

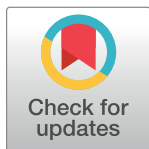
REGISTERED REPORT PROTOCOL

# Core warming of coronavirus disease 2019 (COVID-19) patients undergoing mechanical ventilation—A protocol for a randomized controlled pilot study

Nathaniel Bonfanti<sup>1,2</sup>, Emily Gundert<sup>1,2</sup>, Anne M. Drewry<sup>3</sup>, Kristina Goff<sup>4</sup>, Roger Bedimo<sup>5,6</sup>, Erik Kulstad<sup>1\*</sup>

**1** Department of Emergency Medicine, University of Texas, Southwestern Medical Center, Dallas, TX, United States of America, **2** Department of Anesthesia/Critical Care, University of Texas, Southwestern Medical Center, Dallas, TX, United States of America, **3** Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO, United States of America, **4** Department of Anesthesiology and Pain Management, University of Texas, Southwestern Medical Center, Dallas, TX, United States of America, **5** Infectious Diseases Section, VA North Texas Health Care System, Dallas, TX, United States of America, **6** Department of Internal Medicine, University of Texas, Southwestern Medical Center, Dallas, TX, United States of America

\* [erik.kulstad@utsouthwestern.edu](mailto:erik.kulstad@utsouthwestern.edu)



This is a Registered Report and may have an associated publication; please check the article page on the journal site for any related articles.

## OPEN ACCESS

**Citation:** Bonfanti N, Gundert E, Drewry AM, Goff K, Bedimo R, Kulstad E (2020) Core warming of coronavirus disease 2019 (COVID-19) patients undergoing mechanical ventilation—A protocol for a randomized controlled pilot study. PLoS ONE 15(12): e0243190. <https://doi.org/10.1371/journal.pone.0243190>

**Editor:** Steven Eric Wolf, University of Texas Medical Branch at Galveston, UNITED STATES

**Received:** June 19, 2020

**Accepted:** November 17, 2020

**Published:** December 1, 2020

**Peer Review History:** PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pone.0243190>

**Copyright:** This is an open access article, free of all copyright, and may be freely reproduced, distributed, transmitted, modified, built upon, or otherwise used by anyone for any lawful purpose. The work is made available under the [Creative Commons CC0](https://creativecommons.org/licenses/by/4.0/) public domain dedication.

## Abstract

### Background

Coronavirus disease 2019 (COVID-19), caused by the virus SARS-CoV-2, is spreading rapidly across the globe, with little proven effective therapy. Fever is seen in most cases of COVID-19, at least at the initial stages of illness. Although fever is typically treated (with antipyretics or directly with ice or other mechanical means), increasing data suggest that fever is a protective adaptive response that facilitates recovery from infectious illness.

### Objective

To describe a randomized controlled pilot study of core warming patients with COVID-19 undergoing mechanical ventilation.

### Methods

This prospective single-site randomized controlled pilot study will enroll 20 patients undergoing mechanical ventilation for respiratory failure due to COVID-19. Patients will be randomized 1:1 to standard-of-care or to receive core warming via an esophageal heat exchanger commonly utilized in critical care and surgical patients. The primary outcome is patient viral load measured by lower respiratory tract sample. Secondary outcomes include severity of acute respiratory distress syndrome (as measured by PaO<sub>2</sub>/FiO<sub>2</sub> ratio) 24, 48, and 72 hours after initiation of treatment, hospital and intensive care unit length of stay, duration of mechanical ventilation, and 30-day mortality.

**Data Availability Statement:** All relevant data from this study will be made available upon study completion.

**Funding:** EK declares equity interest in Attune Medical. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** EK declares equity interest in Attune Medical. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

## Results

Resulting data will provide effect size estimates to guide a definitive multi-center randomized clinical trial. ClinicalTrials.gov registration number: NCT04426344.

## Conclusions

With growing data to support clinical benefits of elevated temperature in infectious illness, this study will provide data to guide further understanding of the role of active temperature management in COVID-19 treatment and provide effect size estimates to power larger studies.

## Introduction

Traditionally, fever has been treated because its metabolic costs were felt to outweigh its potential physiologic benefit in an already stressed host [1]. However, increasing data suggest that fever may be a protective adaptive response that should be allowed to run its course under most circumstances [2,3]. Higher early fever is associated with a lower risk of death among patients with an ICU admission diagnosis of infection [4,5]. Fever may enhance immune-cell function [6,7], inhibit pathogen growth [8–10], and increase the activity of antimicrobial drugs [11]. Fever potentially benefits infected patients via multiple mechanisms; *in vitro* and animal studies have shown that elevated temperatures augment immune function, increase production of protective heat shock proteins, directly inhibit microorganism growth, reduce viral replication, and enhance antibiotic effectiveness [3,12]. More rapid recoveries are observed from chickenpox [13], malaria [14], and rhinovirus [15] infections with avoidance of antipyretic medication, and many innate and adaptive immunological processes are accelerated by fever [16–18].

