -0.59, 0.36˚C (18). One limitation of the present study was that the SpotOn™ method was not evaluated in patients with hypothermia, a condition that warrants continuous thermometry in ICUs.

A method-comparison study of urinary bladder thermometry compared to 8 noninvasive methods, including an early model forehead ZHF thermometry device, was conducted in 50 surgical patients in the post-anesthesia care unit setting (14). In contrast to the present study findings, they did not find clinically acceptable levels of agreement and precision in their urinary bladder-forehead ZHF method comparison (0.50 ± 0.41˚C; 95% LOA (± 0.80˚C) -1.31, 0.31˚C). They also found a lower proportion of differences within ± 0.5˚C (0.70, 95% CI 0.62, 0.80) compared to the 0.96 (95% CI 0.93, 0.99) found in the urinary bladder comparison group in the present study.

The present study compared thermometry systems during fever and defervescence in ICU patients due to the inclusion criteria of fever in the primary clinical trial. We found excellent agreement and precision, within ± 0.5˚C clinically acceptable limits, for the SpotOn™ - urinary bladder comparison and excellent agreement with good precision for the SpotOn™ - rectal comparison. Although the temperature range was 34.5˚C to 39.3˚C in the postoperative ICU patient group in the Eshraghi et al (13) study that used the SpotOn™ prototype, an analysis of the proportion of febrile temperature pairs was not reported.

To our knowledge, the present study is the first to evaluate this new thermometry system in patients with neurologic injury (n = 23 of our sample) in whom continuous temperature monitoring is an international neurocritical care guideline recommendation (19). Ten of the neurological patients in the study had external ventricular drains (EVD) with intracranial pressure monitoring as well as rectal thermometry. Similar results were found in a subanalysis of the 200 paired SpotOn™-rectal temperatures in the EVD group (bias -0.29 ± 0.33˚C; 95% LOA (± 0.65˚C) -0.95, 0.36˚C). The agreement for the EVD group comparison was within the *a priori* defined acceptable LOA ± 0.50˚C and the precision was slightly beyond that 95% LOA, similar to our findings in the SpotOn™ - rectal comparison group.

A recent study compared nasopharyngeal and sublingual temperatures to forehead core temperatures (n = 83) using the SpotOn™ system at 3 time points during elective surgical procedures (20). These investigators found excellent agreement and precision in the nasopharyngeal comparison (bias 0.07 ± 0.21˚C; 95% LOA (± 0.41˚C) -0.34, 0.48˚C). The level of agreement and precision they found between SpotOn™ and nasopharyngeal temperatures were similar to the method comparison findings for urinary bladder thermometry in the present

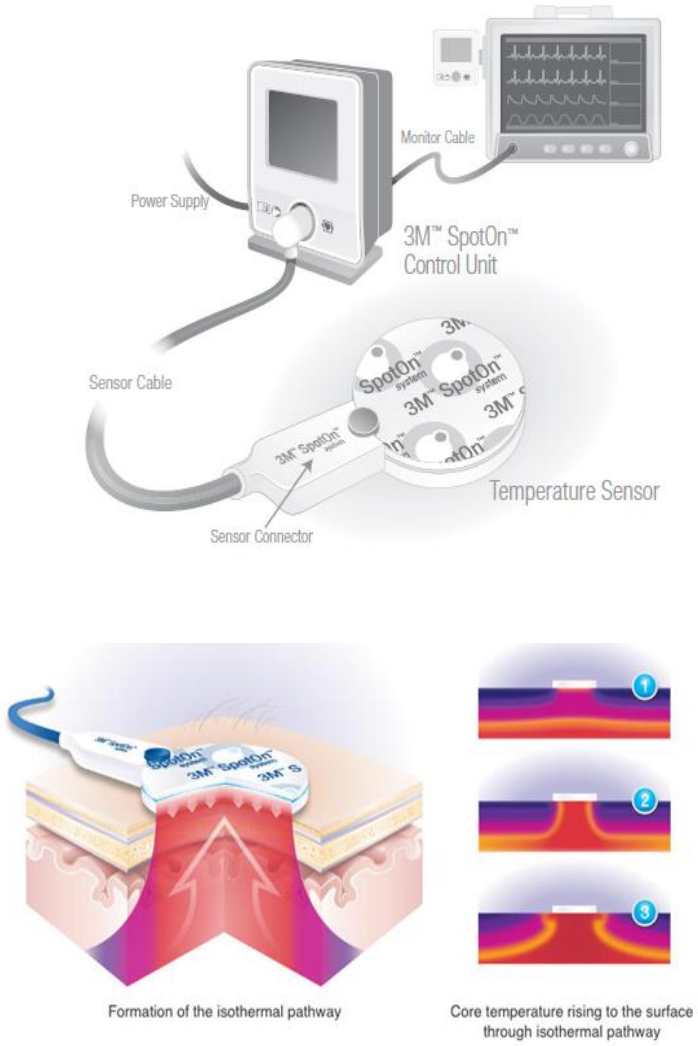
study. Both of these sources are considered accurate and reliable sources of core temperature. However, the sublingual method yielded good agreement and only fair precision.

The 4-hour timeframe of the study period is a limitation of our study. Further evaluation of sensor securement to maintain ZHF insulation and the related reliability over longer periods is warranted. Evaluation of the system with fan use and other physical cooling interventions used in the ICU is also indicated since we did not permit physical cooling including fan use during the study period. Another limitation of the present study is that the SpotOn™ system was not evaluated in patients with hypothermia, which is a condition that warrants continuous thermometry in ICUs. Nevertheless, the present study evaluated agreement and precision during dynamic body temperature alterations including periods of fever and defervescence. This is the first study to evaluate a forehead ZHF thermometry system in neurologically injured patients with invasive drains (EVDs) proximal to the site of core temperature monitoring. The present study findings of excellent agreement and precision for the SpotOn™ temperature monitoring system support clinical use in the ICU as well as further research to address limitations.

Conclusion

This method-comparison study was the first to demonstrate that the SpotOn™ system is an accurate, non-invasive, and comfortable option for continuous thermometry for medical, surgical and neurologically injured ICU patients. The SpotOn™ system is an appealing alternative for continuous temperature monitoring in ICU patients due to the benefits of its unique non-invasive design, especially when alternative methods are contraindicated or not available. Further research to evaluate accuracy and reliability of the SpotOn™ system over longer time periods and during targeted temperature therapies in ICU patients is warranted.

Figure 1: 3M™ SpotOn™ Temperature Monitoring System



Isothermal tunnel formation with zero-heat-flux technology
3M™ SpotOn™ system (Reproduced with permission from ©3M™, 2016)

Figure 1
SpotOn™ Temperature Monitoring System and isothermal tunnel formation with zero-heat-flux technology, 3M™ SpotOn™ system (Reproduced with permission from ©3M™, 2016)

Table 1 – Patient & Environment Characteristics (n = 38)

Characteristic	Mean ± SD (Range) or n (%)
Age (years)	57 ± 15 (Range 20 - 78)
Gender-male/female	20/18 (53%/47%)
Ethnicity	
Asian/Pacific Islander	10 (26%)
Black	2 (5%)
Caucasian	17 (45%)
Hispanic	9 (24%)
Admitting diagnosis type	
Medical	9 (24%)
Neurologic	23 (60%)
Surgical	6 (16%)
APACHE II	24 ± 6 (Range 14 - 43)
Body Mass Index	29.8 ± 6.6 (Range 18.1 – 48.2)
Mechanically ventilated	26 (68%)
Etiology of fever	
Infectious	28 (74%)
Neurologic	10 (26%)
Ambient ICU room temperature	21.4 ± 1.2˚C
Urinary bladder -SpotOn™ temperatures	
Urinary bladder (n=180)	38.2 ± 0.61˚C (Range 36.9 – 39.9˚C)
Forehead core (n=180)	38.2 ± 0.71˚C (Range 36.7 – 39.9˚C)
Rectal -SpotOn™ temperatures	
Rectal (n=568)	38.4 ± 0.53˚C (Range 36.9 – 39.7˚C)
Forehead core (n=568)	38.2 ± 0.59˚C (Range 36.6 – 39.4˚C)

