Great Ormond Street Hospital for Children NHS Foundation Trust

Measuring the metabolic cost of fever: Indirect calorimetry in children with fever on the intensive care unit.

Protocol Version 2 (07.08.2016)

STUDY INVESTIGATORS:

Principal Investigator: Dr Samiran Ray
PhD Student,
Respiratory, Critical Care and Anaesthesia Section,
UCL Great Ormond Street Institute of Child Health, London, UK
samiran.ray@gosh.nhs.uk

Chief Investigator: Professor Mark J Peters
Professor Paediatric Intensive Care Medicine
Respiratory, Critical Care and Anaesthesia Section,
UCL Great Ormond Street Institute of Child Health, London UK
mark.peters@ucl.ac.uk

INTRODUCTION

Fever is a common immune response in children with infection or inflammation. While fever may potentiate the immune system to fight the pathogenic stimulus, energy is required to generate the raised temperature. This may be scarce in critical illness, particularly in children. We do not know how much energy is used in generating fever by children in the intensive care unit. This study aims to measure energy expenditure in children during and before/after they have a fever. We aim to do this using indirect calorimetry in at least 15 children, who are invasively ventilated on the intensive care unit. We will then calculate the average increase in energy expenditure required per 1°C rise in temperature in this population. If fever does not require a significant increase in energy expenditure in children on the intensive care unit, then treatment of fever may not have any benefits. If fever does require an increase in energy expenditure, this may counter the immunological benefits that fever confers. In such a case a randomised controlled trial comparing treatment and non-treatment of fever would be required.

BACKGROUND

Fever is an innate immune response to danger. Stimuli such as pathogens or tissue damage lead to a cascade of cytokine signals, including the release of pro-inflammatory cytokines such as TNF-α, Il-6 and IL-1. Many of these pro-inflammatory cytokines act upon the thermoregulatory centre of the hypothalamus via the release of prostaglandins, to increase the body's temperature set-point. The body responds by both reducing heat loss and increasing heat production to raise the body temperature[1,2].

The conservation of the fever response through billions of years of evolution (plants, insect, reptiles and mammals all increase their temperature in response to infection[3-11]) suggest that fever has a beneficial effect. Animal studies show the following immunological benefits of fever range hyperthermia: (i) increased neutrophil release from the bone marrow, (ii) increased neutrophil tissue infiltration, for example in lungs tissue, (iii) increased cytotoxic activity of innate immune cells such as neutrophils and NK cells, (iv) increased phagocytic activity, (v) increased antigen presentation by dendritic cells, (vi) increased cytokine production and release[2].

This correlates with some clinical outcome studies. Malaria induced fever was successfully used to treat neurosyphilis in the pre-antibiotic era[12]. Anti-pyretic treatment increases the duration of virus shedding and illness in varicella and rhinovirus infection[14-15]. Population level influenza rates may increase with regular anti-pyretic treatment[16]. In critically-ill patients, especially those with infection, a maximum temperature at intensive care unit admission of 38.5-39.5°C was associated with the lowest risk of mortality[17-18]. However randomised controlled trials treating fever with anti-pyretics or placebo in critical illness have not demonstrated any risks of treating fever[19-23].

Balancing the immunological benefits of fever are several potential detrimental effects. Hyperthermia can cause protein degeneration, leading to direct cell damage and death. This can lead to loss of gastrointestinal tract integrity, decrease in glomerular filtration rate, liver dysfunction, myocardial damage and arrhythmias, brain injury and lowering of the seizure threshold[24]. Most of these deleterious effects occur in sterile forms of pyrexia, especially at high grade temperatures. However in critical illness the generation of fever itself may be deleterious. Energy is required to produce heat: in fever, this can be through uncoupling of the electron transport chain leading to heat dissipation in brown fat, or through shivering[24]. As critical illness is characterised by an

imbalance of energy delivery and consumption, the energy requirements to generate a fever may be unaffordable[25].

The energy requirements of fever have previously been measured in adult patients on the intensive care unit. Manthous et al studied 12 febrile patients on the intensive care unit during cooling after sedation and paralysis. For each 1°C drop in temperature, the reduction of energy expenditure was 10% of the baseline. This was also accompanied with a reduction in cardiac output, and no change in oxygen extraction (the ratio between oxygen consumption and delivery)[26]. Similar associations between temperature reduction and decrease in energy expenditure with cooling have been demonstrated in the context of brain injury[27-28].