Randomized controlled trials have consistently failed to find benefits to treating fever of infectious etiology [16,19–25]. Reducing patient temperature to below normal in sepsis likewise has been found to be of no benefit, or harmful [26,27]. On the other hand, warming appears to have substantial benefits in sepsis. Multiple aspects of both humoral and cellular immunity (including antibody production, T lymphocyte trafficking, T cell adhesion and migration, heat shock protein 90 (Hsp90)-induced  $\alpha 4$  integrin activation and signaling, and macrophage function) are boosted by elevated temperature [28]. A retrospective cohort study evaluating 1,264 patients requiring mechanical ventilation found that high fever ( $\geq 39.5^{\circ}\text{C}$ ) was associated with increased risk for mortality in mechanically ventilated patients; however, in patients with sepsis, moderate fever ( $38.3^{\circ}\text{C}$ – $39.4^{\circ}\text{C}$ ) was protective, and antipyretic medication was not associated with changes in outcome [29]. Prospective data show that afebrile patients have higher 28-day mortality (37.5% vs 18.2%), increased acquisition of secondary infections (35.4% vs. 15.9%), and suppressed HLA-DR expression suggestive of monocyte dysfunction over time [30]. As recently as the 1910's, the "malaria fever cure" (inducing fever to treat a range of conditions, an approach known as "pyrotherapy") was widespread, with the originator of the idea receiving the Nobel Prize in Medicine or Physiology in 1927 [31,32]. Currently, the UK National Institute for Health and Care Excellence (NICE) recommend not using antipyretic agents "with the sole aim of reducing body temperature in children with fever [16,33]". Actively inducing hyperthermia by directly heating the body has been used in cancer treatment, with minimal adverse effects [34–37]. Hyperthermia has been found to have positive impacts on the immune system, causing increased levels of heat-shock proteins [28,38,39], which are directly related to antigen presentation and cross-presentation, activation of macrophages and lymphocytes, and activation and maturation of dendritic cells [40]. A

pilot study of external warming of septic patients (ClinicalTrials.gov Identifier: [NCT02706275](https://clinicaltrials.gov/ct2/show/study/NCT02706275)) has recently been completed.

Many viruses replicate more robustly at cooler temperatures, such as those found in the nasal cavity (33–35°C) than at warmer core body temperature (37°C) [41–45]. Coronavirus disease 2019 (COVID-19) currently has limited treatment options besides dexamethasone [46], but its causative virus (SARS-CoV-2) may behave similarly to other viruses susceptible to temperature changes [47]. Simulations of the receptor binding domain (RBD) of SARS-CoV-2 found high flexibility near the binding site, suggesting that the RBD will have a high entropy penalty upon binding angiotensin-converting enzyme II (ACE2), and that consequently, the virus may be more temperature-sensitive in terms of human infection than other coronaviruses [48]. Notably, fever has often abated by the time a COVID-19 patient requires mechanical ventilation [49]. Additionally, patients with severe COVID-19 tend to have a high viral load and a long virus-shedding period, suggesting that the viral load of SARS-CoV-2 might be a useful marker for assessing disease severity and prognosis [50]. The aim of this study is to determine the effect of active core warming patients diagnosed with COVID-19 and undergoing mechanical ventilation. We hypothesize that active core warming will reduce the severity of acute respiratory distress syndrome, reduce the duration of mechanical ventilation, and improve survival compared to standard of care.

### Study objectives

The purpose of the proposed pilot study is to determine if core warming improves respiratory physiology of mechanically ventilated patients with COVID-19, allowing earlier weaning from ventilation, and greater overall survival.

### Primary objective

1. Determine the change in viral load measured in lower respiratory tract sample after implementation of core warming of ventilated patients, and compare this change to patients undergoing standard care.

### Secondary objectives

1. Measure the impact of esophageal core warming on severity of acute respiratory distress syndrome as measured by PaO<sub>2</sub>/FiO<sub>2</sub> ratio 24, 48, and 72 hours after initiation, and compare this to standard care.
2. Compare the duration of mechanical ventilation of patients treated with core warming to patients treated with standard care.
3. Compare the length of ICU and hospital stay of patients treated with core warming to patients treated with standard care.
4. Compare the 30-day mortality of patients treated with core warming to patients treated with standard care.

### Methods

This is a single-center pilot study to evaluate if core warming improves respiratory physiology of mechanically ventilated patients with COVID-19, allowing earlier weaning from ventilation, and greater overall survival. The protocol was reviewed and approved by the Institutional

Review Board of Washington University. The study is listed on ClinicalTrials.gov with identifier NCT04426344. This prospective, randomized study will include 20 patients diagnosed with COVID-19, and undergoing mechanical ventilation for the treatment of respiratory failure. Patients will be randomized in a 1:1 fashion with 10 patients (Group A) randomized to undergo core warming with an esophageal heat transfer device, and the other 10 patients (Group B) serving as the control group. Patients randomized to Group A will have the esophageal heat transfer device placed in the ICU or other clinical environment in which they are being treated after enrollment and provision of informed consent from appropriate surrogate or legally authorized representative. This study is posted on ClinicalTrials.gov with registration number: NCT04426344. The IRB of Washington University, St. Louis, is performing full review of the final protocol and expected to provide approval; the study will not start prior to IRB approval.