Figure 2
Bland Altman Plot of SpotOn™ Core and Urinary Bladder Temperatures

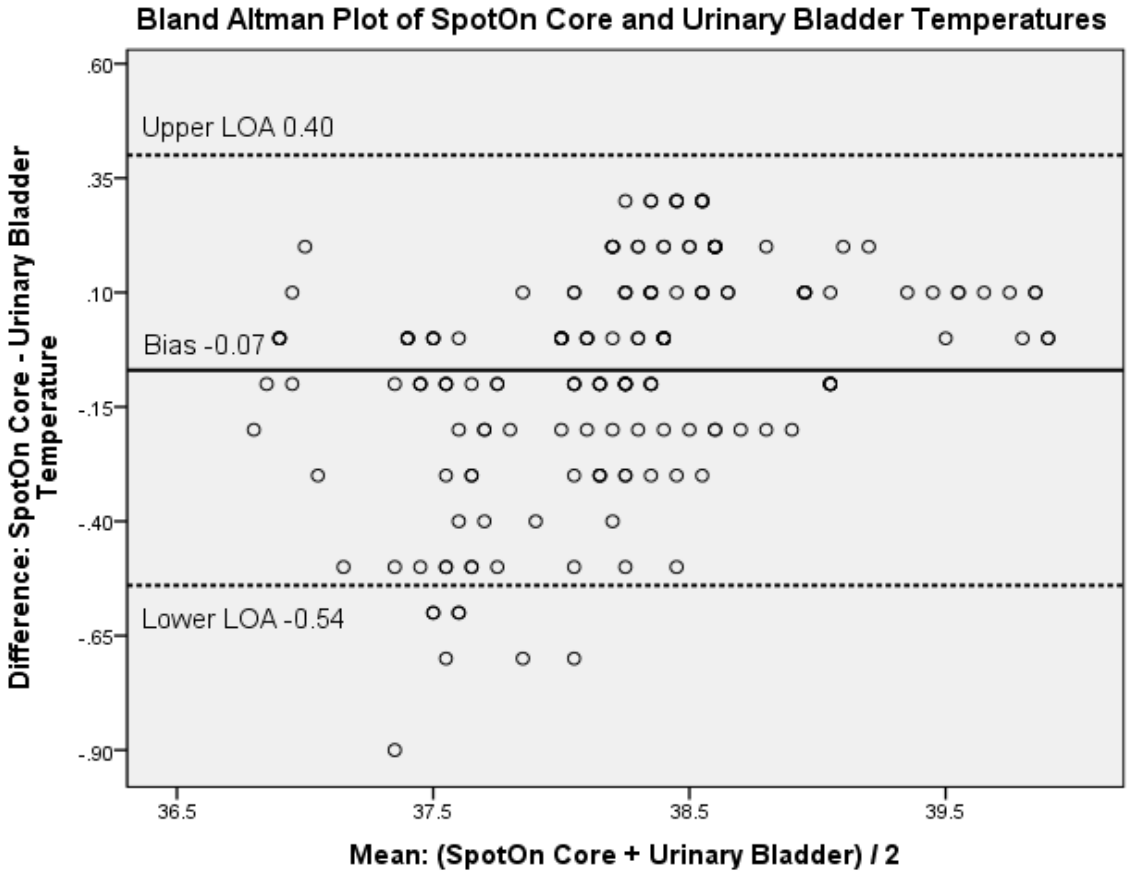


Figure 2
SpotOn™ forehead core and urinary bladder temperatures (n=180 paired measurements)
Bias -0.07˚C (SD ± 0.24˚C); 95% Limits of Agreement (LOA) = -0.54, 0.40

Figure 3
Bland Altman Plot of SpotOn™ Core and Rectal Temperatures

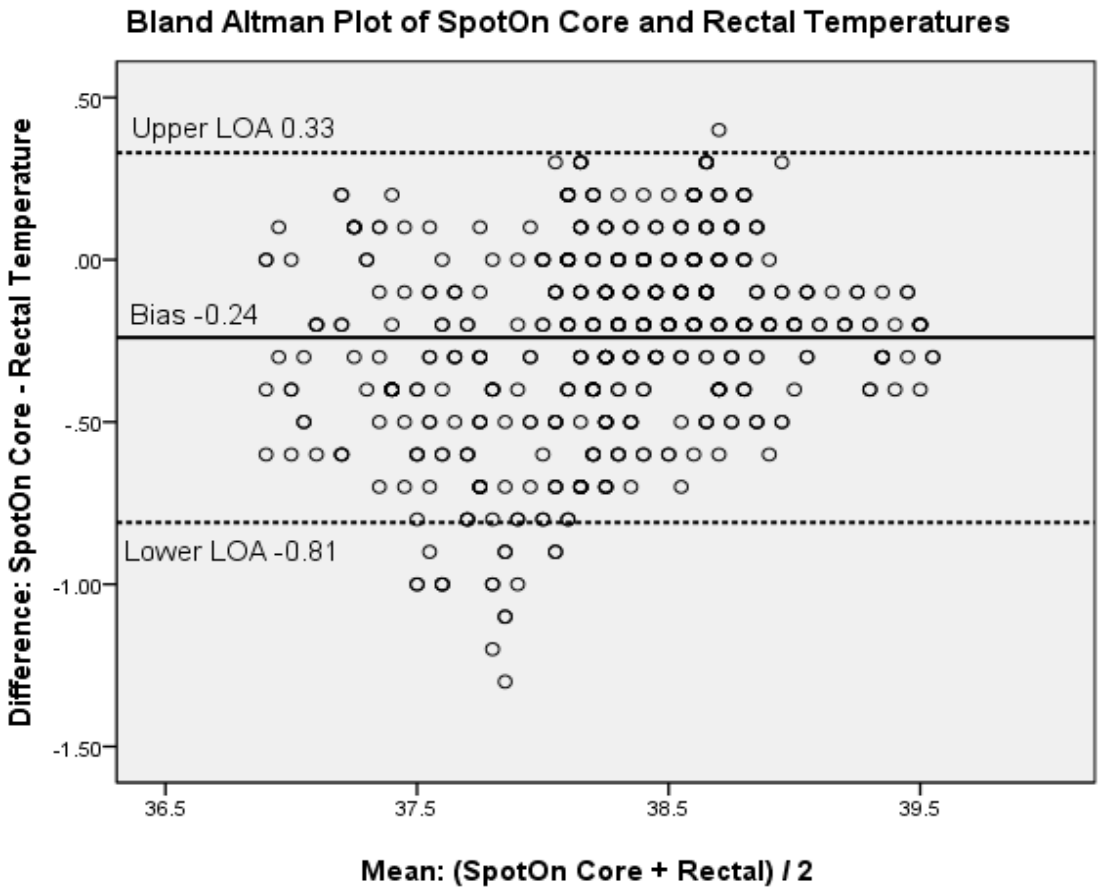


Figure 3
SpotOn™ forehead core and rectal temperatures (n=568 paired measurements)
Bias -0.24˚C (SD ± 0.29˚C); 95% Limits of Agreement = -0.81, 0.33

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Chapter 4

Effects of intravenous acetaminophen on body temperature and hemodynamic responses in febrile critically ill adults: a randomized clinical trial

Abstract

Background: Acetaminophen is the most common antipyretic medication administered to intensive care unit (ICU) patients. There is limited evidence from randomized, controlled trials on the antipyretic and hemodynamic effects of intravenous acetaminophen in febrile ICU patients.

Purpose: This study aimed to investigate the effects of intravenous (IV) acetaminophen on body temperature (BT) and hemodynamic responses in febrile (≥ 38.3˚C) ICU patients.

Methods: This randomized, double blind, placebo-controlled trial was conducted in 3 adult ICUs at a large academic medical center. Forty one febrile ICU patients were randomly assigned to receive a single dose of either 1 gram of IV acetaminophen or 0.9% sodium chloride placebo. Core body temperature (BT), heart rate (HR), blood pressure, and respiratory rate (RR) were measured at baseline and at 5 to 15 minute intervals for 4 hours after infusion of study drug. The primary outcome was time-weighted average (TWA) BT adjusted for baseline BT. Secondary outcomes include TWA BT, HR, blood pressure, and RR as well as vital sign change over time outcomes.

Results: Of the 40 patients included in the analysis, demographic and patient characteristics were similar at baseline between groups. There was a significant difference in adjusted TWA BT between groups, with a mean difference of 0.47˚C lower in the acetaminophen group ($p = 0.002$). The acetaminophen group also had significantly lower adjusted mean differences in TWA HR ($p = 0.03$), TWA SBP ($p < 0.001$), and TWA MAP ($p = 0.02$), yet no difference was

found in both adjusted TWA DBP ($p = 0.05$) and adjusted TWA RR ($p = 0.42$) between groups. Significant differences were found between groups in change-over-time outcomes for BT, HR, and blood pressures in the first 2 hours after study drug administration, yet there were no significant differences at 4 hours.

Conclusions: There is a reduction in BT after administration of IV acetaminophen compared to placebo in febrile ICU patients, yet the small difference has little clinical relevance. There is a clinically meaningful reduction in HR and blood pressure after IV acetaminophen compared to placebo, especially within 2 hours of administration. Further study of the antipyretic and hemodynamic response to acetaminophen in a larger sample of critically ill patients is warranted to inform evidence-based practice guidelines for safe and effective fever management strategies, when indicated.

Background

Fever is a common occurrence in intensive care unit (ICU) patients, with reported incidence rates ranging from 26% to 70% (1-6). Infection and neurologic injury are frequent causes of fever in critically ill patients (4, 6, 7). Fever is a complex physiologic response and is associated with increases in oxygen consumption, heart rate, blood pressure, and respiratory rate (8-13). Although fever is typically a beneficial adaptive response to infection and injury, the associated cardiopulmonary and metabolic stress is a concern of clinicians caring for patients with critical illness. Despite the limited evidence relating adverse outcomes to cardiopulmonary or metabolic stress from fever in critically ill patients, clinicians routinely administer antipyretic interventions.

Fever in neurologically injured critically ill patients has been associated with worse outcomes including extension of neurologic injury, longer ICU length of stay, poor functional outcomes, and increased mortality, yet a direct cause has not been established (14). The local effects of fever in the brain may lead to cerebral edema, reduced cerebral perfusion pressure, and potential ischemia (15, 16). Prolonged fever and intracranial hypertension plus fever are significant prognostic indicators for poor outcomes in traumatic brain injury patients (17). Although the American Heart Association and American Stroke Association recommend treatment of fever with antipyretic medications in patients with acute ischemic stroke, the recent guidelines for management of spontaneous hemorrhagic stroke only recommend that treatment of fever be considered (18, 19). Authors of the recently published European Stroke Organization guidelines for management of temperature in patients with ischemic stroke could not make a recommendation for treating fever due to the low level of evidence relating fever suppression to improved outcomes (20). Despite the disparate evidence relating fever to poor outcomes in

neurologically injured patients, antipyretic interventions have become commonplace in neurological ICUs in the past decade (14, 21, 22).