In children, energy expenditure has been shown not to be raised in febrile infants admitted to hospital. In a cohort of 12 children, although 8 had an increase in energy expenditure when febrile, overall there was no difference[29]. However this was conducted in children who were not critically unwell or in intensive care. It is possible that these children were able to increase their temperature by preventing heat loss. Children in intensive care may not have the ability to do so, due to disease related factors such as shock and vasoplegia, or treatment related factors, such as exogenous vasodilators. Children admitted to hospital with over 40% burns had an increase in energy expenditure with fever by up to 30% of baseline[30]. These children were likely to have more unregulated surface heat loss due to skin barrier compromise, but equally were likely to be hypermetabolic following their initial injury. In an analysis of cytokine levels and metabolic rate in critically-ill children, Briassoulis et al found that the predominant metabolic pattern in acute critical illness in children was that of hypometabolism, during which energy expenditure did not correlate with levels of IL-6 and IL-10, both fever-inducing cytokines[31].

Therefore we still do not know if energy expenditure is increased in children with febrile illness in the intensive care unit. Given the immune benefits of fever, there may be an argument to not treat fever in critically ill children as any advantage in host response may be beneficial. However, if the energy expenditure associated with fever is high, treatment of fever may have a benefit.

AIM OF STUDY

To understand the changes, if any, in the energy expenditure of critically-ill children with fever

STUDY OBJECTIVES

To measure the energy expenditure using indirect calorimetry in mechanically ventilated children admitted to the intensive care unit before, during and after fever.

HYPOTHESIS

Null hypothesis: Fever will be associated with <10% difference of baseline energy expenditure per 1°C change in temperature in critically-ill children ventilated on the intensive care unit

Alternative hypothesis: Fever will be associated with a >10% difference of baseline energy expenditure per 1°C change in temperature

STUDY DESIGN

Prospective observational cohort study

STUDY POPULATION

Children admitted to the paediatric intensive care unit at Great Ormond Street Hospital with suspected infection, following trauma or major surgery, who are likely to develop a fever.

ELIGIBILITY CRITERIA

Inclusion criteria:

- Children >10kg (The MedGraphic Ultima CCM calorimeter has been used safely in children as low as 10kg)
- Children with suspected infection, following trauma, or post-major surgery

Exclusion criteria:

- Children post brain injury
- Children with refractory status epilepticus
- Children post cardiac arrest
- Children post cardiac bypass
- Children with cardiac arrhythmias
- Children not invasively ventilated
- Children with a greater than 5% leak around their endotracheal tube
- Children with a fraction of inspired oxygen (FiO_2)>0.60
- Children above 16 years of age

STUDY OUTCOMES

Primary outcome: Change in energy expenditure per degree Centigrade change in temperature

Secondary outcome: Change in oxygen extraction ratio (ratio of oxygen consumption to oxygen delivery) per degree Centigrade change in temperature using oxygen delivery data from the Lidco Rapid (LIDCO Ltd, UK) cardiac output monitor if in place.

STUDY PROCEDURES

Screening and Recruitment

- All patients will be screened each morning (Mon-Fri) by the PI for weight, ventilation status and likelihood of developing a fever (The PI is part of the wider clinical team)
- The PI will ask the clinical team on call if calorimetry is suitable for the identified patient/s
- If the clinical team feel this is appropriate, the PI will ask consent of the parents to undertake indirect calorimetry

Study procedure

1. Once consented, calorimetric measurement will be undertaken using the MedGraphic Ultima CCX, Minnesota, USA). This will be done in the following steps:
    a. Assess the patient for stability:
        i. no change in inotropes (dopamine, adrenaline, noradrenaline, vasopressin, milrinone, dobutamine) in previous hour
        ii. no change in ventilator settings including FiO_2 in the previous hour
        iii. FiO_2 <0.6
        iv. tidal volume ventilation >60ml (ideally greater than 100ml)
        v. air leak around endotracheal tube (ETT)<5%
        vi. no increases in sedation in past hour
        vii. no major stimulatory events (physiotherapy, turning, suction) in the previous hour