### Screening

Subjects will be recruited from the ICU or other clinical environment in which they are being treated (Emergency Department, step-down unit, etc.). Patients will be identified by the PI or other study investigators/coordinators as available, and will be restricted to those who have been undergoing mechanical ventilation for three days or less. All patients without a DNR order with a diagnosis of COVID-19 and meeting inclusion criteria will be eligible for screening for any exclusion criteria. Written informed consent for the research study will be obtained from patient's surrogate or legally authorized representative prior to enrollment. A formal screening log will be maintained for the trial, and available data on patients not entered into the study will be compared to those entered into the study. Baseline variables of patients entered into the study will additionally be compared by randomization arm.

### Study intervention and monitoring

Participants who have a signed research study consent form (via surrogate or legally authorized representative) will be randomized in a 1:1 fashion to core warming or to standard of care (standard temperature management and treatment). The esophageal heat transfer device will be used according to FDA 510(k) labeling (for patient warming). Patient temperature measurements will be collected for both the device and standard-of-care arms during the study period (up to 72 hours). Device placement will be performed using standard protocol per instructions for use. The esophageal heat transfer device will be set to 42°C temperature after initial placement, and maintained at 42°C for the duration of treatment. All patients will have usual standard of care labs, vital signs, and imaging for patients in critical condition undergoing mechanical ventilation in the ICU. Specific parameters to be measured include PaO<sub>2</sub> at regular intervals appropriate for patients undergoing mechanical ventilation, and FiO<sub>2</sub> at the time of obtaining blood gases for PaO<sub>2</sub> measurement, to allow calculation of P/F ratio.

Control group patients will be managed as per standard of care currently utilized in the ICU, which will include the use of other methods of temperature management as warranted. This would include warming with a forced air blanket only in hypothermic patients (core temperature < 36°C) or antipyretic therapy for febrile patients, as requested by the treating physician. Episodes of hypothermia are infrequent and transient in this population, and the current standard of care generally utilizes a permissive approach to fever (allowing patients to remain mildly febrile) which will continue in the control group without modification (no intentional elevation of temperature will be provided in the control group).

## Study endpoints

The purpose of this pilot study is to determine initial estimates on outcomes (viral load, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, duration of mechanical ventilation, and mortality) in order to determine adequate sample size to properly power definitive studies. Measurements will be compared at time points 24, 48, and 72 hours after initiation. Sampling for viral measurements will utilize lower respiratory tract samples, as these have been shown to be of greater sensitivity and reliability for patient monitoring [47,51,52].

## Primary study endpoints

*The primary endpoint of this study will be:*

1. Viral load measured in lower respiratory tract sample 72 hours after initiation of core warming

*Secondary study endpoints include:*

1. PaO<sub>2</sub>/FiO<sub>2</sub> ratio 24, 48, and 72 hours after initiation of core warming
2. Duration of mechanical ventilation
3. Duration of ICU and hospital stay
4. Patient mortality

## Inclusion criteria

1. Patients above the age of 18 years old.
2. Patients with a diagnosis of COVID-19 on mechanical ventilation.
3. Patient maximum baseline temperature (within previous 12 hours) < 38.3°C.
4. Patients must have a surrogate or legally authorized representative able to understand and critically review the informed consent form.

## Exclusion criteria

1. Patients with contraindication to core warming using an esophageal core warming device.
2. Patients known to be pregnant.
3. Patients with <40 kg of body mass.
4. Patients with DNR status.
5. Patients with acute stroke, post-cardiac arrest, or multiple sclerosis.

## Subject recruitment

Subjects will be recruited from the ICU or other clinical environment in which they are being treated (Emergency Department, step-down unit, etc.). Patients will be identified by the PI or other study investigators/coordinators as available. All patients without a DNR order with a diagnosis of COVID-19 and meeting inclusion criteria will be eligible for screening for any exclusion criteria. Written informed consent for the research study will be obtained from patient's surrogate or legally authorized representative prior to enrollment. If a patient enrolled

in the study gains the capacity to consent for him/herself while the study is in progress, the patient will be approached by a study team member and the consent document will be presented directly to the patient. All questions the patient might have will be answered. The patient will be given the opportunity to either withdraw from the study or sign the consent form. The patient will be informed that his or her decision to withdraw from the study will not affect his or her medical care

### **Duration of study participation**

Participants will be involved for approximately 1 month, including screening, treatment, and follow-up. After consent, patient participation in the intervention phase will last 72 hours for active treatment. The follow up for determination of outcome and duration of mechanical ventilation will occur at 1-month post-treatment. Additional data will be collected via chart review.

### **Total number of subjects and sites**

This single-site study aims to recruit and randomize 20 patients. It is expected that up to 30 subjects may be consented in order to produce 20 randomized & evaluable subjects.