Currently, there are no research-based guidelines for fever suppression in non-neurologically injured critically ill patients. Fever suppression interventions are widespread in hospitals, with reports that up to 50% of ICU patients receive antipyretic interventions (3, 23, 24). Routine management of fever in ICU patients includes administration of antipyretic medications and/or physical cooling interventions to reduce body temperature (3, 10, 23-26). Acetaminophen is the most common antipyretic medication ordered for ICU and hospitalized patients (25, 27, 28). Survey responses from critical care physicians and nurses consistently report that acetaminophen is the first line antipyretic intervention chosen for febrile patients and physical cooling methods as second line interventions when fevers persist (22, 23).

Although acetaminophen is routinely administered for fever suppression in ICUs, there are limited prospective data on the antipyretic efficacy of acetaminophen in adult critically ill patients. The mechanism of antipyretic action of acetaminophen is not fully understood, but it has been shown to inhibit synthesis of prostaglandins in the central nervous system (29). Pharmacokinetic studies of acetaminophen in critical illness have found variability in time to peak serum concentrations with enteral and rectal routes of administration as well as an increase in volume of distribution in critical care compared to acute care patients (30-32).

A meta-analysis that evaluated the antipyretic and analgesic efficacy of acetaminophen compared to ibuprofen could not make conclusions about antipyretic effects for adults with fever due to lack of evaluable data (33). The recent large randomized trial comparing the effect of IV acetaminophen 1 gram to IV 5% dextrose placebo every 6 hours while febrile on outcomes in critically ill patients with infection reported a small difference in daily mean temperatures between

groups (0.34˚C; 95% CI .05 to 0.20) (34). The largest randomized trial evaluating the effect of acetaminophen 6 grams daily to placebo on functional outcomes in neurologically injured patients (ischemic and intracerebral hemorrhage stroke) did not find a significant outcome benefits for the acetaminophen group (35). Although the sample had a mix of febrile and afebrile patients, the acetaminophen group had a lower mean temperature by only a small difference after 24 hours (0.26˚C; 95% CI 0.18 to 0.31). Challenges to interpretation of antipyretic efficacy study findings include the variability of acetaminophen dosages, administration routes, thermometry methods, temperature thresholds for fever, and time intervals used to measure body temperature change. There is still a lack of high-grade evidence to guide the use of acetaminophen for fever suppression in critically ill patients.

Anecdotal reports of reduced blood pressure after administration of acetaminophen in ICU patients prompted further research since hypotension was not recognized as a potential adverse effect in the manufacturer drug information (36, 37). There are mixed results from studies examining the incidence of hypotension after acetaminophen administration in ICU patients (30, 36-42). In a prospective observational study (n =127) examining the effect of IV acetaminophen on systolic blood pressure (SBP) when administered for pain or fever, hypotension (defined as a 20% decrease in SBP from baseline) was observed in 13% of the medical-surgical ICU patients with a very low incidence of only 1.3% after 1507 doses (41). Another observational study found a significant decrease in SBP (at least 15% reduction from baseline) in 59% of febrile ICU patients that received enteral or IV acetaminophen (38). The mixed findings may be related to study design; the mixed indications of pain and/or fever for administration; variable threshold definitions of hypotension; and the multiple confounders, such as sepsis and shock diagnoses and vasoactive

medications that are common to ICU patients. There are limited prospective controlled studies of the impact of IV acetaminophen on hemodynamic variables in critically ill patients.

The recently published large randomized trial that evaluated the impact of IV acetaminophen compared to placebo on outcomes in febrile ICU patients with infection found no significant differences in ICU-free days and 90-day mortality (34). Despite the neutral impact of acetaminophen on outcomes, the evidence of its limited effect on body temperature reduction, and the question of potential acute adverse effects on hemodynamics, acetaminophen is widely administered to ICU patients with fever.

To better understand the therapy response and potential acute adverse effects of this commonly administered medication in febrile critically ill patients, we conducted a randomized, double blind, placebo-controlled trial to evaluate the effect of IV acetaminophen on body temperature and hemodynamic responses. We hypothesized that there would be a significant difference in time-weighted average (TWA)-body temperature (BT), -heart rate (HR), -systolic blood pressure (SBP), -diastolic blood pressure (DBP), -mean arterial pressure (MAP) and –respiratory rate (RR) over 4 hours after administration of IV acetaminophen compared to placebo in ICU patients with fever. Since evaluation of patient response to interventions in clinical practice typically involve assessment of absolute change over time, we also hypothesized that there would be a significant difference in change values for BT, HR, SBP, DBP, MAP, and RR at 1-hour, 2-hours, and 4-hours post study drug administration.

Methods

Study design

A randomized, double-blind, placebo-controlled trial was conducted to evaluate the effects of IV acetaminophen on body temperature and hemodynamic responses in adult critically

ill patients with fever. The study was approved by the Committee on Human Research at the University of California, San Francisco (UCSF). Informed consent was obtained from the patient or surrogate prior to randomization. Informed consent for use of data was also obtained from patients who had surrogate consent and were able to participate in informed consent before hospital discharge. The study was registered with the ClinicalTrial.gov registry (number NCT01869699).

Patients

Patients from 3 adult ICUs at a large academic medical center were recruited for study enrollment between September 2013 and August 2015. Patients in the Medical-Surgical-, Neuroscience-, and CardiacThoracicVascular-ICUs were screened for fever (temperature of 38.3ºC or higher) and study eligibility. Inclusion criteria included 18 years of age or older; weight of 50 kg or greater for standard drug dosing; and fever before enrollment and start of the study protocol. Exclusion criteria included acetaminophen hypersensitivity or allergy; acute liver injury or failure (43); heat stroke, malignant hyperthermia, or neuroleptic malignant syndrome; extracorporeal blood circuit therapies: continuous renal replacement therapy, ventricular assist device, extracorporeal membrane oxygenation; around-the-clock scheduled administration of acetaminophen-containing medications or nonsteroidal anti-inflammatory drugs; targeted temperature management during the study period and/or non-English speaking patient or surrogate to participate in informed consent.

The study protocol was initiated after the following timeframes if these drugs had been administered: acetaminophen (9 hours), non-steroidal anti-inflammatory drugs (6 hours), and aspirin (1 hour). Clinical stability, defined as no active resuscitation with fluids, blood products,

or vasoactive medication dose increases within 1-hour of study drug administration, was also required prior to initiation of the study protocol.

Randomization and Study Drug

Prior to randomization, patients were stratified by etiology of their fever into infectious or non-infectious (neurologic) strata to help ensure even distribution between study drug groups. It is unclear if the mechanism of fever and/or response to antipyretic medications is different based on stimulus for fever, infectious or non-infectious. Stratification was based on review of microbiologic culture test orders and results; antimicrobial medication orders indicated for treatment of suspected or confirmed infection; and reference to suspected or confirmed infection or neurologic etiology of fever in the physician notes from the medical record. Within each stratum, patients were randomized by the pharmacist on a 1:1 basis to receive a single IV infusion of either acetaminophen 1 gram or 0.9% sodium chloride as placebo using a blocked randomization schedule generated with a commercial spreadsheet program. Study drugs were prepared by the pharmacist and dispensed in indistinguishable 100 mL bags. The patients, clinical team, and investigators were blinded to the study group assignment.

Outcome measures

The primary outcome measure was the 4-hour time-TWA BT that was adjusted for baseline BT. The 4-hour study period was selected based on the rapid onset for IV acetaminophen and the reported 4 to 6 hour duration of action which coincides with commonly ordered time intervals for repeat administration. The TWA BT was calculated by summing the temperature multiplied by their measured time intervals and dividing the sum by 240 minutes.

$$\text{TWA BT} = \sum (BT_5 \times 5) + (BT_{10} \times 5) + (BT_{15} \times 5) + (BT_{15\ldots240} \times 15) / 240 \text{ minutes}$$

Secondary outcomes were 4-hour TWA HR and TWA SBP, TWA DBP, TWA MAP, and TWA RR that were adjusted for baseline vital sign values. The same aforementioned TWA calculation was used with the collected HR, SBP, DBP, MAP and RR measurement data. Change values from baseline to the 5- and 15-minute intervals over 4 hours for BT, HR, SBP, DBP, MAP, and RR were also calculated and analyzed.

Study Protocol/Procedure

The study protocol was initiated when the patient's temperature from the standard thermometry method reached the threshold for fever (38.3 ºC or higher). The forehead core temperature thermometry system was then applied and the study drug was administered only if the core temperature was 38.0ºC or higher after at least 5 minutes of equilibration time. Forehead core temperature was measured on all patients using the non-invasive 3M™ SpotOn™ Temperature Monitoring System (Eden Prairie, MN) during the 4-hour study period. SpotOn™ thermometry technology is an accurate measure of core temperature with good agreement and precision compared to pulmonary artery blood temperatures (44). After the skin was cleansed with alcohol, the zero-heat-flux sensor was placed on the patient's left lateral forehead above the orbital ridge, and the system equilibrated the deeper tissue to skin surface temperatures (3M™ SpotOn™ Temperature Monitoring Sensor-Model 36000 and Control Unit-Model 370). A single sheet and thin bath blanket were applied per standard of care and to maintain privacy. Administration of additional antipyretic medications, physical cooling (fans, baths, ice packs, cooling blankets), and warming interventions were not permitted during the 4-hour study period.

HR and RR were measured via electrocardiogram (ECG) on bedside monitor (Solar® 8000 Bedside Monitor, GE Healthcare). BP was measured via a transduced arterial catheter system (Transpac® Disposable Pressure Transducer, ICU Medical Inc.) or via non-invasive BP

measurement device (Solar® 8000 Bedside Monitor, GE Healthcare). The measurement methods were not changed during the 4-hour study period.