    b. Record demographic data, ventilator settings and measurements, calorie intake, heart rate, blood pressure, cardiac index (if monitored), drug infusion rates, use of paralysis, COMFORT or sedation score, temperature
    c. If the patient is stable, then start measurement of energy expenditure (calibrate prior to measurement, attach gas sampler to end of ETT to ventilator end of capnograph/flow sensor.
    d. Stop measurement immediately if any deterioration in ventilation with measurement
    e. After 30 minutes (or sooner if steady state is reached i.e. 5 consecutive minutes of less than 10% variation in O_2 and CO_2 concentrations) stop measurement
2. If patient develops temperature >38°C (axillary or central measurement) within the next 4 hours (or longer only if all variables are the same as baseline), repeat step 4 a-c prior to anti-pyretic administration (with half hourly data collection). The calorimeter will be left on the patient for continuous data collection until the temperature falls below 38°C.
3. If continuous measurement is not possible because of clinical needs (nursing or medical request, need for suctioning, patient instability), a 3rd measurement will be taken when the temperature is below 38°C

If the patient is febrile at screening, measurement will start at step 2

Patient safety

The calorimeter fits in to the ventilator circuit. This requires very brief disconnection of the circuit to attach the sampling connector. Disconnection of this nature is routine practice in the intensive care unit (for example during suctioning) and is well tolerated.

The calorimeter samples air from the ventilator circuit at a constant rate of 100ml/min. This may affect ventilation in small children. The Medgraphic Ultima CCM is licensed for use for pateints with tidal volumes of 100ml or more. This will usually equate to children around 15kg. However our collaborators in Addenbrooke's Hospital, Cambridge (Dr N Pathan) have used the Medgraphic Ultima CCM safely in children down to 10kg.

During measurement we will monitor the child's respiratory rate, oxygen saturation levels and end tidal CO2. If any of these values change significantly, as judged by the bedside nurse or the PI, calorimetry will be discontinued.

Data collection

Data will be collected for

- Demographic data (ID, weight, height, age, sex, diagnosis)
- Inspired and expired O2 and CO2; VO2 and VCO2; Respiratory Quotient; Energy expenditure (as measured and displayed by the MedGraphics Ultima CCM calorimeter)
- Physiological variables (heart rate, blood pressure)
- IF CARDIAC OUTPUT MONITOR IN PLACE: stroke volume and cardiac index (as measured by Lidco Rapid, LIDCO Ltd, UK) and latest haemoglobin
- Inotrope infusion doses
- COMFORT or sedation score as recorded
- Paralysis (yes/no)
- Temperature
- Nutritional intake in last 24 hours or since admission

Data apart from demographic data will be collected at the start of each recording and hourly if continuous recording

If cardiac monitoring is in place, continuous data (as recorded by the Lidco Rapid) will be used to calculate oxygen delivery.

STATISTICAL ANALYSIS

Sample size: Not enough data exists to ascertain the standard deviation of energy expenditure using the Medgraphics Ultima CCM calorimeter in critically ill children over the time period to be measured. However a standard deviation of 10% has been observed in critically ill children by groups who have measured energy expenditure in large numbers of children (personal communication from Dr R Meyer, Imperial College, London). Based on this, for a 10% effect size, with a one-tailed α of 0.05 and (1-β) of 0.8, a sample size of 10 children would be needed, provided a 1^{o}C of temperature is seen. An analysis of temperature change following over 5000 doses of paracetamol in febrile children suggested a mean reduction of temperature by 0.7^{o}C. Based on this therefore we will need 10 x 1/0.7 = 15 patients

However it is likely that our sample will have several confounders which will need to be taken into account by multi-variable analysis. Therefore we will aim to recruit at least 15 children with measurements with and without fever (ideally before-during and after fever), but will try and recruit as many children as possible over the 12 month study period. Approximately 300 patients admitted to PICU at Great Ormond Street Hospital per year are above 10kg. Of these, approximately 75-100 patients are electively admitted, 30 post-major surgery (mostly spinal surgery). 30% of children post spinal surgery develop a fever in the first 24 hours. In addition the remaining 200 children are admitted as an emergency. 80% of children admitted as an emergency are treated for a suspected infection, the remainder post trauma. Again 30-50% of children admitted with an infection or trauma develop a fever within the first 24 hours. Therefore each year approximately 75-80 patients will be >10kg, ventilated, and will develop a fever within the first 24 hours of admission, with a proportion developing fever later on in admission (e.g. from nosocomial infections).