### **Core temperature modulation**

Core temperature control and warming will be performed with a commercially available esophageal heat exchange device (ensoETM, Attune Medical, Chicago, IL). This device is currently used world-wide for various patient temperature management goals, including post-cardiac arrest therapeutic hypothermia [53–56], warming of burn patients [57], warming general surgical patients [58], cooling traumatic brain injury [59], cooling heat stroke [60], and the treatment of central fever [61,62]. The device is a multi-chambered silicone tube placed in the esophagus and connected to a heat exchanger to provide heat transfer to or from a patient (video available at <https://vimeo.com/306506411>). Modulation and control of the patient's temperature is achieved by adjusting setpoint on the external heat exchanger, which in turn controls the circulating water temperature. Two lumens of the device connect to the external heat exchanger, while a third central lumen provides stomach access for gastric decompression or tube feeding. It is a single-use, disposable, non-implantable device with an intended duration of use of 72 hours or less.

### **Intervention regimen**

Patients who are randomized to core warming will have the esophageal heat transfer device placed in the ICU or other treatment area where patient is undergoing mechanical ventilation. The device will remain in place until the study is completed (72 hours). The device will be set to 42°C for the duration of the study period. It is expected that patient temperature will increase from baseline by 1°C to 2°C, but due to ongoing heat loss from the patient, the expected maximum patient temperature is below 39°C. The time course of illness of COVID-19 is such that patients often no longer have fever by the time of mechanical ventilation [41]. If patient temperature increases above this range and reaches 40°C, the device will be set to an operating temperature of 40°C, thereby preventing any further increase in patient temperature. Patient temperature will be followed at intervals per standard of care in the intensive-care setting for mechanically ventilated patients (typically hourly).

## Blinding

Due to the nature of this study, the physicians will not be blinded to the randomization assignment, however participants will be blinded. Once a subject is randomized, the research team will receive the randomization assignment (core warming or standard of care) and proceed with the procedures per the assignment.

## Data collection

- Demographics (including sex/gender, race, ethnicity, and age via date of birth)
- Past medical history, social history, physical exam findings and physicians notes
- Concurrent medications
- Physical exam
- Vital signs: temperature, blood pressure, heart rate, respiration rate, height and weight
- Clinical labs: complete blood count (CBC), chemistry profiles, liver function tests, inflammatory markers (CRP, ferritin), d-dimer, arterial blood gas for determination of PaO<sub>2</sub>
- Upper (nasopharyngeal) and lower (tracheal aspirate, sputum) respiratory tract viral load (cycle threshold)
- Severity of illness: APACHE III, sequential organ failure assessment (SOFA) scoring systems
- Ventilator settings
- Pregnancy test for women of childbearing age
- Adverse events or unanticipated problems

Data will be collected via chart review, and is expected to be available from routinely obtained laboratory and vital sign data recorded at routine intervals (i.e., when labs are drawn for routine care in the ICU).

## Schedule of procedures and data collection

Study Phase	Screening	Randomization/Intervention Phase			Follow-up
	Day -1 to 0	Day 0	Day 1-2	Day 7, 14	Day 30
Informed Consent	X				
Review Inclusion/Exclusion Criteria	X				
Demographics	X				
Medical History/Interim History*	X		X		X
Physical Examination*	X		X		X
Vital Signs: Temperature, BP, HR, RR*	X		X		X
Height and Weight	X				
Pregnancy Test	X				
Clinical Laboratory Evaluation	X	X	X		
Respiratory tract viral load				X	
Ventilator settings	X	X	X		
APACHE III and SOFA scores	X	X	X		

(Continued)



Study Phase	Screening	Randomization/Intervention Phase			Follow-up
	Day -1 to 0	Day 0	Day 1–2	Day 7, 14	Day 30
Clinical Imaging	X	X	X		
Prior/Concomitant Medications	X				X
Randomization		X			
Temperature monitoring		X	X		
PaO <sub>2</sub> , FiO <sub>2</sub> , parameter recording		X	X		
Discharge			X		
Adverse Event / Unanticipated Problems Assessment		X	X		X

\* Interim medical history, physical exam, and vitals will be collected via chart review from routine clinical care.

<https://doi.org/10.1371/journal.pone.0243190.t001>

### Sample size and power determination

Based on a prior study in patients with sepsis, a maximum temperature of 38.3°C to 39.4°C was associated with survival (aHR 0.61 [95% CI, 0.39–0.99]) [29]. However, the effect of warming specific to COVID-19 patients remains uncertain, and as such, it is not possible to accurately perform a power calculation for this pilot study. It is believed that a total of 10 patients for each group will yield the sufficient pilot data to make an appropriate conclusion regarding the potential utility of core warming in reducing viral load, improving pulmonary physiology, reducing mechanical ventilation duration, and increasing patient survival. It is anticipated that data from this pilot study can be used for planning future larger studies.