Skin temperatures were measured and skin temperature gradients were calculated to determine if thermoregulatory vasomotor changes were associated with acetaminophen administration. Skin temperature gradients are a reliable measure of blood flow related to thermoregulatory vasoconstriction of arteriovenous shunts in the fingers (45, 46). Skin temperature sensors (Smiths Medical ASD Inc.) were applied to the patient's medial forearm and also to the index finger tip on the same side. The arm with sensors was exposed to ambient environment during the study period. Skin temperature gradients were calculated by subtracting fingertip from forearm skin temperatures.

The blinded study drug, either acetaminophen 1 gram/100 mLs (Ofirmev®, Mallinckrodt Pharmaceuticals) or 0.9% sodium chloride/100 mLs, was administered intravenously over 15 minutes. Forehead core-BT, HR, SBP, DBP, MAP, and RR were collected at baseline (the time just prior to study drug administration); every 5 minutes for 15 minutes; and then every 15 minutes for 4 hours. Other variables collected at the same time intervals during the study period were body temperature from the standard thermometry source in use as well as the index finger and forearm skin temperatures. Patient demographic, characteristic, and therapy data that might influence BT differences were collected.

The study's rescue protocol had a threshold temperature of 40˚C or higher during the study period. The rescue protocol included notification of the primary physician, unblinding of study group assignment to the physician, and new orders for antipyretic medications or physical cooling at the discretion of the physician.

Statistical analysis

The null hypothesis was that there was no statistically significant difference in TWA BT between the acetaminophen and placebo groups. The power analysis for sample size estimated that at least 20 patients per group would provide power of 80% to detect a difference in means of 0.60ºC, with a common standard deviation of 0.67ºC, using a two group t-test with a 0.05 two-sided significance level. The mean difference of 0.60 ºC with a common standard deviation of 0.67 ºC was estimated from data in a previous study of IV acetaminophen in healthy male volunteers with induced fever (47).

Patient characteristic data were analyzed to compare groups for baseline differences, with categorical variables assessed using chi-square or Fisher's exact tests and continuous variables assessed using t-tests. In addition, between-group standardized differences were calculated (difference in means or proportions divided by standard error) to evaluate the magnitude of differences and to ensure differences were captured with this sample size (48). An absolute value of greater than 0.30 (moderate to large effect size) for standardized differences was used to identify potential covariates.

A t-test or Mann-Whitney U test was used to analyze the effect of treatment with acetaminophen compared to placebo on the primary and secondary outcome variables. Analysis of covariance (ANCOVA) using study drug group as the fixed effect and baseline values as covariates was performed to further explore the TWA outcomes while adjusting for baseline values. Baseline vital signs and patient characteristics that had a statistically significant difference ($p < 0.05$) between groups and/or a standardized difference of means or proportions greater than 0.30 were included as covariates in the model if they were also related to the outcome. To test for a moderator effect of an interaction between study drug group and etiology

of fever group (infectious and noninfectious) on TWA BT, adjusted TWA BTs were analyzed using a two-way ANCOVA. Analysis of covariance using baseline values as covariates was also performed to analyze differences in change values from baseline to 1-, 2-, and 4-hours between groups. Two-sided P values of less than 0.05 were selected to indicate statistical significance. Statistical analyses were performed using SPSS® statistical software, version 23 (SPSS® Inc).

Results

Of the 6,090 patients screened between September 2013 and August 2015, 944 (15.5%) had fever. We enrolled 41 patients in the clinical trial and excluded 903 patients (**Figure 1**). Twenty patients were randomized to the acetaminophen group and twenty-one randomized to the placebo group. Final analysis included 20 patients in each group since one patient in the placebo group withdrew after 1 hour due to surrogate's concern. Demographics and patient characteristics in both groups were similar at baseline with regard to age, gender, ethnicity, ICU admission APACHE II score, BMI, primary diagnosis, etiology of fever, sepsis, medication infusions, and mechanical ventilation (**Table 1**).

Unadjusted 4-hour TWA outcomes for BT, HR, SBP, DBP, MAP, and RR represent the difference between acetaminophen and placebo groups without controlling for differences in baseline values are presented in **Table 2**. The following 4-hour TWA outcome results, presented as mean ± standard error, were adjusted for baseline values to account for the magnitude of standardized differences between groups at baseline for the physiological variables.

There was a significant difference in adjusted TWA BT between acetaminophen (37.9 ± 0.1 ˚C) and placebo (38.4 ± 0.1 ˚C) groups, $p = 0.002$, with a mean difference of 0.47 ˚C lower in the acetaminophen group. Patients assigned to the acetaminophen group also had significantly lower adjusted mean differences in TWA HR ($p = 0.03$), TWA SBP ($p < 0.001$), and TWA MAP

($p = 0.02$). No significant difference was found in both adjusted TWA DBP ($p = 0.05$) and adjusted TWA RR ($p = 0.42$) between acetaminophen and placebo groups. See **Table 3** for adjusted 4-hour TWA outcome results after adjusting for baseline physiologic values. Also, there was no significant interaction effect of study drug group and etiology of fever group on adjusted TWA BT, ($p = 0.24$).

At 1-hour, there was a significant reduction in mean change values from baseline between acetaminophen and placebo groups for BT, SBP, and MAP, but not for HR, DBP, and RR. At 2-hours, all of the vital sign change outcomes were significantly different except for RR. By the end of the 4-hour study period, there were no significant differences for any of the vital sign change outcomes, including BT, between groups. See **Tables, 4, 5** and **6** for mean differences of change values for outcomes at 1-hour, 2-hours, and 4-hours, respectively. **Figures 2 - 6** display the mean differences from baseline to more frequent time intervals for BT, HR, SBP. MAP, and RR by acetaminophen and placebo group.

In the acetaminophen group (n=20), BT primarily decreased by 4 hours, yet a few (10%) patients had increases in BT. The adjusted mean difference in BT change from baseline to 4 hours in the acetaminophen group was a reduction of $0.6 \pm 0.2^{\circ}C$. Of the patients in the acetaminophen group, 11 (55%) had either a small decrease (less than or equal to $0.5^{\circ}C$) or an increase in BT. In this "non-responder" subgroup, 7 (64%) had neurologic injury as primary diagnosis and 9 (82%) had infection as the leading etiology of fever of which 5 patients had microbiologically confirmed bacterial or fungal pathogens. Analysis of the relationship between BT change and hemodynamic change revealed low to moderate correlations at 1-, 2-, and 4-hours after acetaminophen administration ($r \leq 0.52$ for all correlations). Patient BTs in the placebo group also increased and decreased by the end of the 4-hour study period. The adjusted

mean difference in BT change from baseline to 4 hours in the placebo group (n=20) was a reduction of 0.2 ± 0.2˚C. In 8 patients, BT increased by a mean of only 0.4 ± 0.3˚C (range 0.1 – 0.9˚C). Interestingly, of the 12 (60%) patients in the placebo group with BT reductions at 4-hours, the mean reduction was 0.7 ± 0.7˚C (range 0.1 – 2.6˚C) with a decrease greater than 0.5˚C in 6 (50%) of these patients.

Skin temperature gradients analyzed to determine if thermoregulatory vasomotor changes were associated with acetaminophen administration revealed a significant difference in mean skin temperature gradient change from baseline to 1- and 2-hours between the acetaminophen and the placebo groups, yet no difference at 3- and 4-hours was found (See data presented in **Table 7**).

The rescue protocol was never indicated during the clinical trial. There were 8 interventions for acute decreases in blood pressures in 7 patients during the study period. Four patients required an IV fluid bolus for decreased blood pressure, 2 patients required vasopressor infusion up-titrations, and 2 patients required vasodilator infusion down-titrations during the study period. See **Table 8** for infusion types by group.

Discussion

Acetaminophen is a common treatment for fever, yet there is limited prospective, controlled data on the antipyretic efficacy and acute hemodynamic effects of the IV formulation in critically ill patients. To our knowledge, this is the first randomized, double-blind, placebo-controlled trial to evaluate the effects of IV acetaminophen on body temperature and hemodynamics in febrile ICU patients. Although we observed a significant difference in TWA BT 4-hours after acetaminophen administration compared to placebo, the reduction was modest (0.47˚C).

The modest difference in BT between acetaminophen and placebo groups observed in our study is consistent with findings from randomized controlled trials in febrile and afebrile ischemic stroke patients and febrile ICU patients with suspected infection (34, 35). Efficacy of acetaminophen was measured within the treated fever episode in our study compared to measures of daily maximum mean or daily mean temperatures measured in these large trials where acetaminophen or placebo was administered on an around-the-clock basis and with temperature thresholds (34, 35). Interestingly, there was no significant interaction effect with study drug and etiology of fever on BT in our study. This result suggests that the effect of acetaminophen on BT is not moderated by the etiology of fever (infectious or neurologic).

In a retrospective study of the effectiveness of acetaminophen in medical-surgical ICU patients with systemic inflammatory response syndrome and fever, the difference in mean maximum BT change over 5 hours was 0.30°C between acetaminophen-treated fever episodes and untreated fever episodes (49). Although this study had many limitations including the retrospective design, variable acetaminophen doses, and differences in patient characteristics between the treated and untreated groups, their findings are similar to adjusted mean difference of 0.40°C for BT change over 4 hours between treatment groups in our study.