Statistical analysis: Uni-variable analysis using paired t-tests will be undertaken by comparing the energy expenditure with and without fever, divided by the change in temperature. Multi-variable analysis using a multi-level regression model will be used using

- Change in energy expenditure as the outcome variable
- Patient ID as the random effect variable
- Change in temperature, COMFORT score, vasoactive inotrope score, heart rate, blood pressure, and paralysis as a binary variable as fixed effect variables

If cardiac output monitoring is in place, then the oxygen extraction can be calculated as VO2/DO2, where,
DO2 = {cardiac index x ((oxygen saturation of haemoglobin x haemoglobin concentration) + 0.0031 x partial pressure of oxygen)}
and VO2 is measured from the calorimeter

ETHICAL CONSIDERATIONS

The study will be conducted in accordance to Good Clinical Practice principles and the principles of the Declaration of Helsinki.

Informed consent will be sought from parents/guardians with parental responsibility prior to measurement. Consent forms will be stored in the Great Ormond Street Critical Care Research Office securely.

Data will be stored and processed electronically in a secure password protected NHS IT network according the principles of the institutional information governance policy. Patient identifiable data will be minimised to unique patient hospital number. The storage of data will be consented for.

Baseline energy expenditure data may be shared with collaborators anonymously to further the understanding of metabolic activity in critically ill children. Consent for this will explicitly sought.

OUTCOMES AND SIGNIFICANCE

If the null hypothesis is true, then the treatment of fever in critically-ill children can be questioned, especially given the immunological benefits. If the alternative hypothesis is true, then the overall risk- benefit balance of treating or not treating fever in critically illness will have to be assessed in the form of a randomised controlled clinical trial.
Research findings will be disseminated in national and international intensive care conferences, and peer-reviewed medical/scientific journals

REFERENCES

1. Hasday JD, Thompson C, Singh IS. Fever, immunity, and molecular adaptations. Compr Physiol. 2014 Jan;4(1):109-48.
2. Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. Nat Rev Immunol. 2015 Jun;15(6):335-49.
3. Reynolds WW, Casterlin ME, Covert JB. Behavioural fever in teleost fishes. Nature. 1976 Jan 1-8;259(5538):41-2.
4. Kluger MJ. Fever in the frog Hyla cinerea. J Therm Biol. 1977;2:79-81
5. Vaughn LK, Bernheim HA, Kluger MJ. Fever in the lizard Dipsosaurus dorsalis. Nature. 1974 Dec 6;252(5483):473-4.
6. D'Alecy LG, Kluger MJ. Avian febrile response. J Physiol. 1975 Dec;253(1):223-32.
7. Stitt JT. Prosaglandin E1 fever induced in rabbits. J Physiol. 1973 Jul;232(1):163-79