### Statistical methods

We will utilize standard measures to report outcomes and measure differences between groups. Specifically, we will use descriptive statistics, including mean (standard deviation) and median (interquartile range). Kaplan-Meier plots of important time to event outcomes and measures will be produced. Normality will be assessed using histograms and the Kolmogorov–Smirnov test. Formal hypothesis testing is not planned for this pilot feasibility study.

### Efficacy analysis

This is a pilot feasibility study to determine the potential role of core warming during COVID-19 treatment.

### Interim safety analysis

All subjects entered into the study and randomized at the baseline timepoint will have detailed information collected on adverse events for the overall study safety analysis. An interim safety analysis will be performed after the first 10 subjects are enrolled in the trial. At this time the safety and tolerability of the study device will be assessed and if deemed safe and appropriate, enrollment will continue to 20 subjects.

### Subject population for analysis

All patients enrolled, randomized to a study arm, and completed in the study will be included for analysis.



## Conclusion

We describe, before the initiation of any data collection, our approach to obtaining and analyzing data from a pilot randomized-controlled trial of core warming patients undergoing mechanical ventilation due to COVID-19. We anticipate this framework will enhance the utility of the reported results and provide a solid basis from which to design and execute subsequent investigations.

## Supporting information

**S1 File. Case report form—core warming COVID-19.**

(DOCX)

**S2 File. Consent template.**

(DOCX)

**S3 File. Safety and monitoring—protocol—core warming in COVID-19.**

(DOCX)

**S4 File. SPIRIT-checklist-core warming COVID.**

(DOC)

## Author Contributions

**Conceptualization:** Nathaniel Bonfanti, Emily Gundert, Anne M. Drewry, Roger Bedimo, Erik Kulstad.

**Investigation:** Anne M. Drewry.

**Methodology:** Nathaniel Bonfanti, Anne M. Drewry, Kristina Goff, Roger Bedimo.

**Project administration:** Erik Kulstad.

**Supervision:** Anne M. Drewry.

**Writing – original draft:** Nathaniel Bonfanti, Roger Bedimo, Erik Kulstad.

**Writing – review & editing:** Nathaniel Bonfanti, Emily Gundert, Anne M. Drewry, Kristina Goff, Roger Bedimo, Erik Kulstad.

## References

1. Mohr NM, Doerschug KC: Point: Should antipyretic therapy be given routinely to febrile patients in septic shock? Yes. *Chest* 2013, 144(4):1096–1098. <https://doi.org/10.1378/chest.13-0916> PMID: 24081339
2. Ray JJ, Schulman CI: Fever: suppress or let it ride? *Journal of thoracic disease* 2015, 7(12):E633–E636. <https://doi.org/10.3978/j.issn.2072-1439.2015.12.28> PMID: 26793378
3. Drewry AM, Hotchkiss RS: Counterpoint: Should antipyretic therapy be given routinely to febrile patients in septic shock? No. *Chest* 2013, 144(4):1098–1101. <https://doi.org/10.1378/chest.13-0918> PMID: 24081340
4. Saxena M, Young P, Pilcher D, Bailey M, Harrison D, Bellomo R, et al: Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. *Intensive Care Med* 2015, 41(5):823–832. <https://doi.org/10.1007/s00134-015-3676-6> PMID: 25643903
5. Young PJ, Saxena M, Beasley R, Bellomo R, Bailey M, Pilcher D, et al: Early peak temperature and mortality in critically ill patients with or without infection. *Intensive Care Med* 2012.
6. Berman JD, Neva FA: Effect of temperature on multiplication of *Leishmania amastigotes* within human monocyte-derived macrophages in vitro. *Am J Trop Med Hyg* 1981, 30(2):318–321. <https://doi.org/10.4269/ajtmh.1981.30.318> PMID: 7235124