The study used by the U.S. Federal Drug Administration to base approval of IV acetaminophen tested the antipyretic effect and safety of 1 gram IV acetaminophen compared to placebo in young healthy male volunteers with reference standard endotoxin-induced fever (47). They observed a difference in temperature change from baseline to 4 hours of 0.56˚C ($p = 0.0002$) between acetaminophen and placebo groups which was slightly more of a change than we observed in our study, 0.40˚C ($p = 0.11$). This difference may be explained by the critical care therapies or patient conditions that may alter efficacy of acetaminophen. For example,

dexmedetomidine may be associated with alterations in thermoregulation and there are case reports of resistance to antipyretics in ICU patients (50, 51). In our study, 4 of the 11 non-responders (temperature reduction less than or equal to 0.5˚C) in the acetaminophen group received dexmedetomidine infusions with an average dose rate of 0.6 mcg/kg/hour. None of the responders in the acetaminophen group received dexmedetomidine during the study period. The relationship between dexmedetomidine and fever stimulation and resistance to antipyretics warrants further study as the use of this non-benzodiazepine sedative is more common in ICUs today.

Significant differences in HR and blood pressure variables were observed with clinically meaningful reductions in the acetaminophen group compared to placebo, especially soon after administration. Our findings are similar to reductions in blood pressures observed 1-hour after acetaminophen in an observational study of febrile ICU patients (38). The clinical relevance of the blood pressure reductions observed in our study (mean MAP decrease of up to 12 mmHg and mean SBP decrease of up to 24 mmHg) during the 2 hours post administration of IV acetaminophen has significant implications for monitoring, differential diagnosis, and anticipatory management in critically ill patients.

A recent randomized, double-blind, crossover trial evaluating hemodynamic effects of IV acetaminophen to placebo in afebrile healthy volunteers found small transient decreases in SBP, DBP, and MAP after acetaminophen administration compared to no decreases with the placebo intervention (52). They also found a relationship between blood pressure reduction and a transient reduction in SVR within the early post administration period. We also found significant acute reductions in blood pressure after administration of IV acetaminophen compared to placebo, yet the changes we observed were of greater magnitude in the ICU population compared to afebrile

healthy volunteers. These findings in afebrile adults suggest that IV acetaminophen, rather than BT reduction may be the cause of hemodynamic changes. Likewise, our finding of low to moderate correlations between BT changes and both HR and MAP changes after acetaminophen administration suggests that the change in BT alone did not account for the hemodynamic changes observed in our study. Two other observational studies reporting blood pressure reductions after acetaminophen administration in febrile ICU patients also found no parallel relationship between the BT changes and hemodynamic changes (39, 42). Krajcova et al (42) suggest that the blood pressure reductions after IV acetaminophen may be caused by reductions in systemic vascular resistance (SVR) and cardiac index as derived from pulse contour analysis measurements in their study.

Although we did not measure hemodynamic flow and resistance variables in our study, we did measure skin temperature gradients to evaluate peripheral thermoregulatory blood flow changes. The thermoregulatory cutaneous vasomotor response to changes in the hypothalamic thermal set point and/or environmental temperature changes involves arteriovenous shunts in the fingers and toes. These shunts are opened or constricted to alter local cutaneous blood flow to achieve or prevent heat dissipation in response to temperature change (45, 46). During fever the cutaneous vasoconstriction leads to reduced local blood flow to prevent heat loss. The decrease in finger skin temperature results in a larger skin temperature gradient between the forearm and finger. During defervescence there is a reduced gradient between forearm and finger skin temperatures as cutaneous arteriovenous shunts open, increasing skin blood flow which promotes heat loss.

The significant difference in skin temperature gradients between groups that we observed at 1- and 2-hours did not persist at the 3- and 4-hour analysis points. The differences in skin

temperature gradients observed in our study suggest that the cutaneous thermoregulatory effector response for heat dissipation occurs early and lasts approximately 2 hours after IV acetaminophen administration. The timing and 2-hour duration of the skin temperature gradient change match the blood pressure reductions we observed after administration of IV acetaminophen. Boyle et al (38) found a significant increase in skin blood flow using laser Doppler flowmetry 1-hour after acetaminophen administration. This finding along with the skin temperature gradient change we observed suggests a reduction in SVR related to increased vascular capacitance as a plausible mechanism of acute blood pressure reduction associated with IV acetaminophen administration.

Lastly, the lack of significant difference in RR between groups in the adjusted TWA RR and all of the difference-by-time analyses was a surprising finding. Although HR and MAP reductions occur after acetaminophen, the aforementioned findings challenge the common belief that suppression of fever, per se, reduces the RR component of cardiopulmonary stress.

The strengths of our study design and methods including stratification, randomization and blinded intervention minimized selection and performance bias. Internal validity was strengthened by use of a standardized temperature monitoring method and prohibition of physical cooling to reduce the influence of confounders on our primary outcome. The use of the IV formulation of acetaminophen eliminated the potential confounder of unpredictable absorption associated with enteral formulations that are also commonly used in ICUs. Yet, our study also has certain limitations. Generalizability of findings is a limitation due to the single site and small sample size. Although we controlled for confounding variables that impact body temperature, we did not control for confounders that may have impacted hemodynamic outcomes. Although there were no significant differences in proportions of patients receiving vasoactive, sedative, and analgesic

infusions between groups, the dose titrations are potential confounders of the hemodynamic outcome results.

In conclusion, there is a statistically significant difference in the 4-hour adjusted TWA BT after administration of IV acetaminophen compared to placebo in febrile ICU patients, yet the small magnitude of difference has little clinical relevance. There is a clinically meaningful reduction in HR and blood pressure after IV acetaminophen compared to placebo, especially within 2 hours of administration. It is important for clinicians to have a better understanding of the therapy response and potential adverse effects of this commonly administered medication, especially the recently available IV formulation, in critically ill patients. Further study of the antipyretic and hemodynamic response to IV acetaminophen in a larger sample of critically ill patients is warranted to inform evidence-based practice guidelines for safe and effective fever management strategies, when they are indicated.