8. Urison NT, Goelst K, Buffenstein RA. A positive fever response by a poikilothermic mammal, the naked mole rat (Heterocephalus glabei). J Therm Biol. 1973;18(4):245-49
9. Bernheim HA, Kluger MJ. Fever: effect of drug-induced antipyresis on survival. Science. 1976 Jul 16;193(4249):237-9.
10. Covert JB, Reynolds WW. Survival value of fever in fish. Nature. 1977 May 5;267(5606):43-5.
11. Kluger MJ, Vaughn LK. Fever and survival in rabbits infected with Pasteurella multocida. J Physiol. 1978 Sep;282:243-51.
12. Karamanou M, Liappas I, Antoniou Ch, Androutsos G, Lykouras E. Julius Wagner-Jauregg (1857-1940): Introducing fever therapy in the treatment of neurosyphilis. Psychiatriki. 2013 Jul-Sep;24(3):208-12.
13. Graham NM, Burrell CJ, Douglas RM, Debelle P, Davies L. Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers. J Infect Dis. 1990 Dec;162(6):1277-82.
14. Stanley ED, Jackson GG, Panusarn C, Rubenis M, Dirda V. Increased virus shedding with aspirin treatment of rhinovirus infection. JAMA. 1975 Mar 24;231(12):1248-51.
15. Doran TF, De Angelis C, Baumgardner RA, Mellits ED. Acetaminophen: more harm than good for chickenpox? J Pediatr. 1989 Jun;114(6):1045-8.
16. Earn DJ, Andrews PW, Bolker BM. Population-level effects of suppressing fever. Proc Biol Sci. 2014 Jan 22;281(1778):20132570.
17. Young PJ, Saxena M, Beasley R, Bellomo R, Bailey M, Pilcher D, Finfer S, Harrison D, Myburgh J, Rowan K. Early peak temperature and mortality in critically ill patients with or without infection. Intensive Care Med. 2012 Jan 31
18. Lee BH, Inui D, Suh GY, et al Fever and Antipyretic in Critically ill patients Evaluation (FACE) Study Group. Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study. Crit Care. 2012 Feb 28;16(1):R33.
19. Young P, Saxena M, Bellomo R, Freebairn R, Hammond N, van Haren F, Holliday M, Henderson S, Mackle D, McArthur C, McGuinness S, Myburgh J, Weatherall M, Webb S, Beasley R; HEAT Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Acetaminophen for Fever in Critically Ill Patients with Suspected Infection. N Engl J Med. 2015 Dec 3;373(23):2215-24.
20. Bernard GR, Wheeler AP, Russell JA, Schein R, Summer WR, Steinberg KP, Fulkerson WJ, Wright PE, Christman BW, Dupont WD, Higgins SB, Swindell BB. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. N Engl J Med. 1997 Mar 27;336(13):912-8.
21. Schortgen F, Clabault K, Katsahian S, Devaquet J, Mercat A, Deye N, Dellamonica J, Bouadma L, Cook F, Beji O, Brun-Buisson C, Lemaire F, Brochard L. Fever control using external cooling in septic shock: a randomized controlled trial. Am J Respir Crit Care Med. 2012 May 15;185(10):1088-95.
22. Gozzoli V, Schöttker 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 Jan 8;161(1):121-3.
23. Honarmand H, Abdollahi M, Ahmadi A, Javadi MR, Khoshayand MR, Tabeefar H, Mousavi S, Mahmoudi L, Radfar M, Najafi A, Mojtahedzadeh M. Randomized trial of the effect of intravenous paracetamol on inflammatory biomarkers and outcome in febrile critically ill adults. Daru. 2012 Aug 28;20(1):12. doi:10.1186/2008-2231-20-12
24. Walter EJ, Hanna-Jumma S, Carraretto M, Forni L. The pathophysiological basis and consequences of fever. Crit Care. 2016 Jul 14;20(1):200.

25. Schumacker PT, Rowland J, Saltz S, Nelson DP, Wood LD. Effects of hyperthermia and hypothermia on oxygen extraction by tissues during hypovolemia. J Appl Physiol (1985). 1987 Sep;63(3):1246-52.
26. Manthous CA, Hall JB, Olson D, Singh M, Chatila W, Pohlman A, Kushner R, Schmidt GA, Wood LD. Effect of cooling on oxygen consumption in febrile critically ill patients. Am J Respir Crit Care Med. 1995 Jan;151(1):10-4.
27. Hata JS, Shelsky CR, Hindman BJ, Smith TC, Simmons JS, Todd MM. A prospective, observational clinical trial of fever reduction to reduce systemic oxygen consumption in the setting of acute brain injury. Neurocrit Care. 2008;9(1):37-44.
28. Bruder N, Raynal M, Pellissier D, Courtinat C, François G. Influence of body temperature, with or without sedation, on energy expenditure in severe head-injured patients. Crit Care Med. 1998 Mar;26(3):568-72.
29. McIntyre J, Hull D. Metabolic rate in febrile infants. Arch Dis Child. 1996 Mar;74(3):206-9.
30. Gore DC, Chinkes D, Sanford A, Hart DW, Wolf SE, Herndon DN. Influence of fever on the hypermetabolic response in burn-injured children. Arch Surg. 2003 Feb;138(2):169-74
31. Briassoulis G, Venkataraman S, Thompson A. Cytokines and metabolic patterns in pediatric patients with critical illness. Clin Dev Immunol. 2010;2010:354047.