7. Mace TA, Zhong L, Kilpatrick C, Zynda E, Lee C-T, Capitano M, et al: Differentiation of CD8+ T cells into effector cells is enhanced by physiological range hyperthermia. *Journal of Leukocyte Biology* 2011, 90(5):951–962. <https://doi.org/10.1189/jlb.0511229> PMID: 21873456
8. Chu CM, Tian SF, Ren GF, Zhang YM, Zhang LX, Liu GQ: Occurrence of temperature-sensitive influenza A viruses in nature. *J Virol* 1982, 41(2):353–359. <https://doi.org/10.1128/JVI.41.2.353-359.1982> PMID: 7077746
9. Moench LM: A Study of the Heat Sensitivity of the Meningococcus in Vitro within the Range of Therapeutic Temperatures. *Journal of Laboratory and Clinical Medicine* 1937, 22:665–676.
10. Small PM, Tauber MG, Hackbarth CJ, Sande MA: Influence of body temperature on bacterial growth rates in experimental pneumococcal meningitis in rabbits. *Infection and immunity* 1986, 52(2):484–487. <https://doi.org/10.1128/IAI.52.2.484-487.1986> PMID: 3699893
11. Mackowiak PA, Ruderman AE, Martin RM, Many WJ, Smith JW, Luby JP: Effects of physiologic variations in temperature on the rate of antibiotic-induced bacterial killing. *American journal of clinical pathology* 1981, 76(1):57–62. <https://doi.org/10.1093/ajcp/76.1.57> PMID: 6789670
12. Launey Y, Nessler N, Mallédant Y, Seguin P: Clinical review: fever in septic ICU patients—friend or foe? *Critical care (London, England)* 2011, 15(3):222–222. <https://doi.org/10.1186/cc10097> PMID: 21672276
13. Doran TF, De Angelis C, Baumgardner RA, Mellits ED: Acetaminophen: more harm than good for chickenpox? *J Pediatr* 1989, 114(6):1045–1048. [https://doi.org/10.1016/s0022-3476\(89\)80461-5](https://doi.org/10.1016/s0022-3476(89)80461-5) PMID: 2656959
14. Brandts CH, Ndjave M, Graninger W, Kremsner PG: Effect of paracetamol on parasite clearance time in Plasmodium falciparum malaria. *Lancet* 1997, 350(9079):704–709. [https://doi.org/10.1016/S0140-6736\(97\)02255-1](https://doi.org/10.1016/S0140-6736(97)02255-1) PMID: 9291905
15. Stanley ED, Jackson GG, Panusarn C, Rubenis M, Dirda V: Increased virus shedding with aspirin treatment of rhinovirus infection. *Jama* 1975, 231(12):1248–1251. PMID: 163931
16. Peters MJ, Woolfall K, Khan I, Deja E, Mouncey PR, Wulff J, et al: Permissive versus restrictive temperature thresholds in critically ill children with fever and infection: a multicentre randomized clinical pilot trial. *Critical care (London, England)* 2019, 23(1):69–69. <https://doi.org/10.1186/s13054-019-2354-4> PMID: 30845977
17. Evans SS, Repasky EA, Fisher DT: Fever and the thermal regulation of immunity: the immune system feels the heat. *Nature reviews Immunology* 2015, 15(6):335–349. <https://doi.org/10.1038/nri3843> PMID: 25976513
18. Lee CT, Zhong L, Mace TA, EA Repasky: Elevation in body temperature to fever range enhances and prolongs subsequent responsiveness of macrophages to endotoxin challenge. *PLoS One* 2012, 7(1):e30077. <https://doi.org/10.1371/journal.pone.0030077> PMID: 22253887
19. Schulman CI, Namias N, Doherty J, Manning RJ, Li P, Elhaddad A, et al: The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. *Surg Infect (Larchmt)* 2005, 6(4):369–375. <https://doi.org/10.1089/sur.2005.6.369> PMID: 16433601
20. Gozzoli V, Schottker P, Suter PM, Ricou B: Is it worth treating fever in intensive care unit patients? Preliminary results from a randomized trial of the effect of external cooling. *Arch Intern Med* 2001, 161(1):121–123. <https://doi.org/10.1001/archinte.161.1.121> PMID: 11146708
21. Young P, Saxena M, Bellomo R, Freebairn R, Hammond N, van Haren F, et al: Acetaminophen for Fever in Critically Ill Patients with Suspected Infection. *New England Journal of Medicine* 2015, 373(23):2215–2224. <https://doi.org/10.1056/NEJMoa1508375> PMID: 26436473
22. Zhang Z: Antipyretic therapy in critically ill patients with established sepsis: a trial sequential analysis. *PLoS One* 2015, 10(2):e0117279. <https://doi.org/10.1371/journal.pone.0117279> PMID: 25710375
23. Dallimore J, Ebmeier S, Thayabaran D, Bellomo R, Bernard G, Schortgen F, et al: Effect of active temperature management on mortality in intensive care unit patients. *Crit Care Resusc* 2018, 20(2):150–163. PMID: 29852854
24. Drewry AM, Ablordeppey EA, Murray ET, Stoll CRT, Izadi SR, Dalton CM, et al: Antipyretic Therapy in Critically Ill Septic Patients: A Systematic Review and Meta-Analysis. *Critical care medicine* 2017, 45(5):806–813. <https://doi.org/10.1097/CCM.0000000000002285> PMID: 28221185
25. Young PJ, Bellomo R, Bernard GR, Niven DJ, Schortgen F, Saxena M, et al: Fever control in critically ill adults. An individual patient data meta-analysis of randomised controlled trials. *Intensive Care Med* 2019, 45(4):468–476. <https://doi.org/10.1007/s00134-019-05553-w> PMID: 30741326
26. Itenov TS, Johansen ME, Bestle M, Thormar K, Hein L, Gyldensted L, et al: Induced hypothermia in patients with septic shock and respiratory failure (CASS): a randomised, controlled, open-label trial. *The Lancet Respiratory medicine* 2018, 6(3):183–192. [https://doi.org/10.1016/S2213-2600\(18\)30004-3](https://doi.org/10.1016/S2213-2600(18)30004-3) PMID: 29325753