Figure 1: CONSORT diagram of screening, randomization, and follow-up

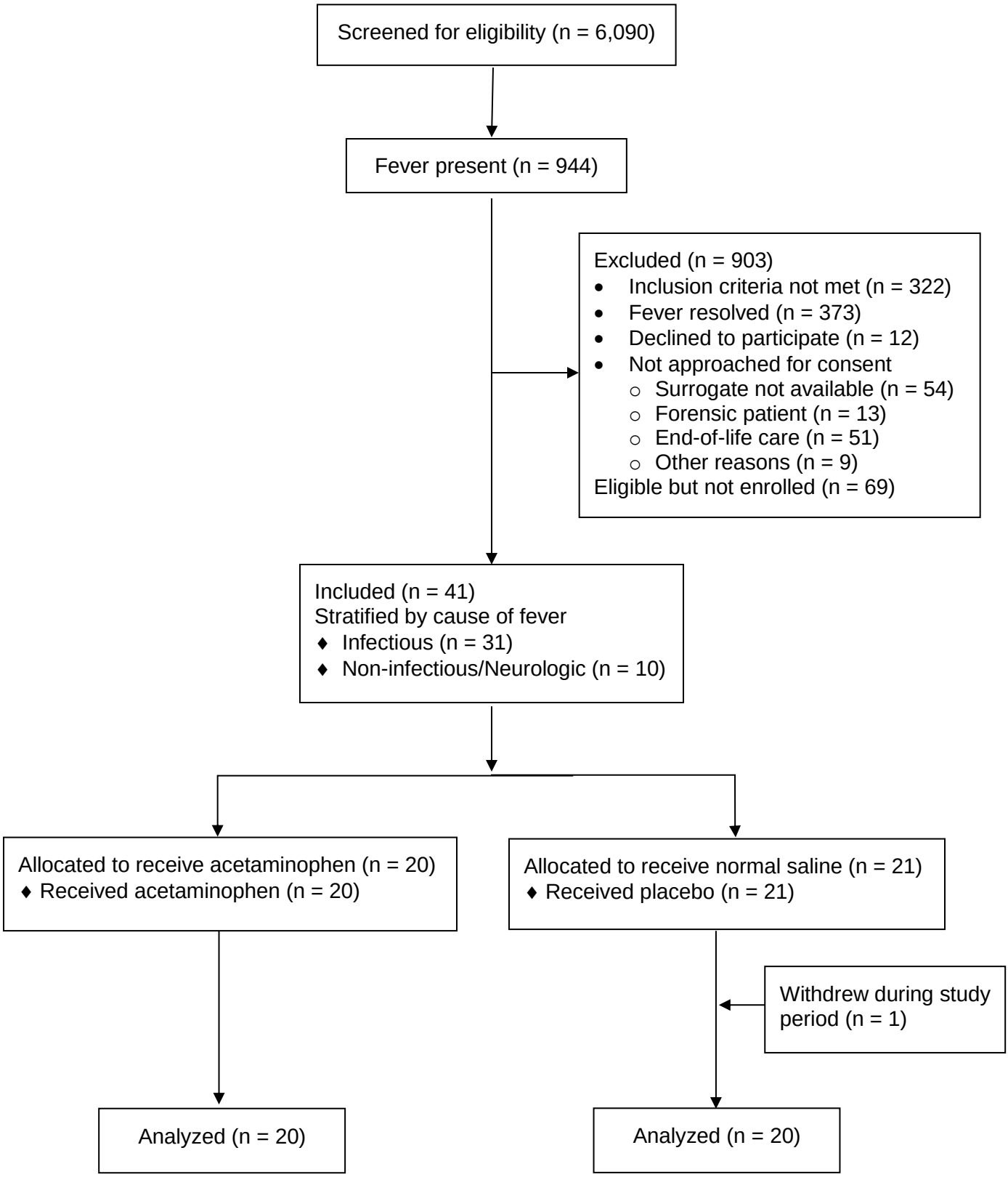


Table 1 – Baseline characteristics

Characteristic[a]	Acetaminophen (n = 20)	Placebo (n = 20)	P value	Standardized Difference[b]
Age (years)	57.6 ± 14.9	57.3 ± 13.2	0.95	0.02
Gender (female)	40%	45%	1.0	-0.10
Ethnicity			0.28	
Asian/Pacific Islander	20%	30%		-0.23
Black	10%	0%		0.64
Caucasian	40%	55%		-0.30
Hispanic	30%	15%		0.36
Body Mass Index	29.4 ± 5.4	31.1 ± 7.4	0.42	-0.27
Primary ICU diagnosis			0.89	
Medical	30%	30%		0
Surgical	10%	20%		-0.28
Neurological	60%	50%		0.20
APACHE II	24.4 ± 6.2	24.2 ± 6.4	0.92	0.27
Etiology of fever				
Infectious	75%	75%	1.0	0
Neurologic	25%	25%	1.0	0
Medication Infusions				
Vasopressor	15%	35%	0.27	-0.48
Vasodilator	10%	10%	1.0	0
Sedative	40%	45%	1.0	-0.10
Analgesic	5%	15%	0.61	-0.34
Sepsis status	65%	70%	1.0	-0.11
Mechanical ventilation	60%	75%	0.50	-0.32
Mode of ventilation			0.69	
Pressure support mode	67%	75%		-0.18
Assist control mode	33%	25%		0.18
Room temperature (°C)	21.4 ± 1.2	21.5 ± 1.4	0.89	-0.05
Body temperature (°C)	38.4 ± 0.3	38.6 ± 0.5	0.13	-0.48
Heart Rate/minute	90.3 ± 13.7	93.4 ± 14.5	0.41	-0.22
Systolic Blood Pressure (mmHg)	151 ± 26	135 ± 26	0.07	0.62
Diastolic Blood Pressure (mmHg)	72.6 ± 14.8	63.8 ± 13.1	0.05	0.63
Mean Arterial Pressure (mmHg)	100.1 ± 19.7	88.7 ± 16.1	0.05	0.79
Respiratory Rate/minute	20.4 ± 6.3	24 ± 5.1	0.05	-0.63

[a]Data are presented as mean ± SD or proportions (%)
[b]Standardized difference: difference in means or proportions divided by standard error. Standardized differences with an absolute value greater than 0.30 (small-moderate effect size) defined an imbalance between groups.

Table 2: Unadjusted 4-hour TWA Outcomes

Outcome **Time-weighted average (TWA)[a]**	**Acetaminophen** (N = 20)	**Placebo** (N = 20)	**Mean Difference**	**95% CI**	**P value**
TWA BT (˚C)	37.8 ± 0.5	38.5 ± 0.6	-0.64	-0.29 – -0.99	0.001
TWA HR (per minute)	86 ± 12	94 ± 14	-8.3	-16.6 – -0.01	0.07
TWA SBP (mmHg)	134 ± 25	136 ± 27	-2.7	-19 – 14	0.74
TWA DBP (mmHg)	69 ± 14	65 ± 13	3.7	-5 – 12	0.49
TWA MAP (mmHg)	91 ± 17	89 ± 17	2.7	-8 – 14	0.61
TWA RR (per minute)	19 ± 6	23 ± 6	-3.6	-7.2 – -0.1	0.045

[a]Time-weighted average (TWA) captures potential fluctuations over 4 hour study period.
Data are presented as mean ± SD or proportions (%)
Mean differences calculated by subtracting data (acetaminophen group minus placebo group)

Table 3: Adjusted 4-hour TWA Outcomes

Outcome **Time-weighted average (TWA)[a]**	**Acetaminophen** (N = 20)	**Placebo** (N = 20)	**Mean Difference**	**P value**
TWA BT (˚C)	37.9 ± 0.1	38.4 ± 0.1	-0.47	0.002
TWA HR (per minute)	87 ± 1.6	92 ± 1.6	-5.5	0.03
TWA SBP (mmHg)	127 ± 2.9	143 ± 2.9	-16.8	<0.001
TWA DBP (mmHg)	65 ± 1.3	69 ± 1.3	-3.9	0.05
TWA MAP (mmHg)	87 ± 1.9	94 ± 1.9	-6.7	0.02
TWA RR (per minute)	20 ± 0.9	21 ± 0.9	-1.0	0.42

[a]Time-weighted average (TWA) captures potential fluctuations over 4 hour study period.
Data are presented as mean ± standard error (SEM)
Mean differences calculated by subtracting data (acetaminophen group minus placebo group)
TWA outcomes adjusted to specific baseline (T0) variables (BT, HR, SBP, DBP, MAP, RR)

Table 4: Change over time in vital sign outcomes at 1-hour ($T_{baseline}$ to $T_{1\ hour}$)

Outcome Change over time[a]	Acetaminophen (N = 20)	Placebo (N = 20)	Mean Difference	P value
BT change (˚C)	0.4 ± 0.07	0.02 ± 0.07	0.4	<0.005
HR change (per minute)	2.1 ± 1.7	-2.1 ± 1.7	4.2	0.08
SBP change (mmHg)	20.3 ± 4.3	-2.2 ± 4.3	22.5	0.001
DBP change (mmHg)	4.2 ± 2.1	1.2 ± 2.1	5.5	0.08
MAP change (mmHg)	9.3 ± 2.8	-0.3 ± 2.8	9.6	0.03
RR change (per minute)	1.0 ± 1.2	1.2 ± 1.2	-0.2	0.92

[a]Outcome value represents mean change from baseline to 1-hour
Data are presented as mean ± standard error (SEM)
Mean differences calculated by subtracting data (acetaminophen group minus placebo group)
Mean differences adjusted to specific baseline (T0) variables (BT, HR, SBP, DBP, MAP, RR)

Table 5: Change over time in vital sign outcomes at 2-hours ($T_{baseline}$ to $T_{2\ hours}$)

Outcome Change over time[a]	Acetaminophen (N = 20)	Placebo (N = 20)	Mean Difference	P value
BT change (˚C)	0.8 ± 1.3	0.1 ± 1.3	0.6	0.002
HR change (per minute)	6.4 ± 2.3	-1.6 ± 2.3	7.9	0.02
SBP change (mmHg)	24.1 ± 4.7	0.1 ± 4.7	24	0.001
DBP change (mmHg)	7.5 ± 2.2	-1.8 ± 2.2	9.3	0.007
MAP change (mmHg)	12.8 ± 3.3	0.04 ± 3.3	12.8	0.01
RR change (per minute)	1.0 ± 1.2	1.2 ± 1.2	0.7	0.69

[a]Outcome value represents mean change from baseline to 2-hours
Data are presented as mean ± standard error (SEM)
Mean differences calculated by subtracting data (acetaminophen group minus placebo group)
Mean differences adjusted to specific baseline (T0) variables (BT, HR, SBP, DBP, MAP, RR)

Table 6: Change over time in vital sign outcomes at 4-hours ($T_{baseline}$ to $T_{4\ hours}$)

Outcome **Change over time**[a]	**Acetaminophen** (N = 20)	**Placebo** (N = 20)	**Mean Difference**	**P value**
BT change (˚C)	0.6 ± 0.2	0.2 ± 0.2	0.4	0.05
HR change (per minute)	5.2 ± 2.2	1.8 ± 2.2	3.4	0.29
SBP change (mmHg)	6.9 ± 3.9	4.4 ± 3.9	2.5	0.66
DBP change (mmHg)	-1.3 ± 1.8	1.6 ± 1.8	-2.8	0.29
MAP change (mmHg)	1.9 ± 2.4	3.4 ± 2.4	-1.4	0.69
RR change (per minute)	2.1 ± 1.0	1.7 ± 1.0	0.4	0.78

[a]Outcome value represents mean change from baseline to 4-hours
Data are presented as mean ± standard error (SEM)
Mean differences calculated by subtracting data (acetaminophen group minus placebo group)
Mean differences adjusted to specific baseline (T0) variables (BT, HR, SBP, DBP, MAP, RR)

Table 7: Change in mean skin temperature gradients by time

Time	Acetaminophen (N = 20)	Placebo (N = 18)	P value
T0 – T60 minutes	-2.9 ± 0.57	-0.67 ± 0.60	0.009
T0 – T120 minutes	-3.9 ± 0.66	-1.3 ± 0.69	0.01
T0 – T180 minutes	-2.7 ± 0.66	-1.5 ± 0.69	0.22
T0 – T240 minutes	-1.9 ± 0.68	-1.8 ± 0.72	0.93

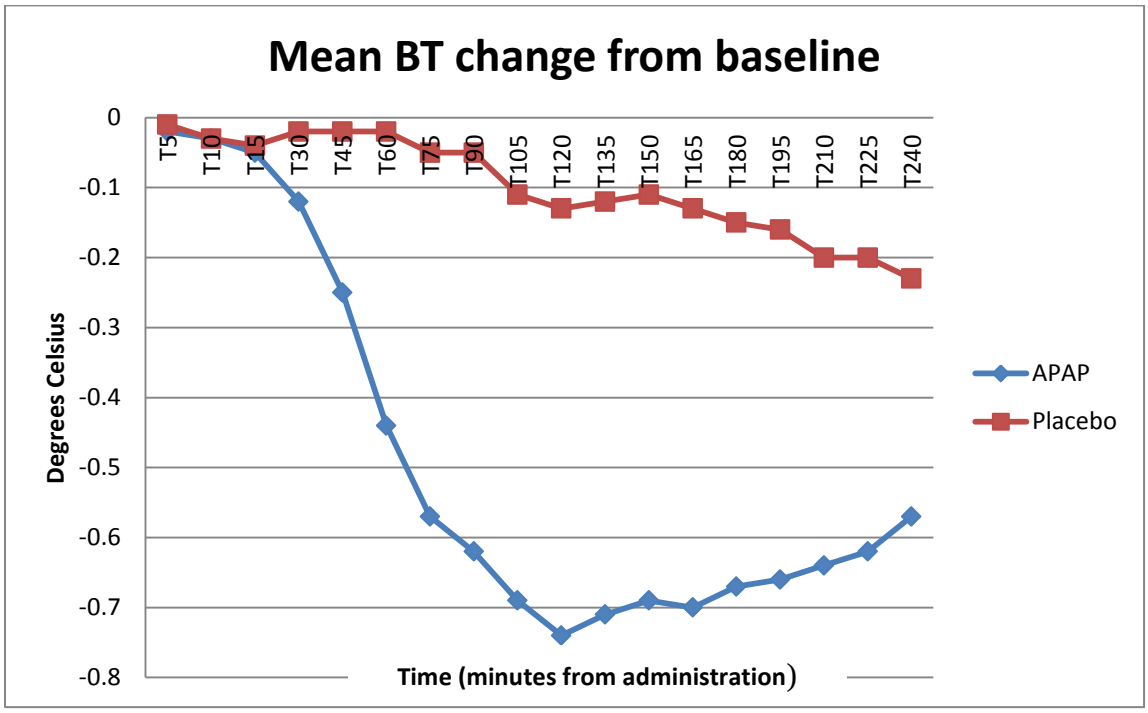
Skin temperature gradient = Finger skin temperature – Forearm skin temperature
Data are presented as mean ± SEM
Means adjusted to baseline (T0) skin temperature gradient

Table 8: Infusion types & Fluid boluses during study period

Infusion Type	Acetaminophen (N = 20)	Placebo (N = 20)
Vasopressor infusions[a]	3 (15%)	7 (35%)
Increase titration	1 (33%)	1 (14%)
Decrease titration	1 (33%)	4 (57%)
No titration	1 (33%)	2 (29%)
Vasodilator infusion[b]	2 (10%)	2 (10%)
Increase titration	0	1 (50%)
Decrease titration	2 (100%)	0
No titration	0	1 (50%)
Sedative infusions	8 (40%)	9 (45%)
Dexmedetomidine	4 (50%)	3 (33%)
Propofol	4 (50%)	6 (67%)
Analgesic infusion[c]	1 (5%)	3 (15%)
Crystalloid fluid bolus	2 (10%)	2 (10%)

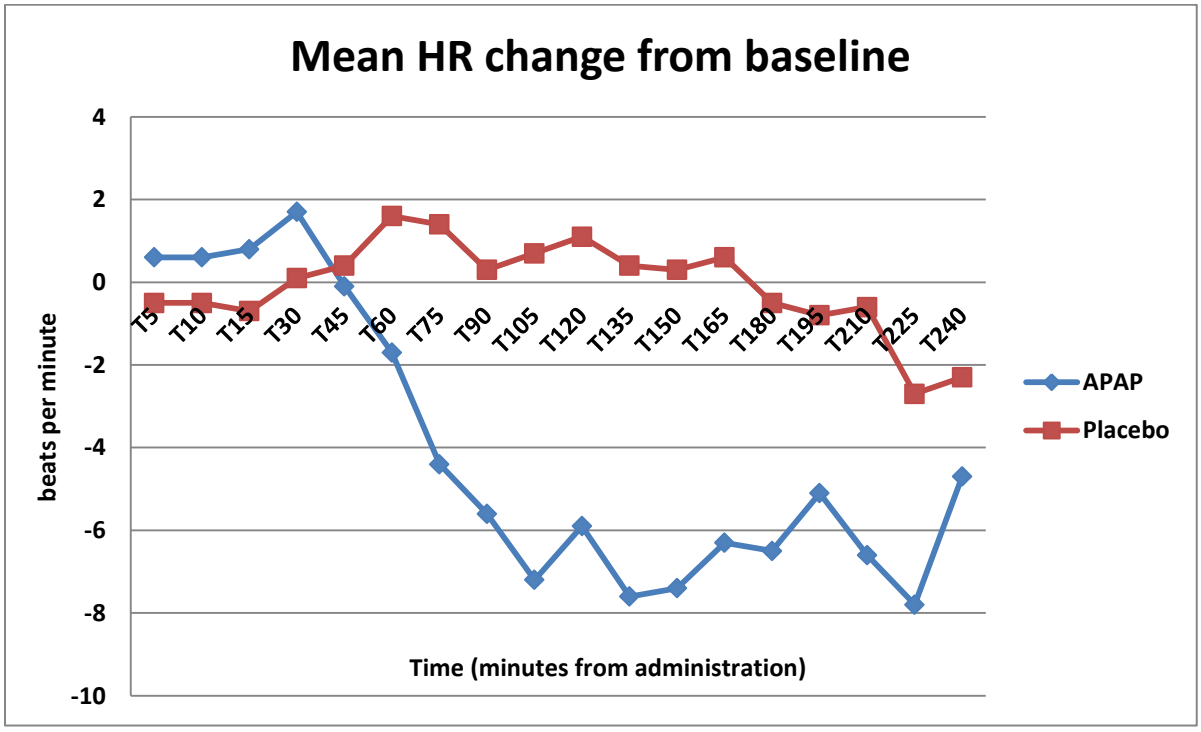
[a] Norepinephrine, Phenylephrine & Epinephrine infusions. 4/10 patients on vasopressors were on 2 vasopressor infusions (2 in acetaminophen group and 2 in placebo group).
[b] Nicardipine infusions
[c] Fentanyl infusions

Figure 2: Mean difference in body temperature (BT) from baseline over 4 hours



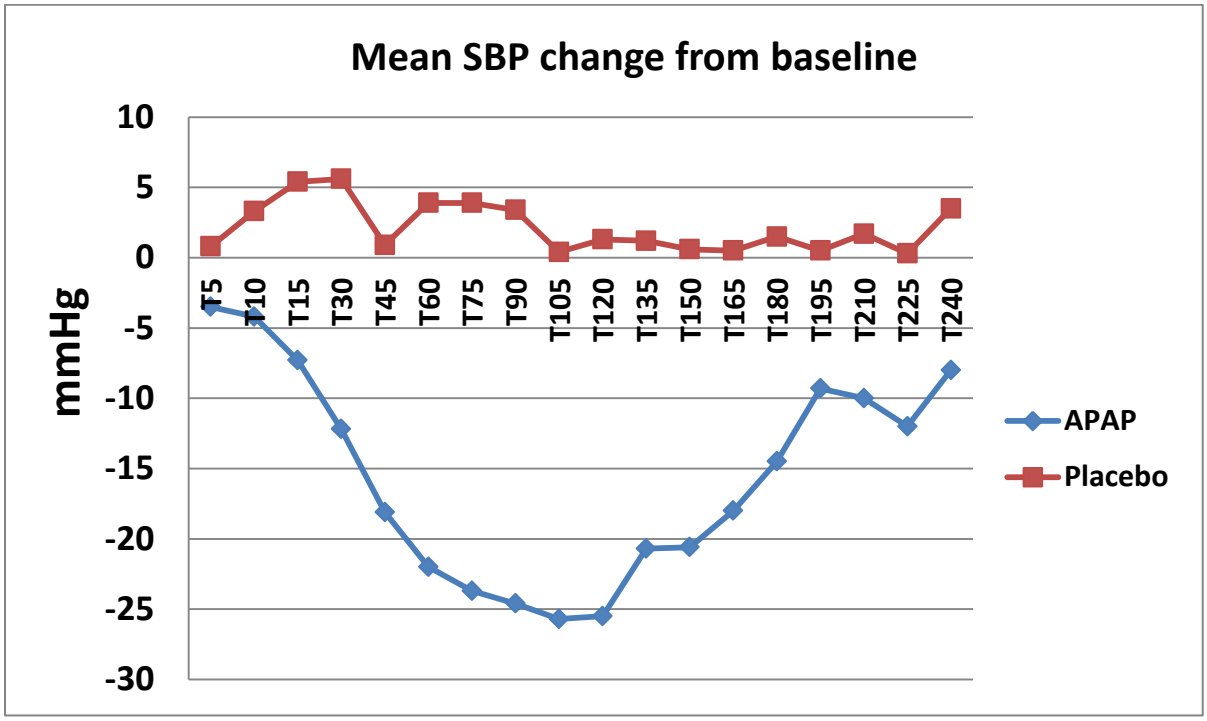
Body temperature (BT) measurements collected every 5 minutes times 3 and then every 15 minutes until 4-hours post study drug administration (T5, T10, T15, T30, T45….T240 minutes).