27. Saoraya J, Musikatavorn K, Puttaphaisan P, Komindr A, Srisawat N: Intensive fever control using a therapeutic normothermia protocol in patients with febrile early septic shock: A randomized feasibility trial and exploration of the immunomodulatory effects. *SAGE Open Medicine* 2020, 8:2050312120928732. <https://doi.org/10.1177/2050312120928732> PMID: 32547753
28. Lin C, Zhang Y, Zhang K, Zheng Y, Lu L, Chang H, et al: Fever Promotes T Lymphocyte Trafficking via a Thermal Sensory Pathway Involving Heat Shock Protein 90 and alpha4 Integrins. *Immunity* 2019, 50(1):137–151.e136. <https://doi.org/10.1016/j.immuni.2018.11.013> PMID: 30650373
29. Evans EM, Doctor RJ, Gage BF, Hotchkiss RS, Fuller BM, Drewry AM: The Association of Fever and Antipyretic Medication With Outcomes in Mechanically Ventilated Patients: A Cohort Study. *Shock* 2019, 52(2):152–159. <https://doi.org/10.1097/SHK.0000000000001368> PMID: 31058720
30. Drewry AM, Ablordeppey EA, Murray ET, Dalton CM, Fuller BM, Kollef MH, et al: Monocyte Function and Clinical Outcomes in Febrile and Afebrile Patients With Severe Sepsis. *Shock* 2018, 50(4):381–387. <https://doi.org/10.1097/SHK.0000000000001083> PMID: 29240644
31. Raju TN: Hot brains: manipulating body heat to save the brain. *Pediatrics* 2006, 117(2):e320–321. <https://doi.org/10.1542/peds.2005-1934> PMID: 16452338
32. Epstein NN: Artificial Fever as a Therapeutic Procedure. *Cal West Med* 1936, 44(5):357–358. PMID: 18743642
33. Davis T: NICE guideline: feverish illness in children—assessment and initial management in children younger than 5 years. *Archives of disease in childhood Education and practice edition* 2013, 98(6):232–235. <https://doi.org/10.1136/archdischild-2013-304792> PMID: 24046395
34. van der Zee J: Heating the patient: a promising approach? *Annals of Oncology* 2002, 13(8):1173–1184. <https://doi.org/10.1093/annonc/mdf280> PMID: 12181239
35. Bull JMC: Clinical Practice of Whole-Body Hyperthermia: New Directions. In: *Thermoradiotherapy and Thermochemotherapy. Medical Radiology (Diagnostic Imaging and Radiation Oncology)*. Berlin, Heidelberg: Springer; 1996.
36. Westermann AM, Grosen EA, Katschinski DM, Jäger D, Rietbroek R, Schink JC, et al: A pilot study of whole body hyperthermia and carboplatin in platinum-resistant ovarian cancer. *European Journal of Cancer* 2001, 37(9):1111–1117. [https://doi.org/10.1016/s0959-8049\(01\)00074-0](https://doi.org/10.1016/s0959-8049(01)00074-0) PMID: 11378341
37. Robins HI, Dennis WH, Neville AJ, Shecterle LM, Martin PA, Grossman J, et al: A nontoxic system for 41.8 degrees C whole-body hyperthermia: results of a Phase I study using a radiant heat device. *Cancer research* 1985, 45(8):3937–3944. PMID: 4016761
38. Shi H, Cao T, Connolly JE, Monnet L, Bennett L, Chapel S, et al: Hyperthermia Enhances CTL Cross-Priming. *The Journal of Immunology* 2006, 176(4):2134–2141. <https://doi.org/10.4049/jimmunol.176.4.2134> PMID: 16455969
39. Basu S, Srivastava PK: Fever-like temperature induces maturation of dendritic cells through induction of hsp90. *International Immunology* 2003, 15(9):1053–1061. <https://doi.org/10.1093/intimm/dxg104> PMID: 12917257
40. Tsan M-F, Gao B: Heat shock proteins and immune system. *Journal of Leukocyte Biology* 2009, 85(6):905–910. <https://doi.org/10.1189/jlb.0109005> PMID: 19276179
41. Foxman EF, Storer JA, Fitzgerald ME, Wasik BR, Hou L, Zhao H, et al: Temperature-dependent innate defense against the common cold virus limits viral replication at warm temperature in mouse airway cells. *Proceedings of the National Academy of Sciences* 2015, 112(3):827–832. <https://doi.org/10.1073/pnas.1411030112> PMID: 25561542
42. Ping CK: Rapid response to: Graphic Outbreak of severe acute respiratory syndrome in Hong Kong Special Administrative Region: case report. *BMJ* 2003, 326(850).
43. Laporte M, Stevaert A, Raeymaekers V, Boogaerts T, Neelmeier I, Chiu W, et al: Hemagglutinin Cleavability, Acid Stability, and Temperature Dependence Optimize Influenza B Virus for Replication in Human Airways. *Journal of Virology* 2019, 94(1):e01430–01419. <https://doi.org/10.1128/JVI.01430-19> PMID: 31597759
44. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al: SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med* 2020, 382(12):1177–1179. <https://doi.org/10.1056/NEJMc2001737> PMID: 32074444
45. Chan KH, Peiris JS, Lam SY, Poon LL, Yuen KY, Seto WH: The Effects of Temperature and Relative Humidity on the Viability of the SARS Coronavirus. *Advances in virology* 2011, 2011:734690. <https://doi.org/10.1155/2011/734690> PMID: 22312351
46. Dexamethasone in Hospitalized Patients with Covid-19—Preliminary Report. *New England Journal of Medicine* 2020.
47. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al: Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *Jama* 2020. <https://doi.org/10.1001/jama.2020.3786> PMID: 32159775