Figure 3: Mean difference in heart rate from baseline over 4 hours



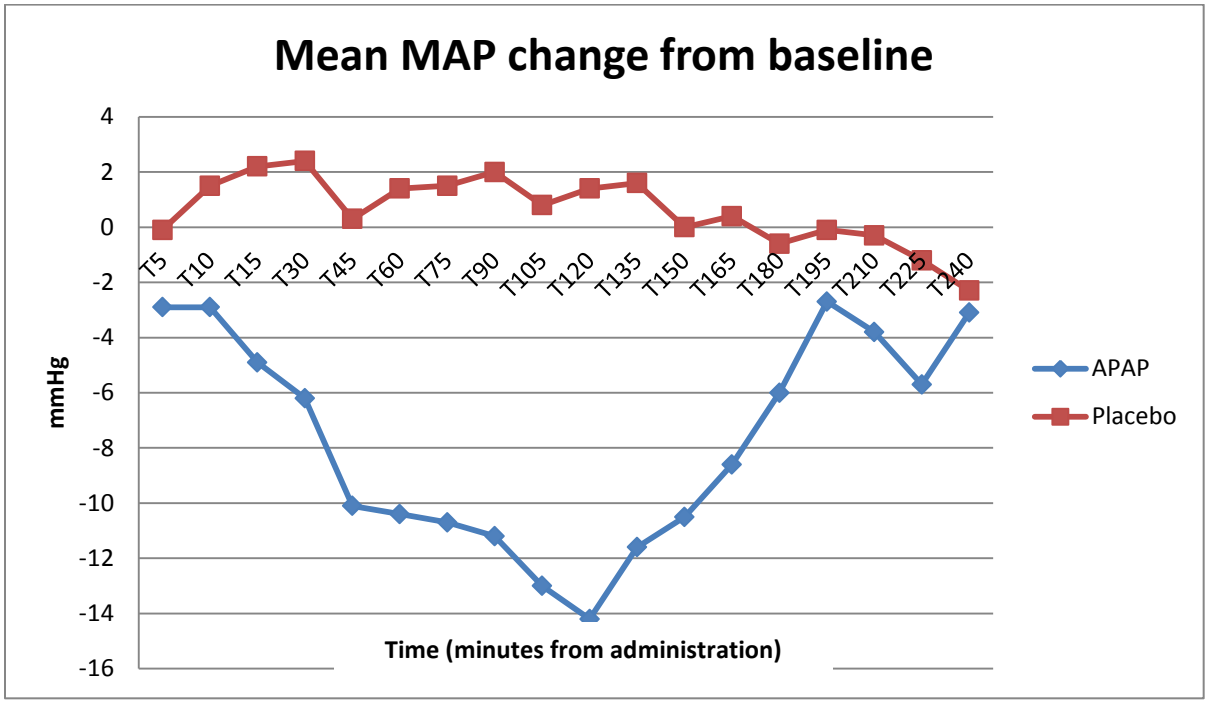
Heart rate (HR) measurements collected every 5 minutes times 3 and then every 15 minutes until 4-hours post study drug administration (T5, T10, T15, T30, T45….T240 minutes).

Figure 4: Mean difference in systolic blood pressure (SBP) from baseline over 4 hours



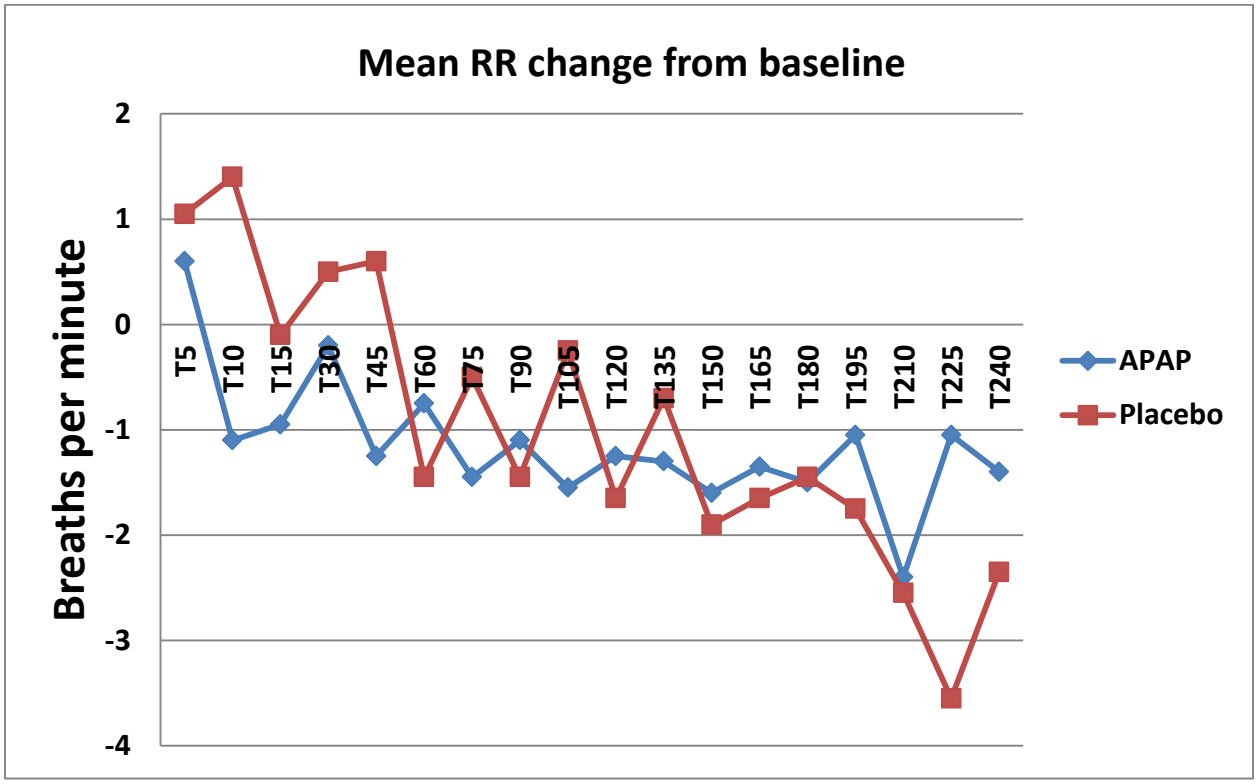
Systolic blood pressure (SBP) measurements collected every 5 minutes times 3 and then every 15 minutes until 4-hours post study drug administration (T5, T10, T15, T30, T45….T240 minutes).

Figure 5: Mean difference in mean arterial pressure (MAP) from baseline over 4 hours



Mean arterial pressure (MAP) measurements collected every 5 minutes times 3 and then every 15 minutes until 4-hours post study drug administration (T5, T10, T15, T30, T45….T240 minutes).

Figure 6: Mean difference in respiratory rate (RR) from baseline over 4 hours



Respiratory rate (RR) measurements collected every 5 minutes times 3 and then every 15 minutes until 4-hours post study drug administration (T5, T10, T15, T30, T45….T240 minutes).

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Chapter 5

Conclusion

As more evidence of the impact of fever on outcomes in subpopulations of critically ill patients is gained from well-designed clinical trials, guidelines can be developed to inform health care decisions for fever management. In the ARDS subpopulation of critically ill patients, we found that higher body temperature was associated with decreased mortality and that there was a significant trend toward lower mortality in patients with fever compared with normothermic patients. The heterogeneity of critically ill patients related to critical illness diagnosis, co-morbid conditions, and critical care therapies may impact fever response and fever-related benefit or harm. Rather than an all-or-none recommendation for treating fever, an evidence-based, risk-stratified model for fever management in critically ill patients should be considered in the future. Further research on the impact of fever on recovery and survival outcomes in critically ill patients while considering common ICU subpopulations is necessary to guide decision-making regarding fever management by nurses and physicians.

Temperature monitoring is a core nursing responsibility that includes evidence-based procedures to ensure accurate monitoring. Body temperature alterations in critically ill patients are common and may be related to the patient's clinical diagnosis, the therapies administered, and/or exposure in the ICU environment (such as during bathing and procedures). Temperature monitoring in the ICU requires precise and reliable technology with capacity for continuous monitoring. Frequent monitoring of body temperature facilitates early detection of changes in clinical condition and patient responses to therapies. The method-comparison study in this dissertation was the first study to compare the recently available SpotOn™ system to two thermometry methods commonly used to monitor medical, surgical, and neurologically injured

ICU patients. Study results demonstrated that the SpotOn™ system had excellent agreement with the established clinical thermometry systems and that it is an accurate, non-invasive, and comfortable option for continuous thermometry in ICU patients. Future research of the SpotOn™ system is warranted to evaluate accuracy and reliability in hypothermic patients and during targeted temperature management therapies. Clinical evaluation of the SpotOn™ system for reliability of temperature monitoring over longer periods of time compared to the 4-hour period observed in our study is also indicated before introduction of this new technology into ICU clinical practice.

Although acetaminophen is administered widely to ICU patients for fever suppression due to concern of the associated metabolic and cardiopulmonary stress, gaps in evidence related to its antipyretic, metabolic, and hemodynamic effects exist. The results of the randomized, double-blind, placebo-controlled clinical trial completed for this dissertation have important clinical implications. Although mean body temperature decreased after acetaminophen, the magnitude of change in temperature was modest and a few patients had increases in temperature. Further research is warranted to better understand why the antipyretic response to acetaminophen is variable, including nonresponse, in critically ill patients. The host, environment, and critical care therapies are potential moderators of the antipyretic effect of acetaminophen in ICU patients. The hemodynamic response findings from this clinical trial have clinical and research implications. The clinically significant blood pressure reductions observed after IV acetaminophen administration warrant further study to explain the mechanism and identify risk factors. A better understanding of the duration of blood pressure response and mechanism of hypotension can guide decision-making for management (e.g. no treatment due to transient nature, IV fluid therapy, or vasopressor therapy). Clinical implications of these findings include

recommendations for more frequent blood pressure monitoring in the first 2-hours after administration of IV acetaminophen, especially in patients with targeted blood pressure therapies. Addition of recent IV acetaminophen administration to the differential diagnosis of acute hypotension in critically ill patients can prevent unnecessary, resource intensive, diagnostic work ups (e.g. severe sepsis work up with blood cultures, lactate lab tests, and fluid bolus interventions).

The dissertation research contributes new knowledge to the bodies of scientific evidence for 1) outcomes of body temperature alterations in critically ill adults, 2) technology assessment for accurate temperature monitoring in ICU patients, and 3) effects of antipyretic interventions in critically ill patients.

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