48. He J, Tao H, Yan Y, Huang S-Y, Xiao Y: Molecular mechanism of evolution and human infection with the novel coronavirus (2019-nCoV). *bioRxiv* 2020:2020.2002.2017.952903. <https://doi.org/10.3390/v12040428> PMID: 32290077
49. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet* 2020, 395(10229):1054–1062. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3) PMID: 32171076
50. Liu Y, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, et al: Viral dynamics in mild and severe cases of COVID-19. *The Lancet Infectious Diseases*. [https://doi.org/10.1016/S1473-3099\(20\)30232-2](https://doi.org/10.1016/S1473-3099(20)30232-2) PMID: 32199493
51. Williams TGS, Snell LB, Taj U, Douthwaite ST: The role of lower respiratory tract samples in the diagnosis of COVID-19. *Infectious Diseases* 2020, 52(7):524–525. <https://doi.org/10.1080/23744235.2020.1761999> PMID: 32400235
52. Yu F, Yan L, Wang N, Yang S, Wang L, Tang Y, et al: Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients. *Clinical Infectious Diseases* 2020, 71(15):793–798. <https://doi.org/10.1093/cid/ciaa345> PMID: 32221523
53. Goury A, Poirson F, Chaput U, Voicu S, Garcon P, Beeken T, et al: Targeted Temperature Management Using The "Esophageal Cooling Device" After Cardiac Arrest (The COOL Study): A feasibility and safety study. *Resuscitation* 2017, 121:54–61. <https://doi.org/10.1016/j.resuscitation.2017.09.021> PMID: 28951293
54. Hegazy AF, Lapierre DM, Butler R, Martin J, Althenayan E: The esophageal cooling device: A new temperature control tool in the intensivist's arsenal. *Heart & Lung: The Journal of Acute and Critical Care* 2017, 46(3):143–148. <https://doi.org/10.1016/j.hrtlng.2017.03.001> PMID: 28410771
55. Markota A, Fluher J, Kit B, Balazic P, Sinkovic A: The introduction of an esophageal heat transfer device into a therapeutic hypothermia protocol: A prospective evaluation. *Am J Emerg Med* 2016, 34(4):741–745. <https://doi.org/10.1016/j.ajem.2016.01.028> PMID: 26906333
56. Khan I, Haymore J, Barnaba B, Armahizer M, Melinosky C, Bautista MA, et al: Esophageal Cooling Device Versus Other Temperature Modulation Devices for Therapeutic Normothermia in Subarachnoid and Intracranial Hemorrhage. *Ther Hypothermia Temp Manag* 2018, 8(1):53–58. <https://doi.org/10.1089/ther.2017.0033> PMID: 29236581
57. Williams D, Leslie G, Kyriazis D, O'Donovan B, Bowes J, Dingley J: Use of an Esophageal Heat Exchanger to Maintain Core Temperature during Burn Excisions and to Attenuate Pyrexia on the Burns Intensive Care Unit. *Case Reports in Anesthesiology* 2016, 2016: 6. <https://doi.org/10.1155/2016/7306341> PMID: 27018074
58. Kalasbail P, Makarova N, Garrett F, Sessler DI: Heating and Cooling Rates With an Esophageal Heat Exchange System. *Anesth Analg* 2018, 126(4):1190–1195. <https://doi.org/10.1213/ANE.0000000000002691> PMID: 29283916
59. Bhatti F, Naiman M, Tsarev A, Kulstad E: Esophageal Temperature Management in Patients Suffering from Traumatic Brain Injury. *Ther Hypothermia Temp Manag* 2019. <https://doi.org/10.1089/ther.2018.0034> PMID: 30657435
60. Martin KR, Naiman M, Espinoza M: Using Esophageal Temperature Management to Treat Severe Heat Stroke: A Case Report. *J Neurosci Nurs* 2019.
61. Hegazy AF, Lapierre DM, Butler R, Althenayan E: Temperature control in critically ill patients with a novel esophageal cooling device: a case series. *BMC anesthesiology* 2015, 15:152. <https://doi.org/10.1186/s12871-015-0133-6> PMID: 26481105
62. Markota A, Košir AS, Balažič P, Živko I, Sinkovič A: A Novel Esophageal Heat Transfer Device for Temperature Management in an Adult Patient with Severe Meningitis. *Journal of Emergency Medicine* 2017, 52(1):e27–e28.